Changing Trends in Hepatitis C–Related Mortality in the United States, 1995-2004

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The disease burden and mortality from hepatitis C are predicted to increase in the United States as the number of persons with long-standing chronic infection grows. We analyzed hepatitis C mortality rates derived from US Census and multiple-cause-of-death data for 1995-2004. Deaths were considered hepatitis C–related if: (1) hepatitis C was the underlying cause of death, (2) chronic liver disease was the underlying cause and hepatitis C was a contributing cause, or (3) human immunodeficiency virus was the underlying cause and chronic liver disease and hepatitis C were contributing causes. A total of 56,409 hepatitis C–related deaths were identified. Mortality rates increased 123% during the study period (1.09 per 100,000 persons to 2.44 per 100,000), but average annual increases were smaller during 2000-2004 than 1995-1999. After peaking in 2002 (2.57 per 100,000), overall rates declined slightly, but continued to increase among persons aged 55-64 years. Overall increases were greater among males (144%) than females (81%) and among non-Hispanic blacks (170%) and Native Americans (241%) compared to non-Hispanic whites (124%) and Hispanics (84%). The 7,427 hepatitis C deaths in 2004 (mean age: 55 years), corresponded to 148,611 years of potential life lost. The highest mortality rates in 2004 were observed among males, persons aged 45-54 and 55-64 years, Hispanics, non-Hispanic blacks, and non-Hispanic Native American/Alaska Natives. *Conclusion*: Overall, hepatitis C mortality has increased substantially since 1995. Despite small declines in recent years, rates have continued to increase among persons aged 55-64 years. Hepatitis C is an important cause of premature mortality. (HEPATOLOGY 2008;47:1128-1135.)

Hepatitis C virus (HCV) infection is the most common blood-borne infection in the United States, with an estimated 1.3% of the general US population chronically infected.[1] About 10%-20% of chronically infected persons will develop liver cirrhosis and 1%-5% will develop hepatocellular carcinoma within 20-30 years of infection.[2] In a 2005 report, chronic HCV infection was shown to be the leading indication for liver transplantation in the United States.[3]

Alcohol use, age at infection, duration of HCV infection, and male sex are all associated with progression of liver fibrosis, development of cirrhosis, and subsequent mortality among persons with chronic HCV infection.[4,5] Coinfection with human immunodeficiency virus (HIV) is also an important prognostic factor influencing the course of HCV infection[6] and occurs commonly among persons infected with HCV due to injection drug use and other shared modes of transmission. Advances in antiretroviral therapy have extended the life of many HIV-infected persons, such that persons coinfected with HIV and HCV often live long enough to develop the sequelae of hepatitis C–related chronic liver disease.[7] Liver disease is now a leading cause of death among persons infected with HIV.[8]

Several lines of evidence suggest that the disease burden and mortality from chronic HCV infection may increase in the coming years. Comparison of the age-specific prevalence of HCV infection during 1988-1994 and 1999-2002 showed that the peak prevalence of infection

Abbreviations: AIDS, acquired immune deficiency syndrome; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICD, international classification of diseases; MCOD, multiple cause of death; NHANES, National Health and Nutrition Examination Survey; YPLL, years of potential life lost.

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had shifted from persons 30-39 years of age to persons 40-49 years of age, and that approximately two-thirds of infected participants in both surveys were born between 1945 and 1964.[1,9] These data, as well as results of mathematical models, suggest that the number of persons chronically infected for more than 20 years will continue to rise over the next decade.[10] Results of a mathematical modeling study predicted that the annual number of hepatitis C–related deaths would increase from an estimated 8,000 in 1991 to 18,000 annually between 2010 and 2019, based on past hepatitis C mortality, hepatocellular carcinoma incidence, liver transplantation, alcohol use, and mortality related to other causes.[11]

Few studies provide data on the population impact of chronic HCV infection on mortality in the United States, largely due to the difficulty of correctly identifying the infection as a cause of death. Using US death record data, Vong and Bell found that 4,443 deaths were linked to hepatitis C in 1998, a 220% increase in age-adjusted mortality rates since 1993, although these numbers were considered to be an underestimate.[12] In addition, these data are now nearly a decade old, a time period in which large increases in hepatitis C–related mortality were expected.

We examined United States multiple-cause-of-death (MCOD) data from 1995-2004 in order to provide more current, population-based estimates of trends and demographic differences in hepatitis C–related mortality utilizing a broader case definition than has been employed in previous population-based studies of hepatitis C–related mortality.

Patients and Methods

We obtained MCOD data from the National Center for Health Statistics for deaths due to hepatitis C–related disease from 1995 to 2004 occurring among persons residing in the United States. Data from this period were used because 2004 is the most recent data year available and HCV testing and diagnostic practices did not begin to stabilize until 1995. State and local laws require that death certificates be completed for all deaths, with funeral directors or hospitals required to collect demographic information on decedents and physicians or medical examiners required to complete information on the condition or conditions leading to death. The 2003 Standard US Death Certificate, upon which each state's death certificate is based, has two sections for cause-of-death information.[13] Part I includes information on the conditions involved in the causal chain of events leading to death. This includes the "underlying cause of death", the "immediate cause of death", and any conditions causally linking the underlying and immediate causes of death. The underlying cause of death is typically used to compile traditional mortality statistics and is defined as "the disease or injury that initiated the train of events leading directly to death, or the circumstances of the accident or violence, which produced the fatal injury".[14] Part II includes information on other "significant conditions contributing to death but not resulting in the underlying cause given in Part I."

MCOD files incorporate the information from Parts I and II of the death certificate using three schemes: the entity axis, the record axis, and the underlying cause of death. The entity axis contains every condition recorded in Parts I and II of the death certificate. These data are not cleaned, processed, or recoded and represent a direct transcription of each disease entity listed on the death certificate to the MCOD data file. The record axis represents a cleaned version of the entity axis in which redundant conditions are eliminated, related conditions may be combined for coding efficiency, and causes violating certain logical checks are deleted.[14] The underlying cause of death is a single variable separate from both the entity and record axes, which typically contains the underlying cause of death as recorded in Part I of the death certificate, but may contain a derived value based on selection and modification rules designed to improve the usefulness of underlying cause mortality statistics.[14] For the purposes of the current study, any condition captured in the MCOD data not classified as the underlying cause of death was considered a contributing cause of death. Medical conditions recorded in MCOD data from 1995 to 1998 were coded in accordance with the *International Classification of Diseases, 9th Revision* (ICD-9) and MCOD data from 1999 to 2004 were coded in accordance with the *International Classification of Diseases, 10th Revision* (ICD-10).[15,16]

For this study, a hepatitis C–related death was defined in one of three ways. First, any death with hepatitis C as the underlying cause of death was included (ICD-9 codes 070.4 and 070.5 and ICD-10 codes B17.1 and B18.2). Second, any death with chronic liver disease as the underlying cause (primary liver cancer, esophageal varices, alcoholic liver disease, hepatic failure, chronic hepatitis, liver cirrhosis/fibrosis, portal hypertension, or hepatorenal syndrome) and hepatitis C as a contributing cause in the record axis was included. Third, any death with HIV/acquired immune deficiency syndrome (AIDS) (ICD-9 codes 042-044.9 and ICD-10 codes B20-B24.9) as the underlying cause, chronic liver disease as a contributing cause in the record axis, and hepatitis C as a contributing cause in either the record or entity axis was included. This third definition was employed to ensure that HIV/HCV

coinfected persons with evidence of liver disease were not excluded due to the frequent assignment of HIV as the underlying cause of death when HIV is listed on the death certificate.

To calculate mortality rates, we obtained bridged population estimates from the United States Census Bureau for years 1995-2004.[17] Age-adjusted mortality rates were calculated as well as 95% confidence intervals. Age-adjusted rates were standardized to the age distribution of the year 2000 United States population. Variance estimates for rates were calculated based on a Poisson distribution. Information on age, sex, race, ethnicity, and year of death was also obtained from the MCOD data. A single race/ethnicity variable was created in which any decedent listing Hispanic ethnicity was considered Hispanic, with all remaining non-Hispanic deaths categorized according to the race groups white, black, Asian/Pacific Islander, and Native American/Alaska Native. Linear plots through annual age-adjusted mortality rates were used to quantify rate changes over time. The appropriateness of using a linear model was assessed by visual inspections of the plots as well as calculation of R-squared values. Although among a small number of subgroups annual age-adjusted rates did appear to deviate from the plots, linear methods performed better than the use of Poisson exponential rate models. Years of potential life lost (YPLL) were calculated by subtracting decedents' ages at death from 75 for all deaths occurring before age 75 and summing the individual years of life lost across all decedents. Although numerous methods have been outlined in the literature for calculation of YPLL,[18] we used a single age cutoff of 75 years for all groups in order to be consistent with YPLL data obtained on other infectious causes of death from the Centers for Disease Control and Prevention's Web-based Injury Statistics Query and Reporting System.[19] We analyzed and tabulated data with SAS, version 9.1 (SAS Institute Inc., Cary, NC) and Excel 2002 (Microsoft Corp., Redmond, WA).

Results

In the United States from 1995 to 2004, a total of 84,078 deaths mentioned hepatitis C somewhere on the death certificate, with 56,409 (67.1%) of these meeting one of the three criteria for inclusion in the study. Subjects determined to be ineligible for inclusion tended to be older, were less likely to be non-Hispanic black, and commonly had as underlying causes of death heart disease, HIV/AIDS, malignant neoplasms of sites other than the liver, non-C viral hepatitis, accidents, and diabetes. Of the eligible subjects, 37,211 (66.0%) were included because hepatitis C was listed as the underlying cause of death, 16,863 (29.9%) were included because chronic liver disease was the underlying cause and hepatitis C was mentioned as a contributing cause, and 2,335 (4.1%) were included because HIV was the underlying cause and chronic liver disease and hepatitis C were mentioned as contributing causes. Among the 19,198 decedents included in the study not listing hepatitis C as the underlying cause of death, 39.8% listed liver cancer as the underlying cause, 31.8% listed alcoholic liver disease, 15.1% listed fibrosis or cirrhosis of the liver, 12.2% listed HIV/AIDS, and 1.1% listed other underlying causes. Four deaths were excluded from rate calculations due to missing information on age.

Age-adjusted hepatitis C–related mortality rates increased substantially during the study period, rising from 1.09 deaths per 100,000 persons in 1995 to 2.57 per 100,000 in 2002 before declining slightly to 2.44 per 100,000 in 2004. Average annual mortality rate increases were smaller during 2000-2004 than during 1995-1999 (Fig. 1, Table 1). Although mortality rates from hepatitis C–related disease increased considerably during 1995-2004 for men and women, rates in men did so more rapidly, increasing by an average of 0.26 deaths per 100,000 each year (Fig. 1, Table 1). The most dramatic age-specific increases during the study period were observed among persons 45-54 years of age and persons 55-64 years of age, with rates increasing 376% from 1.76 to 8.01 per 100,000 and 188% from 2.22 to 6.05 per 100,000, respectively (Fig. 2, Table 1). The groups in which peak age-specific mortality rates were seen shifted from persons age 65 and over in 1995 to persons age 45-54 and 55-64 in 2004 (Fig. 2, Table 1). Age-adjusted race/ethnicity-specific mortality rates also increased over the study period for all groups, with the most rapid increases among non-Hispanic blacks and Native Americans/Alaska Natives (Fig. 3, Table 1). Some of the most substantial mortality rate increases observed among specific subgroups during the study period were among non-Hispanic black males aged 55-64 (3.81 to 21.94 per 100,000) and non-Hispanic white males aged 45-54 (2.21 to 11.34 per 100,000).

Relative to the rapid rise in rates during 1995-1999, changes in age-adjusted hepatitis C–related mortality were generally modest during 2000-2004 (Figs. 1-3 and Table 1). Overall hepatitis C–related mortality rates rose by 0.24 deaths per 100,000 per year during 1995-1999 and by 0.02 deaths per 100,000 per year during 2000-2004. Rates declined during 2000-2004 among Hispanics (−0.17 deaths per 100,000 per year) and non-Hispanic Asian/Pacific Islanders (−0.11 deaths per 100,000 per year), and among the youngest and oldest age groups. However, rates continued to rise among persons 45-54 and 55-64 years of age, with similar average in-

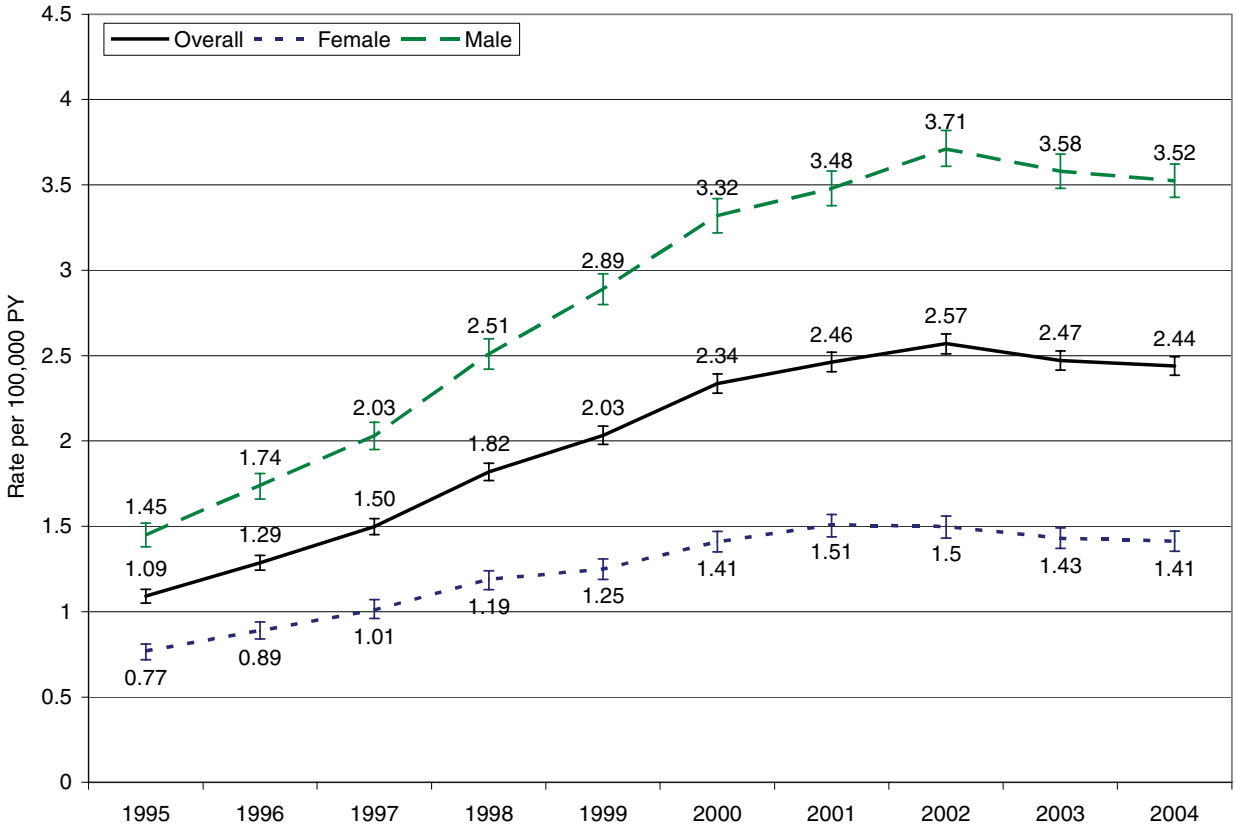

Fig. 1. Annual age-adjusted hepatitis C mortality rates and 95% confidence intervals by sex, United States, 1995-2004.

creases during the two time periods in the latter age group (0.35 deaths per 100,000 per year and 0.37 deaths per 100,000 per year) (Table 1).

In 2004, the most recent data year available, 7,427 hepatitis C–related deaths occurred, representing an age-adjusted mortality rate of 2.44 deaths per 100,000 persons (95% confidence interval 2.38, 2.50) (Table 1). The mean age of death was 55.5 years in 2004, and a total of 148,611 years of potential life were lost. Mortality rates were nearly 2.5 times higher among men than women, and mortality among non-Hispanic blacks, Hispanics, and non-Hispanic Native Americans were roughly double the rates observed for non-Hispanic whites and Asian/Pacific Islanders (Table 1). Age-specific rates were highest among persons 45-54 years of age (Table 1), although peak age-specific mortality varied by race/ethnicity and sex. The highest mortality rates observed for age-race/ethnicity-sex-specific subgroups were among non-Hispanic black and Hispanic men aged 55 to 64 (21.94 and 18.81 per 100,000, respectively) and non-Hispanic black and Hispanic men aged 45 to 54 (19.23 and 17.80 deaths per 100,000, respectively).

Major sequelae of hepatitis C were recorded among nearly all hepatitis C–related deaths in 2004. Overall, 83.8% of deaths had evidence of chronic liver disease in addition to HCV infection, including 43.5% with cirrhosis or fibrosis of the liver, 31.6% with hepatic failure, and 18.3% with primary liver cancer. Alcohol-related conditions were also prominent among hepatitis C–related deaths, with 20.0% including mention of alcoholic liver disease, alcohol dependence syndrome, or harmful use of alcohol as either the underlying or a contributing cause of death. A total of 388 (5.2%) hepatitis C–related deaths mentioned HIV/AIDS in 2004 with a mean age at death of 47.8 years.

Analysis of data limited to deaths listing hepatitis C as the underlying cause yielded similar mortality time trends and demographic disparities as the three-part case definition employed in this analysis.

Discussion

This analysis of recent death certificate data demonstrates the substantial and generally rising burden of hepatitis C–related mortality, and highlights the contribution of hepatitis C–related disease to premature mortality. According to the analysis of YPLL, hepatitis C–related disease was the 16th leading cause of premature death in the United States in 2004, and the fourth leading infectious

Table 1. Trends in Age-Adjusted and Age-Specific Hepatitis C Mortality Rates (per 100,000) by Sex, Race/Ethnicity, and Age

	Tabular Analysis				Linear Regression			
	1995		2004		1995–2004		1995–1999	2000–2004
Characteristic	Deaths	Rate (95% CI)	Deaths*	Rate (95% CI)	Annual Rate Change**	Total Percent Change	Annual Rate Change**	Annual Rate Change**
Overall	2798	1.09 (1.05,1.13)	7426	2.44 (2.38,2.50)	0.17	123.3%	0.24	0.02
Sex								
Male	1702	1.45 (1.38,1.52)	5173	3.52 (3.43,3.62)	0.26	143.5%	0.37	0.05
Female	1096	0.77 (0.72,0.81)	2253	1.41 (1.36,1.47)	0.08	81.4%	0.13	−0.01
Race/ethnicity								
White, non-Hispanic (NH)	1985	0.95 (0.91,1.00)	4794	2.10 (2.04,2.16)	0.14	123.6%	0.19	0.04
Hispanic	360	2.28 (2.03,2.53)	1113	4.23 (3.97,4.48)	0.26	84.2%	0.52	−0.17
Black, NH	347	1.39 (1.24,1.54)	1239	3.87 (3.65,4.09)	0.31	169.5%	0.49	0.05
Asian/Pacific Islander, NH	85	1.39 (1.08,1.70)	192	1.85 (1.58,2.12)	0.05	24.9%	0.11	−0.11
Native American/Alaska Native, NH	21	1.28 (0.72,1.84)	88	3.93 (3.10,4.77)	0.36	241.3%	0.49	0.04
Age								
0–34	90	0.07 (0.05,0.08)	66	0.05 (0.04,0.06)	0.00	−19.1%	0.00	−0.01
35–44	510	1.19 (1.09,1.30)	847	1.92 (1.79,2.05)	0.09	52.8%	0.26	−0.12
45–54	553	1.76 (1.61,1.90)	3334	8.01 (7.74,8.28)	0.80	376.0%	0.93	0.33
55–64	474	2.22 (2.02,2.42)	1759	6.05 (5.77,6.33)	0.44	188.3%	0.35	0.37
65–74	654	3.47 (3.20,3.73)	785	4.25 (3.95,4.55)	0.12	26.4%	0.32	−0.21
75+	517	3.47 (3.17,3.77)	635	3.56 (3.28,3.84)	0.02	4.7%	0.32	−0.33

*One death in 2004 not included in this table due to missing data on age. **Deaths per 100,000 persons per year.

cause of premature mortality behind HIV/AIDS, influenza and pneumonia, and septicemia.[19]

Understanding trends in hepatitis C–related mortality is complicated by changes in hepatitis C diagnostic practices, particularly during the first half of the study period. Observed increases in mortality during this time likely reflect both true increases in mortality and the impact of the growing use of serologic tests for HCV. As such, true increases in hepatitis C–related mortality during 1995-1999 were likely more gradual than the observed trends, and differences in mortality patterns between the time periods are difficult to interpret.

Mortality rates generally increased over the 10-year study period, with a small decline in overall mortality rates observed in the final 2 years of the study. The decline in mortality during these final years appears to be driven by decreases in mortality among persons age 65 and over as well as persons age 35-44. Decreasing rates among persons 35-44 years of age may be due to the fact that the birth cohorts with the highest prevalence of infection moved beyond this age range during the study, whereas the reasons for decreases in persons age 65 are not clear. Rates among persons age 45-54 leveled in the last 2 years of the study, whereas rates among persons age 55-64 continued a strong upward trend. Decedents age 55-64 comprised a growing proportion of persons in the high prevalence birth cohort, 1945-1964, through the study period, explaining the continued rise in mortality rates in this group.

Due to the predicted rise in the prevalence of persons with long-term chronic HCV infection through 2015,[10] models have forecast overall hepatitis C–related mortality to continue to increase over the next decade.[11] Beyond the cohort effects described above, the reasons for the small decline observed in overall mortality rates, if sustained, are not clear. Improvements in survival because of advances in treatment and liver transplantation could delay or prevent some of the anticipated hepatitis C–related mortality. Alternatively, the variable course of chronic HCV infection, reflected imprecisely in mathematical models of hepatitis C natural history, might result in mortality curves that diverge from predicted trends. It will be necessary to continue to monitor hepatitis C–related mortality over time to determine whether the small recent decline represents the beginning of a trend or a temporary fluctuation.

Alcohol consumption is an important cofactor in chronic liver disease progression among HCV-infected persons,[4,20,21] and alcohol-related conditions were observed frequently among hepatitis C–related deaths. Furthermore, the frequency of alcohol-related conditions derived from death certificate data is likely an underestimate, as it has been documented that alcohol dependence and abuse are underreported on death certificates.[22] This finding highlights the importance of existing recommendations that patients with chronic HCV infection should not consume alcohol and of identifying more effective ways to reduce excessive alcohol consumption.[23] HIV in-

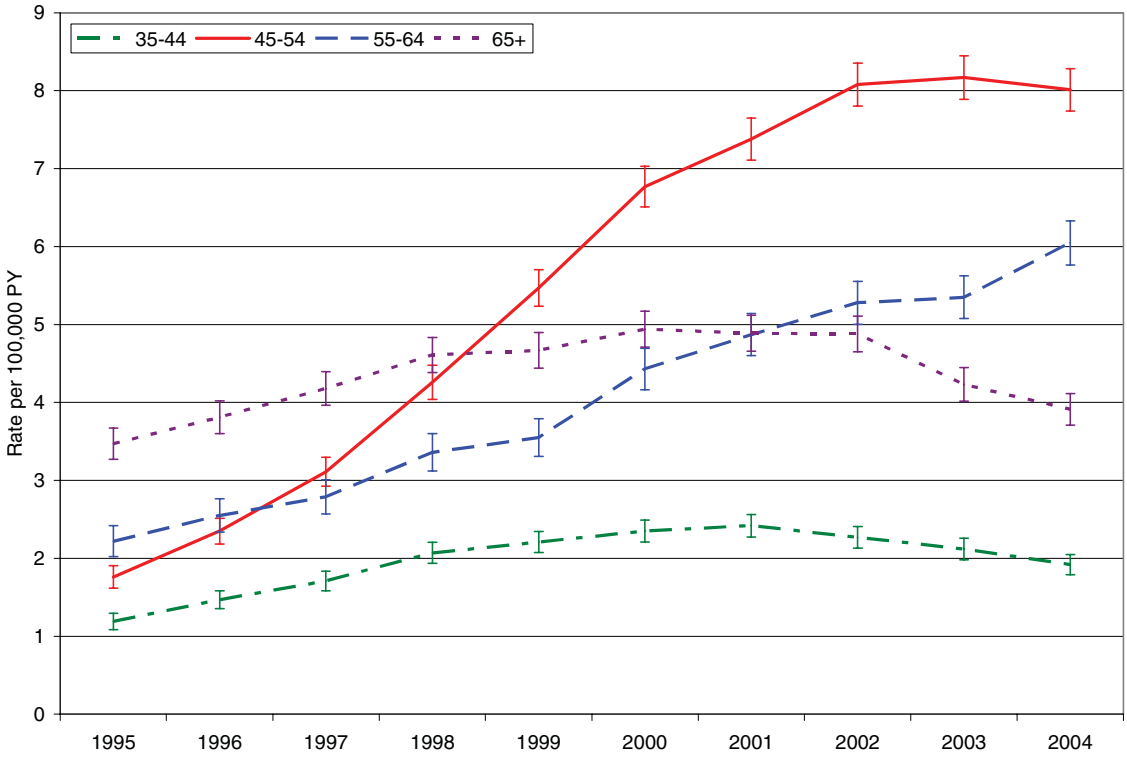

Fig. 2. Annual hepatitis C mortality rates and 95% confidence intervals for selected age groups, United States, 1995-2004.

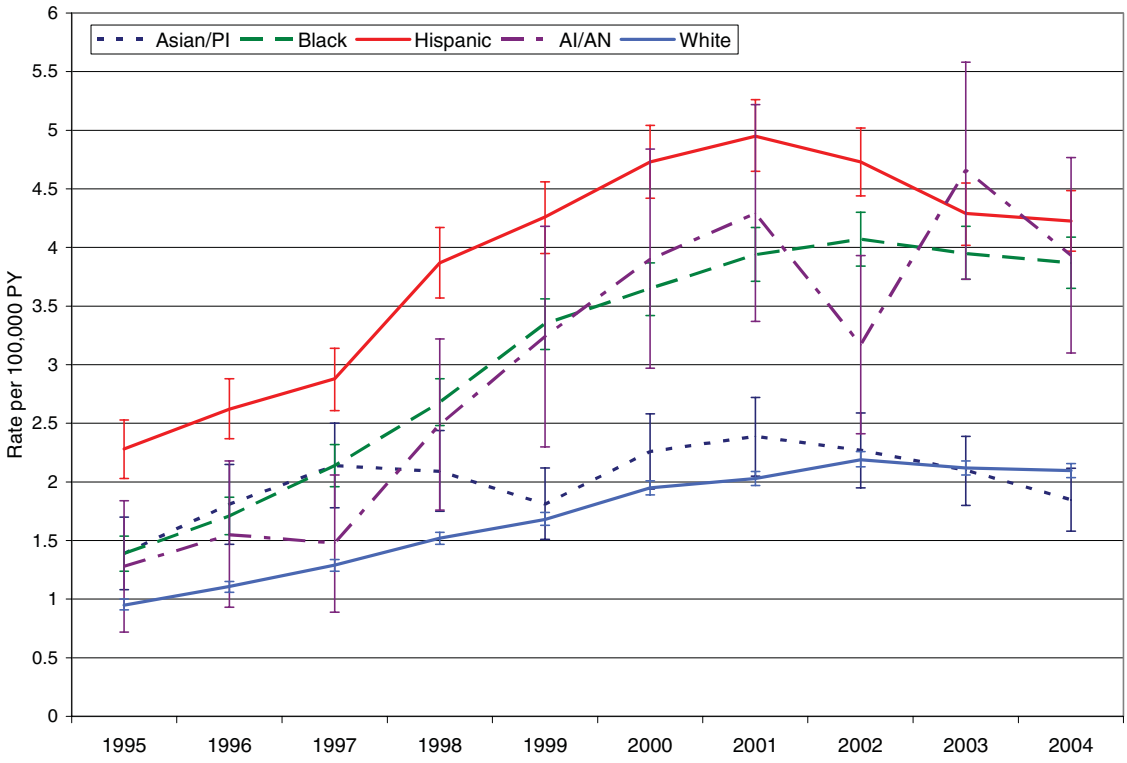

Fig. 3. Annual age-adjusted hepatitis C mortality rates and 95% confidence intervals by race/ethnicity, United States, 1995-2004.

fection has also been shown to hasten the progression of chronic liver disease among patients with hepatitis C.[6] Although HIV/AIDS was reported in a modest number of hepatitis C–related deaths, coinfected persons died at a younger age than persons with hepatitis C alone. Persons infected with HCV should also be counseled on methods to avoid HIV infection, if not already infected.

Demographic disparities in mortality were also largely consistent with observed differences in infection prevalence across subgroups. Non-Hispanic blacks, males, and persons aged 40-49 were observed to have higher prevalence of antibodies to HCV in the most recent analysis of data from the National Health and Nutrition Examination Survey (NHANES) and also were observed to have high mortality rates in the current study.[1] This consistency suggests that much of the difference in mortality rates across demographic groups is simply a function of differences in infection prevalence, although differences in the occurrence of prognostic factors influencing case-fatality may have an effect as well. Mexican Americans had low infection prevalence, similar to that of non-Hispanic whites, in NHANES,[1] but Hispanics were observed to have high mortality rates in the current study. This discrepancy could be explained by higher case-fatality among Hispanics infected with HCV, perhaps related to differences in the occurrence of comorbidities. It could also be accounted for, however, by the NHANES sampling frame not allowing for analysis of infection prevalence among all Hispanics. If non-Mexican Hispanics have high HCV infection prevalence, it would be possible for prevalence of HCV infection among all Hispanics to be similar to that of non-Hispanic blacks.

Death certificate data have a number of well-known limitations, one of which is the potential misclassification of causes of death on the death certificate. It is possible deaths were incorrectly classified as hepatitis C–related due to improper recording of causes of death on the death certificate, mistakes in coding the death certificate data, incorrect diagnosis of HCV infection, as well as errors introduced by the case definition employed. Furthermore, HCV infection may have been under-ascertained because its asymptomatic nature and long latent period could lead to a failure of diagnosis among individuals in whom it contributed substantially to death. Race and ethnicity are also sometimes misclassified on death certificates.[24] This issue is compounded by errors in Census Bureau population estimates due to Census undercounts and unmet model assumptions for intercensal estimates and postcensus projections.[25] Errors in demographic information on both death certificates and population data lead to distortions in rate estimates and may bias mortality rate comparisons made between demographic groups.

Previous research by Wu et al. using capture-recapture techniques with multiple-cause-of-death data and New York State hospital discharge data support the hypothesis that available data sources may substantially underestimate the true number of hepatitis C–related deaths.[26] Death certificates mentioning hepatitis C as either the underlying cause of death or as a contributing cause of death were compared to medical records with hepatitis C listed as a discharge diagnosis, as a part of the patient's history, or as a positive laboratory test. Using MCOD data alone would have only captured 18% of the total number of estimated deaths.[26] Another study utilizing Kaiser Permanente Medical Care Program data for 2000 also found hepatitis C to be underreported on death certificates. Only 64% of deaths attributed to hepatitis C in the Kaiser database listed hepatitis C as a cause of death on the corresponding death certificate.[27] Applying results of these validation studies to data from 2004 suggests that between 12,000 and 41,000 hepatitis C–related deaths occurred, consistent with other published estimates.[2]

An important but infrequently recognized complexity in the analysis of MCOD data pertains to the translation of entity axis codes to record axis codes and may result in an underestimation of cause-specific mortality. Although HIV and hepatitis C are often both listed in the entity axis, they are frequently combined into a single code for HIV disease in the record axis. For example, it is possible for ICD-10 codes K74.6 (other and unspecified cirrhosis of liver), B24 (unspecified HIV disease), and B18.2 (chronic viral hepatitis C) to be listed separately in the entity axis. After processing and translating the entity axis codes, the record axis may only contain B20.3 (HIV disease resulting in other viral infections) and K74.6, with B20.3 listed as the underlying cause of death. This phenomenon could have lead to the exclusion of numerous deaths strongly related to hepatitis C if ICD codes in the entity axis had not been taken into account.

In summary, substantial increases in overall hepatitis C–related mortality rates have occurred since 1995. Despite small declines in overall mortality in the last 2 years of the study, rates have continued to increase among persons aged 55-64 years. Currently, the vast majority of mortality from hepatitis C–related disease is occurring in persons under the age of 60 years, especially men. The relatively young age of persons dying from hepatitis C–related liver disease has made hepatitis C–related disease a leading infectious cause of years of potential life lost as well as an important cause of premature mortality overall. Despite recent declines in hepatitis C incidence, primary prevention of new HCV infections will continue to be important in limiting the future burden of chronic liver disease mortality in the United States. These results also

highlight the need for measures to prevent progression of chronic liver disease among persons already infected with HCV and the importance of ongoing analysis of mortality trends.

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