

# CLINICAL—LIVER, PANCREAS, AND BILIARY TRACT

## Aging of Hepatitis C Virus (HCV)-Infected Persons in the United States: A Multiple Cohort Model of HCV Prevalence and Disease Progression

GARY L. DAVIS,\* MIRIAM J. ALTER,† HASHEM EL-SERAG,§ THIERRY POYNARD,|| and LINDA W. JENNINGS\*

\*Division of Hepatology, Baylor University Medical Center and Baylor Regional Transplant Institute, Dallas, Texas; †Infectious Disease Epidemiology Program, University of Texas Medical Branch, Galveston, Texas; ‡Baylor College of Medicine and Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas; §Assistance Publique Hôpitaux de Paris, Université Pierre et Marie Curie Liver Center, Paris, France

**BACKGROUND & AIMS:** The prevalence of chronic hepatitis C (CH-C) remains high and the complications of infection are common. Our goal was to project the future prevalence of CH-C and its complications. **METHODS:** We developed a multicohort natural history model to overcome limitations of previous models for predicting disease outcomes and benefits of therapy. **RESULTS:** Prevalence of CH-C peaked in 2001 at 3.6 million. Fibrosis progression was inversely related to age at infection, so cirrhosis and its complications were most common after the age of 60 years, regardless of when infection occurred. The proportion of CH-C with cirrhosis is projected to reach 25% in 2010 and 45% in 2030, although the total number with cirrhosis will peak at 1.0 million (30.5% higher than the current level) in 2020 and then decline. Hepatic decompensation and liver cancer will continue to increase for another 10 to 13 years. Treatment of all infected patients in 2010 could reduce risk of cirrhosis, decompensation, cancer, and liver-related deaths by 16%, 42%, 31%, and 36% by 2020, given current response rates to antiviral therapy. **CONCLUSIONS:** Prevalence of hepatitis C cirrhosis and its complications will continue to increase through the next decade and will mostly affect those older than 60 years of age. Current treatment patterns will have little effect on these complications, but wider application of antiviral treatment and better responses with new agents could significantly reduce the impact of this disease in coming years.

It is estimated that up to 4 million persons in the United States have chronic hepatitis C virus (HCV) infection (CH-C).<sup>1,2</sup> Despite the marked decrease in newly acquired infections in recent years, overall prevalence of CH-C has not fallen.<sup>2</sup> Most individuals with CH-C acquired their infection 20–40 years ago, before identification of the virus and availability of screening tests.<sup>3</sup> Because CH-C typically progresses slowly and does not

result in morbidity for many years, most remain undiagnosed. We are only now beginning to recognize the magnitude of the consequences of infection that has persisted for decades.<sup>4,5</sup>

Outpatient and hospital visits for CH-C have doubled in recent years and show no sign of leveling off.<sup>6–8</sup> In the United States, complications of CH-C are the leading indication for liver transplantation and the disease is reported to contribute to 4600–12,000 deaths per year based on death certificate documentation,<sup>2,6,9,10</sup> despite the limitations of this method in estimating true death rates.<sup>11,12</sup> Although some have suggested that the health care burden resulting from complications of CH-C has reached a plateau,<sup>10</sup> others have projected a further increase in cirrhosis and its complications for another 2 to 3 decades.<sup>13,14</sup>

Several models have been developed during the last decade to predict the future course of CH-C.<sup>13–16</sup> However, simple transition-state (Markov) models have significant limitations in that the studied cohort is considered homogeneous and traverses through their disease at a fixed and predictable rate over time. In reality, however, the population is quite heterogeneous due to factors such as age at infection, gender, and disease duration; therefore, the course of disease is variable and nonlinear over time.<sup>17–19</sup> Also, previous models used standard population mortality, which recent studies suggest might underestimate true mortality in a chronic disease population.<sup>11,20,21</sup>

Advances in computer software now permit construction of complex models that allow parallel cohorts with different disease states and probabilities to run over time in order to provide a more realistic estimation of end-

*Abbreviations used in this paper:* CH-C, chronic hepatitis C; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; NHANES III, Third National Health and Nutrition Examination Survey.

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0016-5085/10/\$36.00

doi:10.1053/j.gastro.2009.09.067

**Table 1.** Model Variables by Cohort

Cohort F0-30	F31-50	F>50	M0-30	M31-50	M>50	Variable
1	2	3	4	5	6	Cohort
1950	1950	1950	1950	1950	1950	Start year
0.45	0.2	0.1	0.25	0.15	0.1	p SpontaneousRecover from acute infection
0.005	0.005	0.005	0.005	0.005	0.005	p FulmHepatitis
0.85	0.85	0.85	0.85	0.85	0.85	p FulmToDeath
0.15	0.15	0.1	0.15	0.15	0.1	p RecoveryFulm
0.01	0.005	0.001	0.01	0.005	0.001	p ChronicRecover
0.0420	0.0550	0.0770	0.0930	0.1550	0.1938	p F0 to 1
0.0525	0.0688	0.0770	0.1163	0.1938	0.1938	p F0 to 1 after age 50
0.0450	0.0510	0.0714	0.0635	0.1058	0.1323	p F1 to 2
0.0563	0.0714	0.0714	0.0794	0.1323	0.1323	p F1 to 2 after age 50
0.0920	0.0700	0.0980	0.0904	0.1506	0.1883	p F2 to 3
0.1150	0.0875	0.0980	0.1130	0.1883	0.1883	p F2 to 3 after age 50
0.0700	0.0480	0.0672	0.0946	0.1577	0.1971	p F3 to 4
0.0875	0.0600	0.0672	0.1183	0.1971	0.1971	p F3 to 4 after age 50
0.03	0.03	0.03	0.03	0.03	0.03	p F4toDecomp
0.5	0.5	0.5	0.5	0.5	0.5	p DecompProgressive
0.3	0.3	0.3	0.3	0.3	0.3	p DecompProgToStable
0.1	0.1	0.1	0.1	0.1	0.1	p DecompToDeath
0.0004	0.0004	0.0016	0.001	0.001	0.004	p ChronicF2_3toHCC
0.004	0.004	0.012	0.01	0.01	0.03	p F4toHCC
0.006	0.006	0.018	0.02	0.02	0.045	p F4toHCC after 10 years of cirrhosis
0.8	0.8	0.85	0.8	0.8	0.85	p NewHCCtoDeath first year
0.35	0.35	0.35	0.35	0.35	0.35	p HCC to death after 1 year

NOTE. In the column under the heading variable, p represents the transitional rate for moving from one state to another. For example, p ChronicRecover is the proportion moving from chronic hepatitis to resolved infection within an annual cycle of the model. HCC, hepatocellular carcinoma.

point events. The purpose of this project was to utilize state-of-the-art statistical modeling techniques and the latest epidemiologic, demographic, and natural history data to more accurately model the evolution of CH-C during the last 60 years and project its course in the coming decades.

## Materials and Methods

### Model Construction

Construction and computer simulations of our model utilized TreeAge Pro 2009 Suite (TreeAge Software, Williamstown, MA) linked with Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA). TreeAge allows construction of complex Markov models with progression rates that can be varied with time according to calendar year, patient age, year of disease, or dwell time within a specific state, eg, years of cirrhosis. It also allows the dynamic import of information such as disease incidence, population demographic change, and other factors from Excel spreadsheets.

The model was developed in stages starting with a traditional bubble diagram of disease states that served as the basis for developing a more detailed mathematical model that followed infected persons from the time of acute infection until death. Both the bubble diagram and the more detailed TreeAge model are provided in Supplementary Figures 1 and 2 available in the online version of this article. Acute infection could resolve, evolve to

fulminant hepatitis, progress to chronic hepatitis, or end with death due to background (nonhepatic) mortality. CH-C was modeled through fibrosis stages (Metavir F0 to F4), disease complications, and death. The model cycled at yearly intervals allowing individuals to move to another state; however, all states except acute infection and fulminant hepatitis could resolve back into themselves indefinitely.

It has become apparent in recent years that age at infection and gender greatly influence the risk of developing chronic infection and progressing to fibrosis.<sup>18-26</sup> To accommodate this heterogeneity, we divided acutely infected individuals into 6 cohorts, each with their own cohort-specific transition states for chronicity, fibrosis progression, and complications (Table 1). The output of the 6 models was then collated and exported as an Excel spreadsheet defining cohort-specific and overall projections by year. Cohort and population projections included numbers with resolved infection, chronic infection, stage of fibrosis (F0 to cirrhosis), liver failure, hepatocellular carcinoma (HCC), liver-related deaths, and age- and gender-specific (nonliver) deaths.

Antiviral treatment, ablation of tumors, and liver transplantation could not be modeled because the indications for these practices and procedures are not standardized, their use varies considerably by geography, none is widely applied, and the outcomes are not well-defined in subgroups. Of these, only antiviral treatment

has the possibility of significantly altering disease end points from a population perspective. Therefore, we subsequently modified the model to estimate the potential impact of antiviral treatment on cirrhosis and its complications. To do so, we considered treatment penetrance ranging from 0% to 100% in the infected population and sustained viral response rates of 40% to 80%. All cases were treated in 2010 and outcomes were calculated for the year 2020. It was assumed that patients with sustained viral response had no chance of progressing to cirrhosis or, if already cirrhotic, had no chance of subsequent hepatic failure.<sup>27</sup> The risk of progressing from cirrhosis to HCC after sustained viral response was assumed to be 0.66% per annum.<sup>27</sup> Other assumptions of the model were unchanged.

#### Data Sources

Medical literature was reviewed by the authors to provide best estimates of the range of probabilities for moving between disease states. Because reported progression rates vary between studies, a consensus rate was chosen (Table 1). We used conservative estimates when a particular transition was in doubt. Transition rates varied for some states according to the age and gender of the cohorts.<sup>23–28</sup> For example, in the young female cohort, progression from acute to chronic infection was lower (55%) and the rate of fibrosis progression was slower than the oldest male cohort.

Transition rates for moving from one fibrosis stage to another largely utilized the pooled rates from a meta-analysis reported by Thein and colleagues.<sup>17,23</sup> However, our model also included tunnel states that kept a portion of the cohort with minimal fibrosis (F0 and F1) from progressing to the next state for variable periods of time in order to simulate slower rates of progression or no progression in some persons. To accommodate the tunnel states, fibrosis transitions were adjusted accordingly such that overall rates remained consistent with those of Thein and colleagues<sup>23</sup> (Table 1). Alcohol intake was not modeled separately because its influence in the different cohorts is unknown; rather our transition rates are based on observational studies in which excessive alcohol use was present in 19% of the cohorts.<sup>23</sup> Risks of developing HCC in persons with bridging fibrosis or cirrhosis were taken from longitudinal studies in North America and Europe.<sup>19–32</sup> HCC risk in those with bridging fibrosis was estimated to be 10% of that in cirrhosis. HCC risk in females was estimated to be 40% of that in males.<sup>33</sup> Finally, transition rates for fibrosis progression and HCC risk were allowed to increase after age 50 or 10 years of cirrhosis, respectively, consistent with previous observations that these risks are not linear.<sup>17–19,33,34</sup> Confirmation of the accuracy of the estimated transition rates was done by comparing the projected chronic infection prevalence in 1994 to results from the Third National Health and Nutrition Examination survey (NHANES III) and the

projected cirrhosis and HCC prevalence in the different cohorts to published observations in similar groups.

Annual numbers with newly acquired HCV infections between 1960 and 2006 were generated from a previously published model that estimated the past incidence of acute HCV infection given the actual prevalence measured at the time (1988–1994) of the NHANES III.<sup>1,14,35</sup> Annual infections were stratified by age and gender based on actual distributions of these variables for cases of acute hepatitis reported to the Centers for Disease Control and Prevention's Sentinel Counties Study for each year from 1979 to 2006<sup>2,36</sup> (personal communication, MJ Alter, November 25, 2008). For years when data from the Sentinel Counties Study were not available, number and distribution were assumed to be the same as the closest year with data. We sequentially entered these incident infections in annual cycles into the cohort models and projected disease outcomes through the year 2030. Annual incidence data and cohort distribution utilized in the model are shown in Supplementary Table 1 available online.

Age- and gender-specific all-cause mortality was derived from standard US mortality tables.<sup>37</sup> The ages within each cohort were tracked through the annual cycles of the model such that background mortality would be appropriate as the cohorts aged.

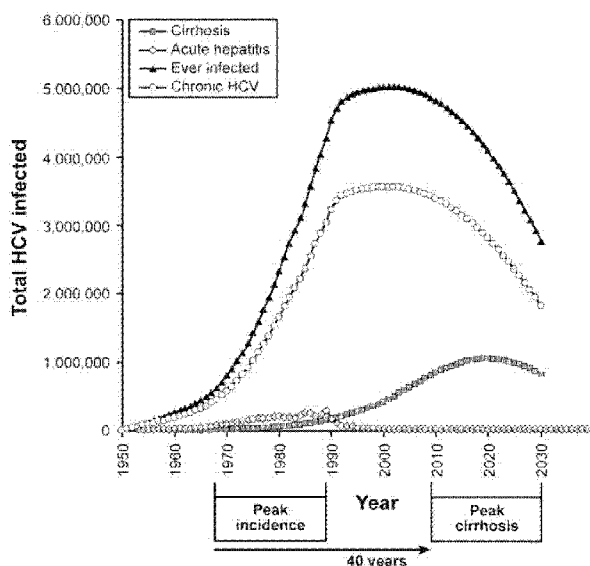
#### Sensitivity Analysis and Validation

Sensitivity analysis was performed to assess the extent to which the model's calculations were affected by uncertainty in our assumptions. The ranges utilized in the sensitivity analysis were derived from the medical literature.<sup>31,38–47</sup> and are reported in Supplementary Table 2 available online. Sensitivity analyses were confined to the young female and oldest male cohorts because these were the most disparate in transition probabilities and, therefore, most likely to identify potential sources of weakness within the model assumptions. First, one-way sensitivity analysis with tornado diagrams were utilized to identify dominant variables and to rank the impact of different variables on disease outcome (cirrhosis). If no dominant variable was identified, a second one-way sensitivity analysis was done. Finally, we examined the impact of increasing background mortality, consistent with some reports that suggest higher all-cause mortality in persons with CH-C.<sup>5,15</sup>

## Results

### Population-Based Model Outcomes

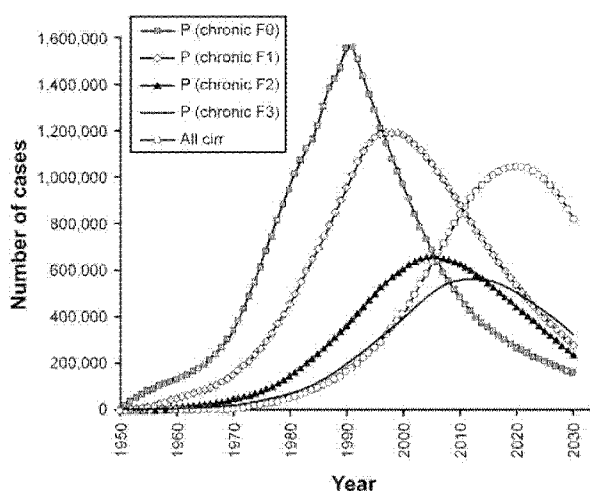
There was a rapid increase in the prevalence of CH-C between 1970 and 1990, when the incidence of acute HCV infection was greatest (Figure 1). We estimated 3.49 million infected persons in 1994, which is similar to previous predictions based on NHANES III.<sup>13,14</sup> Estimated prevalence peaked at 3.57 million in



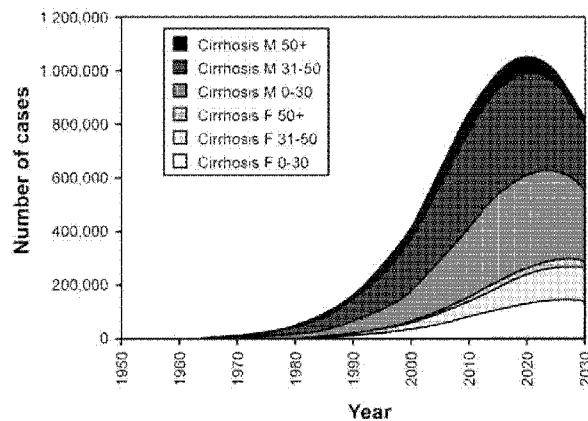
**Figure 1.** Estimates by year of prevalent cases ever infected (top line), with chronic hepatitis C (open circles), and cirrhosis (solid squares). Acute infections (solid gray line) peaked between 1970 and 1990. The peak of chronic hepatitis prevalence was 2001, while the highest prevalence of cirrhosis is projected to be between 2010 and 2030, about 40 years after the peak of acute infections.

2001 and began to decline slowly thereafter, reaching about half its peak level by the year 2030 (Figure 1). Similarly, the model estimated that the number of persons who had ever been infected (resolved or chronic) peaked in 2001 at 5.04 million.

Predicted distribution of histologic stages of fibrosis over time is shown in Figure 2. In 1970 and throughout



**Figure 2.** Distribution of histologic stages of fibrosis by year in persons with chronic hepatitis C (F0 = closed black squares, F1 = closed gray diamonds, F2 = open triangles, F3 = solid gray, and cirrhosis (including decompensated and hepatocellular carcinoma) = fine line with closed circles).

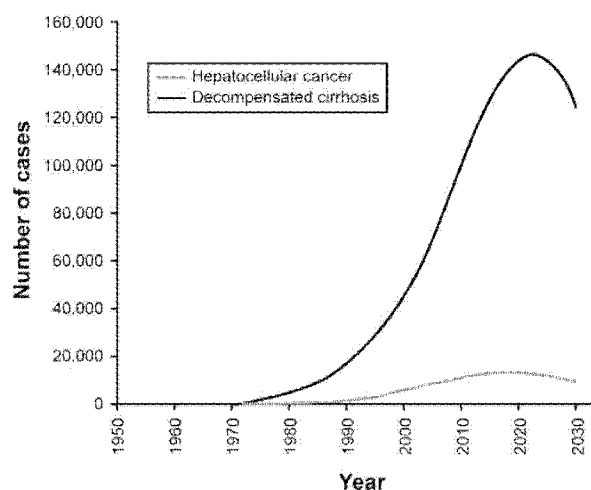


**Figure 3.** Stacked prevalence curves showing number of cases by year with cirrhosis according to gender and age at time of initial hepatitis C virus infection.

the period during which HCV prevalence grew, the majority of cases were stage F0 or F1 (1970: 86.5%, 1980: 84.2%, 1990: 77.6%). Indeed, F0 and F1 fibrosis accounted for the majority of cases of CH-C until just recently. Currently, 41.8% of infected persons have minimal-to-mild fibrosis (F0 or F1), and 39.5% have F3 or F4 fibrosis.

Cirrhosis accounted for just 5% of all cases (diagnosed and undiagnosed) of CH-C in 1989, 10% in 1998, and 20% in 2006 (Figures 1 and 2). This proportion began to rise sharply after 1990, as the age and duration of infection of those infected began to increase. Indeed, the proportion with cirrhosis is projected to reach 24.8% in 2010, 37.2% in 2020, and 44.9% in 2030, although the total number of persons with cirrhosis is expected to peak at 1.04 million (30.5% higher than its current level) in 2020 and slowly decline thereafter. Men, particularly those infected before age 50, account for the majority of cases of cirrhosis today (73.6%) because of their more rapid rate of progression (Figure 3). Although men who acquired their infection after age 50 have the most rapid disease progression, they account for a small proportion of all cirrhosis (7.7%) because they often died of other causes before their fibrosis had a chance to progress. Although females who acquired infection before age 50 accounted for almost the same proportion of acute HCV infections as similarly aged men during the peak incidence years (43.0% vs 50.3%), they represent a much smaller proportion of those who have progressed to cirrhosis as of 2009 (16.1%) because chronicity was less likely and CH-C had a slower rate of progression than men.

Hepatic decompensation and HCC are late complications of CH-C occurring in persons with advanced fibrosis. The model suggests that decompensation became more common after 1995 and is currently estimated to be present in 11.7% of persons with cirrhosis (Figure 4). The proportion of cirrhotics with decompensation is expected



**Figure 4.** Projected number of cases by year of decompensated cirrhosis (*black*) and hepatocellular carcinoma (*gray*). The model assumes a first year mortality of 80% to 85%, so in contrast to the decompensated cirrhosis projection, the number of cases of hepatocellular carcinoma the prevalence demonstrated here closely resembles annual incidence of liver cancer.

to continue to rise at least through 2030, although the total number of persons with liver failure will start to decline after 2022. The number with HCC began to rise steeply after 1990 (Figure 4). The model estimated 37,697 cases between 1990 and 1999 compared to 86,765 (+130%), 130,366 (+50%), and 124,298 (−5%), respectively in each of the subsequent decades. The incidence of HCV-related HCC is projected to peak in 2019 at almost 14,000 cases per year if the risk in HCV-infected persons

with fibrosis remains stable. Assuming that 55% of HCC cases are due to hepatitis C, the HCC projections in males and females in 2005 approximate estimates from a recent report based on the Surveillance, Epidemiology and End Results database (predicted vs estimated cases: male, 7700 vs 8053; female, 1608 vs 922).<sup>48,49</sup>

We projected that hepatic deaths due to HCV would continue to increase through 2022, although the rate of year-to-year change began to slowly decline after 1991. Consistent with the increasing average duration of infection in persons with CH-C and the severity of liver disease described here, we estimated 29,090 liver-related deaths from 1980 to 1989, 56,377 (93%) in 1990–1999, 145,667 (+158%) in 2000–2009, 254,550 (+74%) in 2010–2019, and 283,378 from 2020 to 2029.

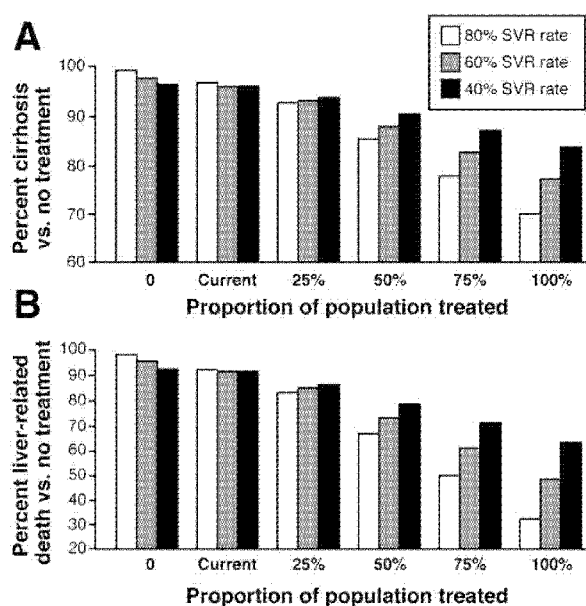
### Cohort Analysis

The proportions with cirrhosis, decompensation, HCC, liver-related death, and non-liver-related death after 10, 20, and 30 years in each of the 6 cohorts are shown in Table 2. These proportions apply to the entire cohort that was ever infected, including those who resolved infection early. For example, although 1.33% of women in the youngest cohort were expected to have cirrhosis after 20 years, these cases occurred only among the 55% who had not resolved acute infection spontaneously; this represented 2.59% of persons with CH-C. Fibrosis and cirrhosis increased over time in all cohorts, but never exceeded 40% within the 30-year observation period. However, if only those who developed CH-C are considered, cirrhosis was predicted in more than half of the 2 older male cohorts after 30 years because progres-

**Table 2.** Projections for Cirrhosis, Decompensation, Hepatocellular Carcinoma, and Death by Cohort

Gender	Age at Infection, y	Years since infection	Not resolved, %	Of all infected, %						Of chronic hepatitis survivors, %		
				All cirrhosis	Decompensation cirrhosis	HCC	Liver death	Non-liver Death	All cirrhosis	Decompensation cirrhosis	HCC	
Female	0–30	10	55	0.10	0.00	0.00	0.43	0.74	0.19	0.00	0.00	
		20		1.33	0.10	0.01	0.49	2.01	2.59	0.20	0.01	
		30		4.24	0.44	0.02	0.92	4.95	8.59	0.90	0.05	
	31–50	10	80	0.12	0.00	0.00	0.43	1.92	0.15	0.00	0.00	
		20		2.38	0.17	0.01	0.52	6.72	3.27	0.23	0.02	
		30		7.75	0.79	0.04	1.28	17.00	12.13	1.23	0.07	
	>50	10	90	0.43	0.01	0.01	0.44	7.58	0.52	0.02	0.01	
		20		4.12	0.32	0.07	0.82	22.63	6.01	0.47	0.10	
		30		7.36	0.80	0.12	2.29	50.46	17.43	1.23	0.28	
Male	0–30	10	65	0.50	0.02	0.01	0.43	1.18	0.71	0.03	0.01	
		20		5.39	0.43	0.07	0.83	2.82	7.76	0.62	0.16	
		30		13.92	1.55	0.19	2.91	6.41	21.47	2.39	0.29	
	31–50	10	80	3.24	0.13	0.03	0.48	2.56	4.01	0.16	0.04	
		20		27.76	2.44	0.34	2.75	8.24	36.86	3.30	0.45	
		30		38.11	5.13	0.50	11.14	21.11	69.31	9.34	0.92	
	>50	10	90	6.39	0.26	0.19	0.70	9.56	7.95	0.32	0.24	
		20		24.27	2.41	0.86	6.08	29.75	42.62	4.23	1.50	
		30		15.24	2.21	0.56	15.06	59.87	70.68	10.24	2.57	

HCC, hepatocellular carcinoma.



**Figure 5.** Estimated reductions in cirrhosis (5A) and liver-related death (5B) by 2020 assuming incremental treatment of zero to 100 percent of infected persons and sustained viral response (SVR) rates of 40%, 60% and 80%.

sion rates were more rapid in these persons. The majority of these remained compensated.

Duration of infection before the peak prevalence of cirrhosis and its complications always varied inversely with the age at acute infection. Therefore, the estimated average ages at the peaks for disease complications were surprisingly consistent in the 6 cohorts (Supplementary Table 3). In the female cohorts, the peak for cirrhosis appeared at ages 71.5–87.0 years, decompensation at 74.5–82.5 years, and HCC at 72.5–87.0 years. In males, cirrhosis appeared at ages 64.5–79.0 years, decompensation at 68.0–82, and HCC at 65.5–80.0 years.

### Effect of Treatment

Our original model was not designed to examine treatment effects so a second model was designed to test the effects of treating various proportions of persons with CH-C and no preexisting complications of liver disease. All treatment was administered in the year 2010. Assuming current estimates that 30% of cases of HCV are diagnosed and up to 25% of those are treated, we would anticipate just a 1.0% reduction in cirrhosis by 2020 compared to 7.8% or 15.6% reductions if half or all of individuals were treated, respectively (Figure 5A). However, if viral clearance increased to 80%, as appears possible with evolving treatments, treatment of half or all of infected persons would reduce cirrhosis by 15.2% or 30.4%, respectively, after just 10 years. The effects are more pronounced when looking at complications of liver disease. Indeed, treatment of half or all of infected persons

in 2010 would result decrease cases of liver failure of 39.4% or 78.9%, HCC by 30.2% or 60.4%, and liver-related deaths by 34.0% or 68.0% over the next decade (Figure 5B).

### Sensitivity Analyses

One-way sensitivity analysis in the youngest female and male cohorts found the rate of chronicity after acute infection was dominant over all other variables in determining the risk of cirrhosis. No other transition rates significantly impacted the risk of cirrhosis after 20 years. The group's predicted estimates of cirrhosis after 17 and 24 years were 0.8% and 2.3%, respectively. These proportions are similar to the 2.0% and 3.1% reported in young Irish women by Kenny-Walsh and Levine<sup>39,40</sup> (Table 3). Similarly, we predicted that a 1.8% hepatic death rate in men infected before age 30, which is similar to the 5.9% observed in the small study of military recruits reported by Seeff and colleagues<sup>41</sup> (Table 3). These projections appear to confirm the accuracy of the assumptions in the younger cohorts. In the oldest males, the initial transition from F0 to F1 had the greatest impact on the risk of cirrhosis. However, when the sensitivity analysis in this group was confined to stage-to-stage fibrosis transition rates, no single transition dominated, and risk of cirrhosis after 20 years varied from just 3.75–6.08% less to 2.39–5.69% more than our model projection. In addition, the projected prevalence of cirrhosis after 20 years in the older male group was 24%, consistent with the high rate of fibrosis progression reported by others in this group.<sup>19,50,51</sup> (Table 3).

Another potential source of uncertainty stems from our use of tunnel states to slow progression during early fibrosis stages and acceleration of progression rates when younger cohorts reached age 50. We felt that these age- and duration-adjusted fibrosis progression rates best reflected the observations from previous reports.<sup>17–19,33,34,39–41</sup> However,

**Table 3.** Comparison of Model Projections to Published Observations

Measure	Observed	Model projection	Reference
Chronic hepatitis C prevalence, millions	2.7–3.9	3.49	13,14
Cirrhosis in females infected at young age, %			
17 years	2.0	0.8	39
25 years	3.1	2.3	40
Cirrhosis in men infected at young age, %	5.9	1.8	41
Incremental change in mortality, %			
1995–1999 to 2000–2004	+123	+94	10
Liver-related death (HCV on death certificate), <i>n</i>			
2004	7426		10
2004	11,292	13,797	6

HCV, hepatitis C virus.

we also tested a fixed stage-to-stage progression rate as reported in the meta-analysis by Thein and colleagues.<sup>23</sup> As expected, this led to front-loading of morbidity and hepatic mortality, particularly in the younger cohorts, during the years when standard age-related mortality was low. As a result, the fixed rate model overestimated cases of cirrhosis, decompensation or HCC, and liver-related death by 41%, 86%, and 41%, respectively, compared to the more conservative base case model, and these estimates were much higher than those reported in previous prospective studies.<sup>39-41</sup> Therefore, we maintained our more conservative assumptions for the base case model.

Finally, we looked at the impact of utilizing higher background (nonhepatic) age- and gender-related mortality rates on our projections of chronic hepatitis and cirrhosis in coming decades. Recent studies have suggested that comorbid medical conditions might increase background mortality in HCV-infected persons by as much as 3 times the reported actuarial rates.<sup>11,12,20</sup> Increasing background mortality rates in the model by 50% or 100% had no impact on the proportion of infected persons with cirrhosis, but it significantly reduced the total number with cirrhosis. A 50% increase in background mortality decreased the number of persons with chronic hepatitis or cirrhosis in 2020 by 35% and 31%, respectively, compared to the base case model projections. A 100% increase decreased the number with chronic hepatitis or cirrhosis in 2020 by 46% and 43%, respectively, compared to base case projections.

Our sensitivity analysis did not include incidence data because no other estimates exist and these data have previously been shown to be consistent with prevalence data as estimated by NHANES III.<sup>1,14</sup>

## Discussion

Our model estimated that the prevalence of CH-C in the United States peaked at 3.6 million in 2001 and will decline to about half this number by 2030. Although the decline in overall infections is encouraging, other trends in the data are of concern. First, similar to reports by others,<sup>13,14,16</sup> the proportion of cases with advanced fibrosis will continue to rise during the next 2 decades, with the number of cases of cirrhosis and hepatic decompensation peaking after the year 2020. Second, the age of those with cirrhosis and its complications will continue to rise. Because about 40 years elapses from the peak incidence years of HCV infection until the peak prevalence of cirrhosis and other complications (Figure 1), it is not surprising that we found the group of persons aged 60 to 80 years to be those most affected. This phenomenon is already beginning to occur.<sup>49,52-54</sup> Indeed, Ferenci and colleagues found that 34% of infected paid plasma donors identified in the 1970s had bridging fibrosis, cirrhosis, or HCC 30 years later.<sup>51</sup> In addition, Thabut and colleagues reported that cirrhosis was more prevalent in the elderly and 14% of them presented with decompensation

compared to just 4% in persons younger than 65 years.<sup>52</sup> Indeed, D'Souza and others have even suggested that patients who live long enough will almost invariably develop advanced hepatic fibrosis.<sup>54,55</sup> We also predicted a modest increase in HCV-related HCC in coming years, despite using a very conservative estimate of the annual risk in our model. HCV infection currently accounts for most of the HCC in the United States.<sup>49</sup> HCC in persons older than the age of 65 years with HCV infection has doubled during the last several years,<sup>48,56</sup> consistent with our predictions. Taken together, our findings suggest that the CH-C that we have become familiar with during the last 30 years is much different than the hepatitis C we will come to know during the next decade or 2.

Although we purposefully chose conservative estimates of disease progression and complications, it is still possible that we and others might have overestimated the number of cases that will progress to liver failure from CH-C due to the influence of competing risks.<sup>11,12,20,57</sup> Indeed, when we increased the background (nonhepatic) mortality by just 50%, there was a striking reduction in the number of cases of cirrhosis, liver failure, and cancer. However, we believe that such high background mortality is unlikely in HCV-infected patients. If it occurs it is probably limited to a short period around the time of acute infection and would be unlikely to influence long-term outcomes. Furthermore, common comorbid conditions, such as diabetes, obesity, and alcohol, lead to more rapid progression of fibrosis, which can offset any potential impact of a change in background mortality.<sup>26,58-60</sup> Competing risks could certainly influence resource utilization and might explain why, for example, the number of liver transplantations related to hepatitis C has started to plateau, despite our prediction of more disease complications.

These projections emphasize how critical it is to identify infected persons and treat their disease before advanced fibrosis or liver failure ensues. Currently, only a small proportion of those with CH-C are aware of their infection and, of these, just 10% to 27% are offered treatment.<sup>61-63</sup> Many physicians still do not ask their patients about risk factors for HCV infection and some remain confused about treatment options and efficacy.<sup>64</sup> And yet, antiviral therapy is becoming increasingly effective<sup>65,66</sup> and eradication of virus clearly reduces risk of liver failure or cancer.<sup>27,67</sup> Certainly, as we have shown, a far higher proportion of cases will need to be identified and treated to impact the dire projections described here. It is in the immediate best interest of patients, providers, insurers, and governments to promote guidelines and encourage better screening for infection and early antiviral treatment.<sup>68</sup> Without such a proactive policy, it is likely that we will spend a considerable amount of resources during the next 2 or 3 decades dealing with liver failure in our elderly population.

## Supplementary Materials

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at [www.gastrojournal.org](http://www.gastrojournal.org), and at doi: 10.1053/j.gastro.2009.09.067.

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Received July 15, 2009. Accepted September 28, 2009.

#### Reprint requests

Address requests for reprints to: Gary L. Davis, MD, Hepatology, 4 Roberts, Baylor University Medical Center, 3500 Gaston Avenue, Dallas, Texas 75246. e-mail: GaryDav@BaylorHealth.edu; fax: (214) 820-8168.

#### Acknowledgments

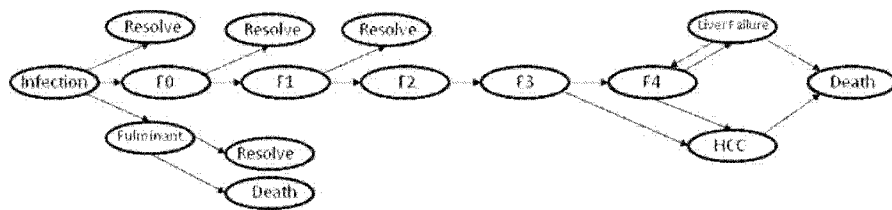
The authors wish to acknowledge Andrew Munzer, TreeAge Software Support, Neil Warnock, MD, MBA, Medical Affairs, Vertex Pharmaceuticals, Cambridge, MA, and Steven Kymes, PhD, Department of Ophthalmology, St Louis University, St Louis, Missouri for technical assistance in the model development.

#### Conflicts of interest

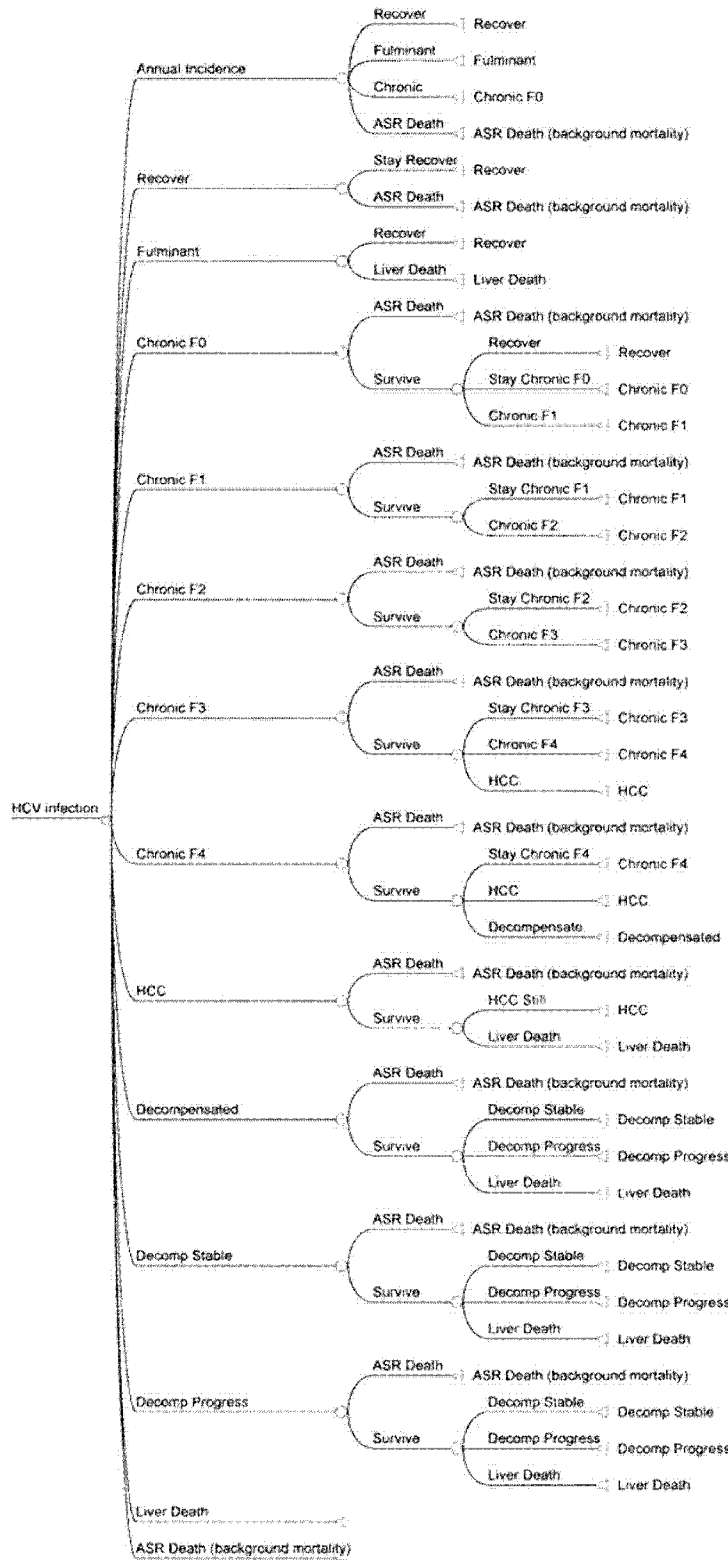
These authors disclose the following: Dr Davis received research funding from Human Genome Science, Merck, Novartis, Roche, Schering Plough, Tibotec, and Vertex Pharmaceuticals. Dr El-Serag received research funding from Schering-Plough and Bayer. Dr Poynard has a research grant from Schering Plough and equity share in BioPredictive. The remaining authors disclose no conflicts.

#### Funding

Sponsored by an unrestricted grant from Vertex Pharmaceutical Inc.



**Supplementary Figure 1.** Bubble diagram showing the transition states incorporated into our Markov model. Subjects moved from left-to-right in 1-year cycles. Each state with the exceptions of acute infection and fulminant hepatitis could resolve to itself (no progression) for periods ranging from 1 year to indefinitely. Each state is subject to normal age- and gender-related mortality based on the age of acute infection plus the number of cycles that had occurred (accrued age). Interventions such as antiviral therapy, tumor ablation, or liver transplantation were not allowed in the model (see text).



**Supplementary Figure 2.** Schematic of the Markov model developed for each of 6 cohorts. Transitions states are listed in the first order branches along the left. All subjects started as acute infection. Subjects move right and downward over time. Possible transitions states for subsequent years after a particular state are listed in the branches to the right of a given state.

**Supplementary Table 1.** Incident Cases for Each of 6 Age and Gender Cohorts by Year from 1950 to 2030

Model cycle	Year	Female			Male		
		Age <30 y	Age 31–50 y	Age >50 y	Age <30 y	Age 31–50 y	Age >50 y
0	1950	7463	4284	838	8748	5029	984
1	1951	7463	4284	838	8748	5029	984
2	1952	7463	4284	838	8748	5029	984
3	1953	7463	4284	838	8748	5029	984
4	1954	7463	4284	838	8748	5029	984
5	1955	7463	4284	838	8748	5029	984
6	1956	7463	4284	838	8748	5029	984
7	1957	7463	4284	838	8748	5029	984
8	1958	7463	4284	838	8748	5029	984
9	1959	7463	4284	838	8748	5029	984
10	1960	7463	4284	838	8748	5029	984
11	1961	8676	4980	974	10169	5846	1144
12	1962	9888	5676	1110	11590	6663	1304
13	1963	11101	6372	1247	13012	7480	1464
14	1964	12313	7068	1383	14433	8298	1624
15	1965	13526	7764	1519	15854	9115	1783
16	1966	16405	9417	1843	19230	11055	2163
17	1967	19285	11070	2166	22605	12996	2543
18	1968	22164	12723	2490	25980	14936	2923
19	1969	25044	14376	2813	29356	16877	3303
20	1970	27924	16029	3137	32731	18817	3682
21	1971	31433	18044	3531	36845	21182	4145
22	1972	34943	20059	3925	40958	23547	4608
23	1973	38452	22073	4320	45072	25912	5071
24	1974	41962	24088	4714	49186	28277	5534
25	1975	45471	26103	5108	53299	30642	5997
26	1976	47784	27430	5368	56010	32201	6302
27	1977	50096	28758	5628	58721	33759	6607
28	1978	52409	30085	5888	61431	35317	6912
29	1979	54721	31413	6147	64142	36876	7217
30	1980	57034	32740	6407	66853	38434	7522
31	1981	55118	31640	6192	64607	37143	7269
32	1982	53202	30541	5977	62362	35852	7016
33	1983	51287	29441	5762	60116	34561	6764
34	1984	59852	34358	6724	70156	40333	7893
35	1985	71150	40843	7993	83399	47947	9383
36	1986	70928	38165	6424	90209	48574	8176
37	1987	58337	31390	5284	74196	39952	6725
38	1988	64927	34936	5880	82577	44464	7484
39	1989	78761	42381	7133	100172	53939	9079
40	1990	34859	28239	5173	56605	46075	8440
41	1991	21759	17627	3229	35333	28760	5268
42	1992	14179	11486	2104	23024	18741	3433
43	1993	11125	9012	1651	18065	14704	2693
44	1994	10507	8512	1559	17062	13888	2544
45	1995	6026	3852	985	13897	8988	2299
46	1996	6024	3850	985	13891	8984	2298
47	1997	6431	4110	1051	14829	9590	2453
48	1998	6907	4414	1129	15926	10300	2635
49	1999	6671	4264	1090	15383	9949	2545
50	2000	3807	8565	1445	6732	15228	2570
51	2001	2350	5287	892	4155	9399	1586
52	2002	2879	6477	1093	5091	11515	1943
53	2003	2780	6253	1055	4915	11118	1876
54	2004	2581	5807	980	4564	10323	1742
55	2005	2085	4690	791	3686	8338	1407
56	2006	1886	4243	716	3335	7544	1273
57	2007	1886	4243	716	3335	7544	1273
58	2008	1886	4243	716	3335	7544	1273
59	2009	1886	4243	716	3335	7544	1273
60	2010	1886	4243	716	3335	7544	1273

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**Supplementary Table 1.** continued

Model cycle	Year	Female			Male		
		Age <30 y	Age 31–50 y	Age >50 y	Age <30 y	Age 31–50 y	Age >50 y
61	2011	1886	4243	716	3335	7544	1273
62	2012	1886	4243	716	3335	7544	1273
63	2013	1886	4243	716	3335	7544	1273
64	2014	1886	4243	716	3335	7544	1273
65	2015	1886	4243	716	3335	7544	1273
66	2016	1886	4243	716	3335	7544	1273
67	2017	1886	4243	716	3335	7544	1273
68	2018	1886	4243	716	3335	7544	1273
69	2019	1886	4243	716	3335	7544	1273
70	2020	1886	4243	716	3335	7544	1273
71	2021	1886	4243	716	3335	7544	1273
72	2022	1886	4243	716	3335	7544	1273
73	2023	1886	4243	716	3335	7544	1273
74	2024	1886	4243	716	3335	7544	1273
75	2025	1886	4243	716	3335	7544	1273
76	2026	1886	4243	716	3335	7544	1273
77	2027	1886	4243	716	3335	7544	1273
78	2028	1886	4243	716	3335	7544	1273
79	2029	1886	4243	716	3335	7544	1273
80	2030	1886	4243	716	3335	7544	1273

**Supplementary Table 2.** Probabilities for Sensitivity Analyses

Probability	Cohort		Variable	References
	Female 0–30	Male >50		
Best estimate	0.450	0.100	p Spontaneous Recover from acute HCV	36,38–43
Low	0.300	0.050		
High	0.500	0.250		
Best estimate	0.005	0.005	p Fulm Hepatitis	44
Low	0.001	0.000		
High	0.010	0.010		
Best estimate	0.850	0.850	p Fulm To Death	44
Low	0.750	0.750		
High	0.900	0.900		
Best estimate	0.150	0.100	p Fulminant Recover	44
Low	0.100	0.100		
High	0.250	0.250		
Best estimate	0.010	0.001	p Chronic (F0-1) Recover	45
Low	0.001	0.000		
High	0.015	0.005		
Best estimate	0.042	0.194	p F0 to 1	17,19,23–26
Low	0.037	0.172		
High	0.047	0.215		
Best estimate	0.045	0.132	p F1 to 2	17,19,23–26
Low	0.040	0.117		
High	0.051	0.149		
Best estimate	0.092	0.188	p F2 to 3	17,19,23–26
Low	0.084	0.171		
High	0.087	0.177		
Best estimate	0.070	0.197	p F3 to 4	17,19,23–26
Low	0.063	0.177		
High	0.078	0.219		
Best estimate	0.030	0.030	p F4 to Decomp	29,30
Low	0.010	0.010		
High	0.050	0.050		
Best estimate	0.500	0.500	p Decomp Progressive	29,30
Low	0.300	0.300		
High	0.600	0.600		
Best estimate	0.300	0.300	p Decomp Prog To Stable	29,30
Low	0.250	0.250		
High	0.400	0.400		
Best estimate	0.100	0.100	p Decomp To Death	29,30
Low	0.100	0.100		
High	0.200	0.200		
Best estimate	0.000	0.004	p Chronic F2_3 to HCC	5,29–34,46,47
Low	0.000	0.001		
High	0.010	0.035		
Best estimate	0.004	0.030	p F4 to HCC	5,29–34,46,47
Low	0.001	0.015		
High	0.020	0.070		
Best estimate	0.800	0.850	p New HCC to Death first year	5,29–34,46,47
Low	0.600	0.600		
High	0.900	0.900		
Best estimate	0.350	0.350	p HCC to Death after 1 year	5,29–34,46,47
Low	0.250	0.250		
High	0.500	0.500		

NOTE. In the column under the heading variable, p represents the transitional rate for moving from one state to another. For example, p ChronicRecover is the proportion moving from chronic hepatitis to resolved infection within an annual cycle of the model. HCC, hepatocellular carcinoma.

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**Supplementary Table 3.** Median Duration of Infection Until Peak Prevalence of Complication and Estimated Age Then in the 6 Cohorts

Cohort	Median age at infection, y	Duration to peak prevalence cirrhosis	Age at peak prevalence cirrhosis, y	Duration to peak decompensation	Age at peak decompensation, y	Duration to peak HCC	Age at peak HCC, y
Female							
<30 years	21.0	50.5	71.5	53.5	74.5	51.5	72.5
31–50 years	40.0	41.0	81.0	42.5	82.5	41.0	81.0
>50 years	57.0	30.0	87.0	32.0	79.0	30.0	87.0
Male							
<30 years	21.0	43.5	64.5	47.0	68.0	44.5	65.5
31–50 years	40.0	29.0	79.0	32.0	72.0	30.0	70.0
>50 years	57.0	22.0	79.0	25.0	82.0	23.0	80.0

HCC, hepatocellular carcinoma.