

The Burden of Hepatitis C in the United States

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According to the third National Health and Nutrition Examination Survey (NHANES), 3.9 million of the U.S. civilian population have been infected with hepatitis C virus (HCV), of whom 2.7 million (74%) have chronic infection. Hepatitis C virus infection is most common among non-Caucasian men, ages 30 to 49 years. Moreover, the prevalence of antibody to hepatitis C virus in groups not represented in the NHANES sample, such as the homeless or incarcerated, may be as high as 40%. The age-adjusted death rate for non-A, non-B viral hepatitis increased from 0.4 to 1.8 deaths per 100,000 persons per year between 1982 and 1999. In 1999, the first year hepatitis C was reported separately, there were 3,759 deaths attributed to HCV, although this is likely an underestimate. There was a 5-fold increase in the annual number of patients with HCV who underwent liver transplantation between 1990 and 2000. Currently, more than one third of liver transplant candidates have HCV. Inpatient care of HCV-related liver disease has also been increasing. In 1998, an estimated 140,000 discharges listed an HCV-related diagnosis, accounting for 2% of discharges from non-federal acute care hospitals in the United States. The total direct health care cost associated with HCV is estimated to have exceeded \$1 billion in 1998. Future projections predict a 4-fold increase between 1990 and 2015 in persons at risk of chronic liver disease (*i.e.*, those with infection for 20 years or longer), suggesting a continued rise in the burden of HCV in the United States in the foreseeable future. (HEPATOLOGY 2002;36:S30-S34.)

In July 2000, the United States Surgeon General declared that hepatitis C represents a “silent epidemic.” Indeed, hepatitis C is the most common chronic bloodborne infection in the United States, affecting almost 3 million Americans. This review focuses attention on the disease burden associated with hepatitis C virus (HCV) infection. The term, “disease burden,” encompasses several aspects of the impact of a disease on the health of a population, ranging from the frequency of the disease, as measured by incidence and prevalence, to its effect on (1) longevity, such as mortality rate and years of life lost because of premature death; (2) morbidity, including impairment in health status and quality of life as well as the need for health care; and (3) finance, including

direct health care expenditures and indirect costs related to lost income from premature death or disability.

Prevalence and Incidence of HCV

Disease frequency may be measured either by the pool of existing cases or by the occurrence of new cases. The former (prevalence) describes the proportion of the population that has the disease in question at a specific point in time, whereas the latter (incidence) describes the frequency of occurrence of new cases during a defined time period.

Prevalence. The most widely quoted data on the prevalence of HCV in the United States are derived from the third National Health and Nutrition Examination Survey (NHANES), a national survey of a representative sample of noninstitutionalized civilian Americans conducted between 1988 and 1994.¹ Of 21,000 people tested for HCV, 380 (1.8%) carried antibodies against the virus, of whom 280 (74%) had detectable viral RNA in their serum. Projecting these numbers to the U.S. population indicates that 3.9 million Americans (95% CI: 3.1 to 4.8 million) have been infected with HCV, of whom 2.7 million (95% CI: 2.4 to 3.0 million) have on-going chronic infection.

Data from the NHANES survey showed that there was significant demographic variation in the HCV prevalence. It was most common in persons 30 to 49 years of

Abbreviations: NHANES, National Health and Nutrition Examination Survey; HCV, hepatitis C virus.

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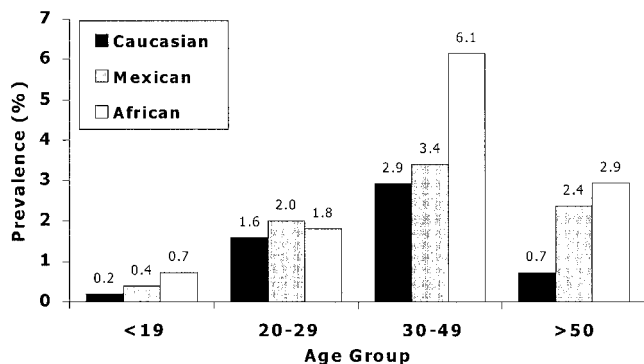


Fig. 1. Age- and race-specific prevalence of antibody to hepatitis C virus. (Data from NHANES.¹) In all racial groups, people between 30 and 49 years of age had the highest prevalence. Conversely, in all age groups, people of non-white race had the highest prevalence.

age; non-Hispanic whites had the lowest prevalence (1.5%) and non-Hispanic blacks had the highest prevalence (3.2%) (Fig. 1). Men were 20% more likely to have hepatitis C than women.

Although these data may be representative of demographic variability in the general population, socioeconomic characteristics may also influence the prevalence of HCV infection. In surveys of emergency medical technicians undertaken in various parts of the country, the seroprevalence of HCV was found to range between 1.3% and 3.2%, comparable to that of the NHANES sample.² On the other hand, a survey conducted at a Veterans Affairs outpatient clinic showed that 18% of those screened ($n = 1,032$) had antibody to hepatitis C virus,³ while in another Veterans Affairs study conducted among homeless veterans ($n = 829$) the prevalence was 40%.⁴ A cross-sectional survey of prison inmates in California showed that 39% of men ($n = 6,536$) and 54% of women ($n = 977$) were positive for HCV at the time of entry.⁵ These are undoubtedly high prevalence rates, but they are comparable to reports from other parts of the world.⁶

Incidence. Hepatitis C virus is a reportable infectious disease in the United States, and the Centers for Disease Control and Prevention has put mechanisms in place to capture incident cases of HCV infection. These include passive surveillance programs such as the National Notifiable Disease Surveillance System and hepatitis-specific active surveillance programs such as the Sentinel Counties Study of Acute Viral Hepatitis. Despite these efforts, the incidence of new HCV infection is very difficult to estimate accurately. This is because many patients with acute HCV infection are asymptomatic and thus do not present themselves for diagnosis. Under-reporting by health care providers of diagnosed cases is also thought to be common. Furthermore, individuals at high risk of infection may not have ready access to health care, decreasing the

likelihood of timely diagnosis of newly acquired HCV infection. Because of these limitations, enumerating reported cases of acute hepatitis C significantly underestimates the true incidence of hepatitis C infection.⁷

Given these caveats, the Centers for Disease Control and Prevention has undertaken mathematical modeling studies to estimate the past incidence of HCV. The model indicated that the annual incidence of acute HCV infection in the United States decreased from an average of approximately 230,000 new cases per year in the 1980s to 38,000 cases per year in the 1990s.⁸ The number of persons with transfusion-associated HCV infection decreased significantly following the introduction in 1985 of guidelines for selecting safer blood donors. It declined further with the institution of screening of blood donors for antibody to hepatitis C virus beginning in 1989 with the first generation test and the second-generation assay introduced in July 1992. In addition, safer needle-using practices among injection drug users facilitated by human immunodeficiency virus prevention programs are also thought to have decreased the incidence of HCV infection.⁸

It may be expected that the reduction in incident cases will eventually lead to a decrease in the prevalence of HCV infection. Indeed, a report based on blood donors from 5 U.S. blood centers indicates that the prevalence of HCV infection may already be on a decline.⁹ Between 1992 and 1996, during which time 1.1 million first-time blood donors were tested, the prevalence of HCV infection over the course of this period decreased from 0.6% to 0.4% ($P < .01$). Among the same blood donors, the prevalence of hepatitis B virus infection over the study period remained unchanged at 0.2%. The anticipated reduction in the prevalence has been corroborated by a report from the Centers for Disease Control and Prevention which projected that, following a peak in the mid-1990s at slightly above 2.0%, prevalence of HCV infection would gradually decrease to 1.0% by 2030.¹⁰

Although the incidence of HCV infection may be decreasing, the prevalence of liver disease caused by HCV is on the rise. This is because there is a significant lag, often 20 years or longer, between the onset of infection and clinical manifestation of liver disease. The Centers for Disease Control and Prevention projects a 4-fold increase in the number of persons with long-standing (20 years or longer) infection between 1990 and 2015.¹⁰ However, it is uncertain whether the projected decline in the HCV prevalence based on NHANES data (non-institutionalized civilians) will translate to a similar decline in other population groups known to have very high prevalences of HCV infection, such as active injection drug users and prison inmates.

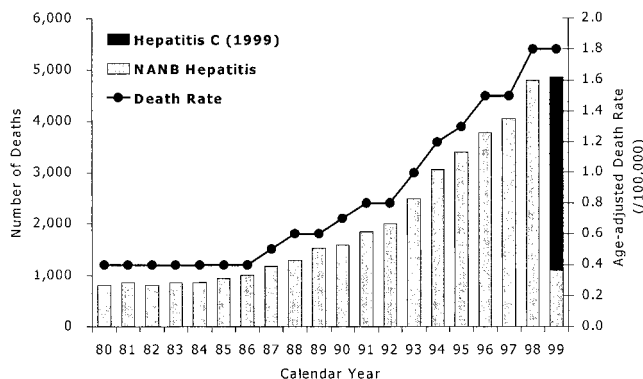


Fig. 2. Deaths caused by hepatitis in the United States (1982-1999).¹¹ Bars represent number of deaths (left axis) from non-A non-B (NANB) hepatitis, whereas dots represent death rate (right axis). Hepatitis C-specific mortality was first reported in 1999, the latest year that mortality statistics were available at the time.

Mortality From HCV Infection

Mortality statistics in the United States are based on the “underlying cause of death” listed on death certificates. Deaths attributable to viral hepatitis result primarily from chronic liver disease and liver failure. Consequently, viral hepatitis may not necessarily be listed as the underlying cause of death. Therefore, it is likely that the death certificate designation may underestimate the true incidence of deaths related to viral hepatitis. Further, until 1999, when the International Classification of Disease version 10 (ICD-10) began to be used to classify causes of death, hepatitis C was not given an independent code, making it difficult to estimate the total number of deaths attributable to HCV infection.

With these caveats in mind, Fig. 2 describes the number of deaths and the age-adjusted death rate classified as death from viral hepatitis (non-A, non-B) between 1982 and 1999. In 1982, 814 deaths were attributed to viral hepatitis, which increased 6-fold by 1999 to 4,853 deaths.¹¹ There was a corresponding increase in the age-adjusted death rate from 0.4 to 1.8 deaths per 100,000 persons per year. Based on data from 1999, the first year hepatitis C was reported separately, the majority (77%; $n = 3,759$) of these deaths were caused by HCV infection. Comparing the deaths in the non-HCV portion of the 1999 data with all viral hepatitis deaths in the early

1980s suggests that the increase in deaths since the late 1980s may be entirely because of hepatitis C.

To estimate the degree of under-reporting of HCV infection as the underlying cause of death in the mortality data, the number of in-hospital deaths from liver disease related to hepatitis C was abstracted from the Healthcare Utilization Project database. In 1998 there were an estimated 4,500 in-hospital deaths in the United States from liver disease related to HCV infection.

Morbidity and Health Care Cost From HCV Infection

Because chronic hepatitis C has a prolonged natural history, and only a relative minority of those affected require on-going medical care for their hepatitis, it is difficult to estimate the magnitude of morbidity at the population level. Patients with advanced stages of liver disease may present with portal hypertension and hepatic decompensation, as manifested by ascites, hepatic encephalopathy, or gastrointestinal bleeding. These complications generally necessitate inpatient care that may include liver transplantation. Thus, data on patients referred for and undergoing orthotopic liver transplantation for end-stage liver disease or hepatocellular carcinoma reflect the most severe degree of morbidity associated with hepatitis C.

In Table 1, the number of liver transplants performed for recipients with and without HCV infection is shown for calendar years 1990 through 2000. There was a 5-fold increase in the number of orthotopic liver transplantation recipients with hepatitis C. The proportion of recipients with HCV infection increased from 12% to 37%. There was a similar increase in the number and proportion of liver transplant candidates with hepatitis C registered on the waiting list (Table 2). The United Network for Organ Sharing reports that as of 2001, there were 9,783 patients with hepatitis C awaiting a cadaveric liver transplantation.

The frequency of inpatient care of HCV-related liver disease has been estimated based on data derived from the Nationwide Inpatient Sample of the Healthcare Utilization Project.¹² This database represents a 20% stratified sample from all non-federal, acute-care hospitals, which

Table 1. Number of Transplants With and Without HCV Infection in the U.S.

	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000
HCV infection	343	565	796	930	1,129	1,190	1,268	1,517	1,625	1,679
All other	2,588	2,464	2,608	2,661	2,750	2,825	2,832	2,899	2,856	2,900
%	12%	19%	23%	26%	29%	30%	31%	34%	36%	37%

Data from the United Network for Organ Sharing.

Table 2. Number of Patients Registered to Liver Transplant Waiting List With and Without HCV Infection

	1995	1996	1997	1998	1999	2000
HCV infection	2,086	2,354	2,798	3,225	3,670	3,886
All other	5,251	5,704	5,832	6,318	6,848	7,007
%	28%	29%	32%	34%	35%	36%

account for approximately 95% of all hospitalizations in the nation. Because liver disease from hepatitis C may not be the main reason for all hospitalizations with a hepatitis C diagnosis, hospitalizations were divided into 3 groups. These included hospitalizations in which liver disease from hepatitis C was the primary reason for hospitalization, those in which liver disease from hepatitis C was a secondary reason, and those in which neither hepatitis C nor liver disease was a primary reason for the hospitalization.

The number of hospitalizations in these categories is shown in Fig. 3. During the 1990s there was a several-fold increase in the total number of hospitalizations in which HCV was listed in the discharge diagnosis. In 1998, an estimated 140,000 discharges listed an HCV diagnosis, accounting for approximately 2% of all discharges in the database. Because of the uncertainty of ascertainment of HCV in the early 1990s, hospitalizations for other chronic hepatitis (non-A, non-B) were also captured.

Some of the increase over time was because of the lack of ascertainment of HCV infection in the early 1990s, because there was a partially corresponding decrease in the non-A, non-B hepatitis hospitalizations during the same period. Figure 3 also shows the total charges associated with these hospitalizations (1998 U.S. dollars). Hospitalizations were weighted differently according to the hospitalization category, including 80% of charges for primary hospitalizations for hepatitis C, 50% for secondary hospitalizations, and 20% of the remainder. The estimated total hospital charges for 1998 were in excess of \$1 billion.

Population-based data on the morbidity in individuals with hepatitis C not requiring hospitalization care are not available at the present time. Health status and quality of life have largely been measured in patients seen at referral centers or participating in randomized trials.¹³⁻¹⁵ These studies have uniformly shown a significant decrement in the subjective health and quality of life in patients with hepatitis C, although the effect of frequently co-existing morbidities such as chemical dependence or depression is difficult to assess separately.¹⁶ Although persons aware of the diagnosis of chronic hepatitis C scored lower on quality-of-life scales than did uninfected persons, it is uncertain how much of this decrement is because of the HCV infection itself or to the awareness of this condition.¹⁷

A cost-of-illness study conducted by the American Gastroenterological Association estimated that there were 317,000 outpatient visits for the treatment of hepatitis C in the United States in 1998.¹⁸ The cost for outpatient physician services was projected to be \$24 million. During the same year, \$530 million was spent for the antiviral treatment of HCV.

Future Research Needs

There is an ongoing, critical need for up-to-date and accurate information on the prevalence, incidence, health care costs, mortality, and morbidity of hepatitis C-related illnesses in the United States. In formulating health care policies to prioritize health interventions and research and to allocate resources accordingly, accurate information about the current and future burden of disease is essential. Chronic HCV infection is common, affecting nearly 2% of the general population and a much higher percentage of people under special circumstances, such as the homeless and incarcerated. Although the incidence of HCV infection appears to have decreased, national statistics indicate that morbidity, mortality, and health care utilization associated with consequences of long-standing infection with hepatitis C have increased since the early 1990s.

Focused studies on the incidence and prevalence of HCV infection and liver disease in specific populations at risk are needed. While population surveys provide an accurate estimate of the prevalence of HCV infection, a significant gap exists between the sero-epidemiologic data and burden of HCV-related liver disease at the population level. This is in part because of the long period between HCV infection and clinically significant liver

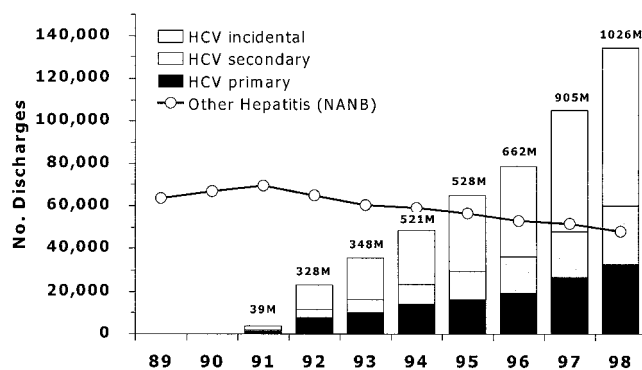


Fig. 3. Hospital discharges with HCV-related diagnosis. (Data from Healthcare Utilization Project.) Discharges were divided into 3 groups, namely those in which hepatitis C was the primary reason for the hospitalization, those in which hepatitis C was a secondary (contributing) diagnosis, and those in which hepatitis C was mentioned without a diagnosis indicative of liver disease. Figures above the bars represent total charges (1998 U.S. dollars).

disease, as well as our incomplete understanding of the natural history of HCV infection at the population level. Most investigations about the extent and natural history of liver disease associated with hepatitis C have been conducted at academic tertiary centers based on patients referred with established disease. By contrast, the majority of the projected 3 million Americans infected with HCV have not been diagnosed, and their liver disease status remains unknown. Studies about liver disease in people with HCV infection in the population at large are necessary to fill this gap in our knowledge. Moreover, systematic epidemiologic studies focused on patients not represented in population-based surveys (*e.g.*, homeless and incarcerated) are needed.

Finally, continuing studies of hepatitis C in patients with other comorbidities are needed. A significant proportion of HCV-infected patients have a number of comorbid conditions, including poly-substance abuse (*e.g.*, alcohol) and mental disorders (*e.g.*, depression and anxiety disorders). It is uncertain the extent to which the morbidity present in people infected with HCV is purely attributable to HCV infection. Determining the extent of the contribution of extraneous comorbidity is important, because in people with comorbid conditions, antiviral therapy alone is unlikely to be successful in improving the health of the individual. Comprehensive yet cost-effective strategies to incorporate treatment for hepatitis C in the management of patients with substance use remain to be defined.

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