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The Increasing Burden of Mortality From Viral Hepatitis in the United States Between 1999 and 2007

Kathleen N. Ly, MPH; Jian Xing, PhD; R. Monina Klevens, DDS, MPH; Ruth B. Jiles, PhD, MPH; John W. Ward, MD; and Scott D. Holmberg, MD, MPH

Background: The increasing health burden and mortality from hepatitis B virus (HBV) and hepatitis C virus (HCV) in the United States are underappreciated.

Objective: To examine mortality from HBV; HCV; and, for comparison, HIV.

Design: Analysis of U.S. multiple-cause mortality data from 1999 to 2007 from the National Center for Health Statistics.

Setting: All U.S. states and the District of Columbia.

Participants: Approximately 22 million decedents.

Measurements: Age-adjusted mortality rates from HBV, HCV, and HIV. Logistic regression analyses of 2007 data generated 4 independent models per outcome (HCV- or HBV-related deaths) that each included 1 of 4 comorbid conditions and all sociodemographic characteristics.

Results: Between 1999 and 2007, recorded deaths from HBV increased significantly to 15 106, whereas deaths from HIV declined to 12 734 by 2007. Factors associated with HCV-related deaths included chronic liver disease, HBV co-infection, alcohol-related conditions, minority status, and HIV co-infection. Factors that increased odds of HBV-related death included chronic liver disease, HCV co-infection, Asian or Pacific Islander descent, HIV co-infection, and alcohol-related conditions. Most deaths from HBV and HCV occurred in middle-aged persons.

Limitation: A person other than the primary physician of the decedent frequently completed the death certificate, and HCV and HBV often were not detected and thus not reported as causes of death.

Conclusion: By 2007, HCV had superseded HIV as a cause of death in the United States, and deaths from HCV and HBV disproportionately occurred in middle-aged persons. To achieve decreases in mortality similar to those seen with HIV requires new policy initiatives to detect patients with chronic hepatitis and link them to care and treatment.

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For author affiliations, see end of text.

Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are leading causes of chronic liver disease and hepatocellular carcinoma in the United States. In 2007, chronic liver disease and cirrhosis were listed among the 15 leading causes of death in the United States (1). Hepatocellular carcinoma accounted for an estimated 18 910 deaths in the United States in 2010 (2), at least one half of which were associated with HCV infection (3).

Recent trend analyses have documented a decline in the rate of death associated with HBV (4) but an increase in deaths associated with HCV through 2004 (4, 5). Models have predicted a 2-fold increase in HCV-related deaths, with direct medical costs exceeding $6.7 billion between 2010 and 2019 (6). Despite declines in the estimated incidence of HBV and HCV infections (7), the size of the population living with viral hepatitis is considerable. An estimated 800 000 to 1.4 million persons are living with chronic hepatitis B (8, 9), approximately one half of whom are Asian or Asian American. National serum surveys indicate that approximately 3.2 million persons in the United States are living with chronic hepatitis C (10), 66% of whom were born between 1945 and 1964 and are now entering a period of risk for HCV-related diseases and premature death.

We sought to use national multiple-cause mortality data from 1999 to 2007 to describe trends in the incidence of deaths associated with HBV and HCV infections. We compared these trends with trends in the incidence of deaths associated with HIV infection and demonstrate associations between selected sociodemographic characteristics and comorbid conditions and hepatitis-related deaths in 2007. We examined the recording of HBV, HCV, and HIV infections as causes of death on death certificates.

METHODS

Every death in the United States requires a death certificate, which is usually completed by a funeral director and an attending physician, a medical examiner, or a coroner. The National Center for Health Statistics developed the 2003 U.S. Standard Certificate of Death (11), which forms the basis for each state's death certificate and ensures uniformity in data collection and processing from state vital registration systems.

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Context

Hepatitis B and C virus infections result in significant morbidity and mortality. However, they are often unrecognized and thus go untreated.

Contribution

Using death certificate data, the authors examined temporal trends in deaths from hepatitis B and C virus and HIV infections in the United States. Annual deaths from hepatitis C now exceed those from HIV, and deaths from hepatitis B and C are concentrated among middle-aged persons.

Caution

Death certificate information can be inaccurate but probably underreports deaths from viral hepatitis compared with those from HIV infection.

Implication

Hepatitis B and C are critical and relatively unrecognized public health issues in the United States that have reached epidemic proportions.

—The Editors

Two sections of the death certificate list information about the cause of death. Part I contains the immediate cause; causes leading to the immediate cause; and the underlying cause of death, which is listed on line 32d or whichever line is filled in last. Part II then lists "significant conditions contributing to death but not resulting in the underlying cause given in Part I," known as "contributing causes." Together, these factors constitute the multiple causes of death. Examples to guide physicians in correctly listing causes of death are available (12).

States compile death records and share them with the National Center for Health Statistics. The World Health Organization uses the International Classification of Diseases (ICD) to classify and code the causes of death. Health facilities may still use the ICD, Ninth Revision, Clinical Modification, for billing and other purposes, but the United States has used the ICD, Tenth Revision (ICD-10), to record data about cause of death on death certificates since 1999 (13).

The National Center for Health Statistics processes death records to produce an annual national data set on multiple-cause mortality, which is then made available for public use (14, 15). The database is a file in which each observation is 1 death with the decedent's demographic characteristics and factors related to the death.

The information on the cause of death from Parts I and II of the death certificate is incorporated into 3 fields: underlying cause of death, entity axis, and record axis. The underlying cause of death lists the 1 condition or disease that probably caused the sequence of events leading to death. The conditions of the entity axis include all causes of death listed on the death certificate. The conditions of the record axis represent a modified version of the conditions of the entity axis, where repetitive conditions and inconsistencies are deleted and links between conditions are considered.

The translation from entity to record axis either consolidates 2 categories into 1 new category, eliminating a contradiction or standardizing the data, or removes 1 category in favor of another to promote specificity of the data or resolve contradictions. For example, if the death certificate cited cirrhosis and alcoholism as 2 separate entities, a favorable translation in the record axis would be to consolidate the 2 conditions to be coded as "alcoholic cirrhosis of the liver" (14, 15).

Because of the higher specificity of the record axis, we analyzed it for underlying or contributing causes of death listed in Parts I and II of the death certificates. We coded HBV infection as ICD-10 codes B16, B17.0, B18.0, and B18.1; HCV infection as B17.1 and B18.2; and HIV infection as B20 to B24.

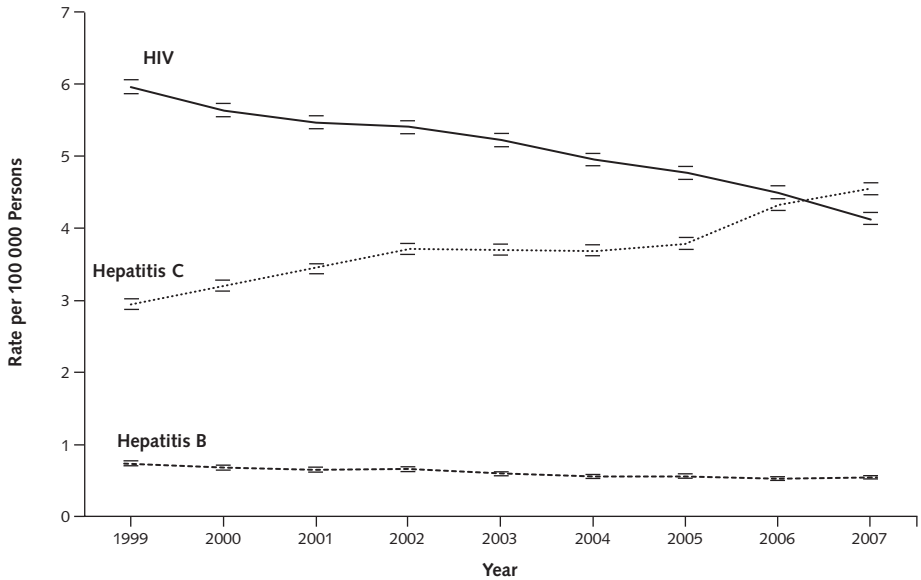
Statistical Analysis

To calculate mortality rates, we divided the number of deaths from HBV, HCV, or HIV infections listed as an underlying or contributing cause in the death certificates by the total U.S. census population for each year, adjusted to the age distribution of the standard U.S. population in 2000 by using the direct method (16). We calculated 95% CIs (1) by using the Poisson distribution to estimate the variance. We calculated the slope for each age-adjusted rate by year to obtain the average annual age-adjusted increase or decrease in mortality rate for each condition by applying the least-squares linear regression method. The statistical significance of each trend was calculated by using the Cochran–Armitage trend test.

We used separate bivariate logistic regressions to determine the crude odds of HBV-related deaths and of HCV-related deaths by using data from 2007. Independent variables were sociodemographic (age, race or ethnicity, sex, education, and marital status) and potentially preventable comorbid conditions of public health concern (HIV infection, chronic liver disease, alcohol-related illnesses, and coinfection with HBV or HCV and HIV) identified from the literature (5, 17).

For the multivariate logistic regression models, 4 models were generated per outcome variable (HBV- and HCV-related deaths). Each model controlled for all sociodemographic characteristics and each comorbid condition. That is, logistic regression analyses generated 4 separate and independent models per outcome variable, each including 1 of the 4 comorbid conditions and all sociodemographic characteristics. Variables with P values of 0.050 or less were considered statistically significant. Statistical analyses were performed by using SAS software, version 9.2 (SAS Institute, Cary, North Carolina).

Figure. **Annual age-adjusted mortality rates from hepatitis B and hepatitis C virus and HIV infections listed as causes of death in the United States between 1999 and 2007.**



Because a decedent can have multiple causes of death, a record listing more than 1 type of infection was counted for each type of infection.

Role of the Funding Source

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RESULTS

This analysis of approximately 21.8 million death certificates (approximately 2.4 million per year between 1999 and 2007) demonstrated an increase in the mortality rate from HCV infection (**Figure**). However, the average annual age-adjusted mortality rate for HBV-related deaths was relatively constant, with a slight decrease of 0.02 death per 100 000 persons per year by using the least-squares linear regression method (Cochran–Armitage trend test, $P = 0.25$).

For HCV-related deaths, we observed a statistically significant average annual age-adjusted mortality rate increase of 0.18 death per 100 000 persons per year ($P = 0.002$). However, for HIV-related deaths, we observed a significant average annual age-adjusted mortality rate decrease of 0.21 death per 100 000 persons per year ($P = 0.001$). In 2007, the mortality rate associated with HCV infections surpassed that from HIV infections (**Figure**).

In 2007, 2 428 343 deaths were registered in the United States (**Table 1**). Hepatitis C virus infection was associated with more total deaths and had the highest mortality rate compared with HBV and HIV infections (**Figure**). Hepatitis B virus infection was listed as the underlying cause of 724 deaths (0.03%) and as the single underlying or contributing cause of 1815 deaths (0.07%) (age-adjusted mortality rate, 0.56 death per 100 000 persons per year [CI, 0.54 to 0.59]) (**Table 1**). Hepatitis C virus infection was listed as the underlying cause of 6605 deaths (0.27%) and as the underlying or contributing cause of 15 106 deaths (0.62%) (age-adjusted mortality rate, 4.58 deaths per 100 000 persons per year [CI, 4.50 to 4.67]) (**Table 1**). Infection with HIV was listed as the underlying cause of 11 332 deaths (0.47%) and as the underlying or contributing cause of 12 734 deaths (0.52%) (age-adjusted mortality rate, 4.16 deaths per 100 000 persons per year [CI, 4.09 to 4.24]) (**Figure**).

In 2007, the greatest proportion of HBV- and HCV-related deaths was among persons aged 45 to 54 and 55 to 64 years; 59.4% of HBV-related deaths and 73.4% of HCV-related deaths occurred in these relatively young age groups (**Table 1**). Men had a greater proportion of HBV- and HCV-related deaths than women. Compared with non–HBV-related deaths, HBV-related deaths among persons of non-Hispanic Asian or Pacific Islander descent were disproportionately represented, and the mortality in this population was approximately 11 times higher (**Table 1**). A similar but less striking relationship was observed for HCV-related deaths among non-Hispanic black (18% vs. 12%), Hispanic (15% vs. 6%), and non-Hispanic American Indian or Alaskan Native (1.3% vs. 0.5%) populations (**Table 1**).

Table 1. **Characteristics of Deaths in the United States for Which Hepatitis B or C Was Listed as a Cause of Death in 2007***

Characteristic	Hepatitis B			Hepatitis C		
	Yes, *n* (%)†	No, *n* (%)†	Unadjusted OR (95% CI)	Yes, *n* (%)†	No, *n* (%)†	Unadjusted OR (95% CI)
Total	1815	2 426 528	–	15 106	2 413 237	–
Age						
0–44 y	246 (13.6)	197 013 (8.1)	1.0 (reference)	1130 (7.5)	196 129 (8.1)	1.0 (reference)
45–54 y	532 (29.3)	184 792 (7.6)	2.3 (2.0–2.7)‡	5937 (39.3)	179 387 (7.4)	5.7 (5.4–6.1)‡
55–64 y	546 (30.1)	287 341 (11.8)	1.5 (1.3–1.8)‡	5145 (34.1)	282 742 (11.7)	3.2 (3.0–3.4)‡
≥65 y	491 (27.1)	1 757 064 (72.4)	0.2 (0.2–0.3)‡	2894 (19.2)	1 754 661 (72.7)	0.3 (0.3–0.3)‡
Race or ethnicity						
White, non-Hispanic	924 (51.1)	1 938 787 (80.0)	1.0 (reference)	9544 (63.4)	1 930 167 (80.1)	1.0 (reference)
Black, non-Hispanic	354 (19.6)	285 939 (11.8)	2.6 (2.3–2.9)‡	2638 (17.5)	283 655 (11.8)	1.9 (1.8–2.0)‡
Hispanic	157 (8.7)	136 745 (5.6)	2.4 (2.0–2.9)‡	2245 (14.9)	134 657 (5.6)	3.4 (3.2–3.5)‡
Asian or Pacific Islander, non-Hispanic	360 (19.9)	43 057 (1.8)	17.5 (15.5–19.8)‡	376 (2.5)	43 041 (1.8)	1.8 (1.6–2.0)‡
American Indian or Alaskan Native, non-Hispanic	8 (0.4)	13 145 (0.5)	1.3 (0.6–2.6)	192 (1.3)	12 961 (0.5)	3.0 (2.6–3.5)‡
Other, non-Hispanic	6 (0.3)	4878 (0.2)	2.6 (1.2–5.8)§	59 (0.4)	4825 (0.2)	2.5 (1.9–3.2)‡
Sex						
Men	1345 (74.1)	1 205 711 (49.7)	2.9 (2.6–3.2)‡	10 561 (69.9)	1 196 495 (49.6)	2.4 (2.3–2.4)‡
Women	470 (25.9)	1 220 817 (50.3)	1.0 (reference)	4545 (30.1)	1 216 742 (50.4)	1.0 (reference)
Education‖						
Less than high school	480 (27.8)	666 781 (29.0)	1.0 (reference)	3922 (27.4)	663 339 (29.0)	1.0 (reference)
Completed high school	710 (41.1)	966 889 (42.0)	1.0 (0.9–1.1)	6645 (46.5)	960 954 (42.0)	1.2 (1.1–1.2)‡
Some college	298 (17.3)	355 632 (15.5)	1.2 (1.0–1.3)§	2573 (18.0)	353 357 (15.4)	1.2 (1.2–1.3)‡
Completed college or beyond	239 (13.8)	312 198 (13.6)	1.1 (0.9–1.2)	1149 (8.0)	311 288 (13.6)	0.6 (0.6–0.7)‡
Marital status						
Single or never married	426 (23.9)	300 764 (12.5)	1.7 (1.5–1.9)‡	2952 (19.9)	298 238 (12.4)	1.6 (1.5–1.6)‡
Married	777 (43.6)	918 927 (38.1)	1.0 (reference)	5737 (38.7)	913 967 (38.1)	1.0 (reference)
Widowed	202 (11.3)	879 715 (36.5)	0.3 (0.2–0.3)‡	1486 (10.0)	878 431 (36.6)	0.3 (0.3–0.3)‡
Divorced	376 (21.1)	313 842 (13.0)	1.4 (1.3–1.6)‡	4635 (31.3)	309 583 (12.9)	2.4 (2.3–2.5)‡
HIV infection						
Yes	100 (5.5)	12 634 (0.5)	11.1 (9.1–13.6)‡	437 (2.9)	12 297 (0.5)	5.8 (5.3–6.4)‡
No	1715 (94.5)	2 413 894 (99.5)	1.0 (reference)	14 669 (97.1)	2 400 940 (99.5)	1.0 (reference)
Chronic liver disease						
Yes	1073 (59.1)	62 696 (2.6)	54.5 (49.6–59.9)‡	8636 (57.2)	55 133 (2.3)	57.1 (55.2–59.0)‡
No	742 (40.9)	2 363 832 (97.4)	1.0 (reference)	6470 (42.8)	2 358 104 (97.7)	1.0 (reference)
Alcohol-related conditions						
Yes	242 (13.3)	45 487 (1.9)	8.1 (7.0–9.2)‡	2927 (19.4)	42 802 (1.8)	13.3 (12.8–13.9)‡
No	1573 (86.7)	2 381 041 (98.1)	1.0 (reference)	12 179 (80.6)	2 370 435 (98.2)	1.0 (reference)
Co-infection with hepatitis B or C						
Yes	541 (29.8)	14 565 (0.6)	70.3 (63.5–77.9)‡	541 (3.6)	1274 (0.1)	70.3 (63.5–77.9)‡
No	1274 (70.2)	2 411 963 (99.4)	1.0 (reference)	14 565 (96.4)	2 411 963 (99.9)	1.0 (reference)

OR = odds ratio.
* Cause of death is defined as the underlying cause or one of the multiple causes of death.
† Missing values are not included in calculations.
‡ $P < 0.001$.
§ $P > 0.010$ and < 0.050.
‖ Less than high school = no formal education, 1–8 y of formal education, 1–3 y of high school education, completed 8th grade or less, or completed 9th–12th grades (no diploma). Completed high school = 4 y of high school education, graduated high school, or received GED credentials. Some college = 1–3 y of college, some college credit but no degree, or associate's degree. Completed college or beyond = 4 y of college; bachelor's degree; ≥5 y of college; or master's, doctorate, or professional degree.

Decedents with HBV or HCV infection listed as a cause of death frequently had co-infection with HIV and with HBV or HCV and a diagnosis of chronic liver disease (including hepatocellular carcinoma) or an alcohol-related condition. Specifically, among the selected comorbid conditions that we examined in decedents with an HBV-related death, the most frequently reported one was chronic liver disease (59%), followed by HCV co-infection (30%), alcohol-related conditions (13%), and HIV co-infection (6%). Among persons with HCV listed as a cause

of death, the most frequently reported comorbid condition of the 4 that we examined was chronic liver disease (57%), followed by alcohol-related conditions (19%), HBV co-infection (4%), and HIV co-infection (3%).

Groups that were more likely to have an HBV-related death included decedents aged 45 to 54 and 55 to 64 years compared with those aged 44 years or younger and also compared with those aged 65 years or older; non-Hispanic persons of Asian or Pacific Islander descent, non-Hispanic black persons, and Hispanic persons compared with non-Hispanic white persons; men compared with women; and decedents who never married or were single compared with married decedents (**Table 1**).

Decedents more likely to have an HCV-related death included those aged 45 to 54 and 55 to 64 years compared with those aged 44 years or younger; members of all racial or ethnic groups compared with non-Hispanic white persons; men compared with women; those who completed high school or some college compared with those with less than a high school education; and those who never married or were single and divorced persons compared with married decedents (**Table 1**).

In all 4 multivariate models, the adjusted relative odds of having an HBV-related death were significantly higher for decedents aged 45 to 54 years and significantly lower for decedents older than 65 years compared with those aged 44 years or younger (**Table 2**). These findings were

Table 2. **Adjusted Relative Odds That a Death Certificate Listed Hepatitis B or C as a Cause of Death in the United States in 2007***

Variable	Adjusted OR for Hepatitis B–Related Death (95% CI)				Adjusted OR for Hepatitis C–Related Death (95% CI)			
	HIV	Chronic Liver Disease	Alcohol-Related Conditions	Hepatitis C	HIV	Chronic Liver Disease	Alcohol-Related Conditions	Hepatitis B
Overall	4.1 (3.2–5.1)†	34.4 (31.0–38.1)†	3.7 (3.2–4.2)†	31.5 (28.0–35.4)†	1.8 (1.6–2.0)†	32.1 (31.0–33.3)†	4.6 (4.4–4.8)†	29.9 (26.5–33.6)†
Age								
0–44 y	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
45–54 y	2.7 (2.3–3.2)†	1.4 (1.2–1.7)†	2.6 (2.2–3.1)†	1.7 (1.4–2.0)†	6.2 (5.8–6.7)†	3.8 (3.5–4.1)†	5.9 (5.5–6.3)†	6.2 (5.8–6.6)†
55–64 y	2.0 (1.7–2.3)†	1.1 (1.0–1.4)	2.0 (1.7–2.3)†	1.4 (1.2–1.6)†	3.7 (3.5–4.0)†	2.4 (2.2–2.6)†	3.8 (3.5–4.1)†	3.7 (3.4–3.9)†
≥65 y	0.4 (0.3–0.5)†	0.4 (0.3–0.5)†	0.4 (0.4–0.5)†	0.4 (0.3–0.5)†	0.4 (0.4–0.5)†	0.4 (0.4–0.5)†	0.5 (0.5–0.5)†	0.4 (0.4–0.5)†
Race or ethnicity								
White, non-Hispanic	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Black, non-Hispanic	1.7 (1.5–1.9)†	1.9 (1.7–2.2)†	1.9 (1.7–2.2)†	1.8 (1.5–2.0)†	1.2 (1.2–1.3)†	1.4 (1.3–1.5)†	1.4 (1.3–1.4)†	1.2 (1.2–1.3)†
Hispanic	1.6 (1.3–1.9)†	1.1 (0.9–1.3)	1.6 (1.3–1.9)†	1.2 (1.0–1.5)‡	2.5 (2.4–2.6)†	1.8 (1.8–2.0)†	2.4 (2.3–2.5)†	2.5 (2.4–2.6)†
Asian or Pacific Islander, non-Hispanic	16.7 (14.7–19.0)†	13.2 (11.5–15.1)†	17.5 (15.3–19.8)†	17.2 (15.1–19.6)†	1.8 (1.6–2.0)†	1.4 (1.2–1.6)†	2.0 (1.8–2.2)†	1.4 (1.3–1.6)†
American Indian or Alaskan Native, non-Hispanic	0.7 (0.3–1.5)	0.5 (0.2–1.0)‡	0.6 (0.3–1.2)	0.6 (0.3–1.3)	1.8 (1.6–2.1)†	1.3 (1.1–1.5)§	1.4 (1.2–1.7)†	1.9 (1.6–2.2)†
Other, non-Hispanic	1.8 (0.8–4.0)	1.7 (0.7–3.8)	1.8 (0.8–4.0)	1.6 (0.7–3.6)	1.8 (1.4–2.3)†	1.8 (1.3–2.3)†	1.8 (1.4–2.3)†	1.8 (1.4–2.3)†
Sex								
Men	2.0 (1.8–2.3)†	1.7 (1.5–1.9)†	2.0 (1.7–2.2)†	1.8 (1.6–2.1)†	1.6 (1.5–1.7)†	1.4 (1.3–1.4)†	1.5 (1.4–1.5)†	1.6 (1.5–1.6)†
Women	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Education‖								
Less than high school	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Completed high school	1.0 (0.9–1.1)	0.9 (0.8–1.1)	1.0 (0.9–1.1)	1.0 (0.9–1.1)	1.0 (1.0–1.1)	1.0 (1.0–1.1)	1.0 (1.0–1.1)	1.0 (1.0–1.1)‡
Some college	0.9 (0.8–1.1)	1.0 (0.8–1.1)	1.0 (0.8–1.1)	1.0 (0.8–1.1)	0.9 (0.9–1.0)‡	0.9 (0.9–1.0)‡	0.9 (0.9–1.0)‡	0.9 (0.9–1.0)‡
Completed college or beyond	0.8 (0.7–1.0)‡	0.9 (0.8–1.0)	0.8 (0.7–1.0)‡	0.9 (0.8–1.1)	0.6 (0.5–0.6)†	0.6 (0.6–0.6)†	0.6 (0.5–0.6)†	0.6 (0.5–0.6)†
Marital status								
Single or never married	1.1 (1.0–1.3)	1.4 (1.2–1.6)†	1.2 (1.0–1.4)‡	1.2 (1.0–1.3)‡	1.1 (1.0–1.2)†	1.2 (1.1–1.3)†	1.1 (1.0–1.1)‡	1.1 (1.1–1.2)†
Married	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Widowed	0.8 (0.6–0.9)§	0.9 (0.7–1.0)	0.8 (0.6–0.9)§	0.7 (0.6–0.9)§	0.8 (0.8–0.9)†	0.9 (0.8–0.9)†	0.8 (0.7–0.8)†	0.8 (0.8–0.9)†
Divorced	1.3 (1.1–1.4)†	1.2 (1.0–1.4)§	1.2 (1.0–1.3)‡	1.1 (1.0–1.3)	1.6 (1.6–1.7)†	1.6 (1.5–1.7)†	1.5 (1.4–1.5)†	1.7 (1.6–1.7)†

OR = odds ratio.
* Cause of death is defined as the underlying cause or one of the multiple causes of death. Each model included the specified morbidity adjusted by age, race or ethnicity, sex, education, and marital status.
† $P < 0.001$.
‡ $P \geq 0.001$ and < 0.010.
§ $P \geq 0.010$ and < 0.050.
‖ Less than high school = no formal education, 1–8 y of formal education, 1–3 y of high school education, completed 8th grade or less, or completed 9th–12th grades (no diploma). Completed high school = 4 y of high school education, graduated high school, or received GED credentials. Some college = 1–3 y of college, some college credit but no degree, or associate's degree. Completed college or beyond = 4 y of college; bachelor's degree; ≥5 y of college; or master's, doctorate, or professional degree.

the same for decedents aged 55 to 64 years in 3 of the 4 models.

In all models, non-Hispanic persons of Asian or Pacific Islander descent and, to a lesser degree, non-Hispanic black persons had higher odds of HBV-related death than non-Hispanic white persons. In 2 models, Hispanic ethnicity was significantly associated with HBV-related death. The adjusted odds of having an HBV-related death were approximately 2 times higher for male decedents than for female decedents in all models.

Each comorbid condition had a highly significant association with a listing of HBV infection as a cause of death (**Table 2**). The comorbid condition most strongly associated with HBV infection was chronic liver disease (adjusted odds ratio [OR], 34.4 [CI, 31.0 to 38.1]) and co-infection with HCV (adjusted OR, 31.5 [CI, 28.0 to 35.4]), followed by HIV infection (adjusted OR, 4.0 [CI, 3.2 to 5.1]) and alcohol-related illnesses (adjusted OR, 3.7 [CI, 3.2 to 4.2]).

In all 4 multivariate models, the adjusted relative odds of having an HCV-related death were significantly higher for decedents aged 45 to 54 years and those aged 55 to 64 years (**Table 2**). The magnitude of the associations in these age groups decreased when chronic liver disease was added to the model, but the findings remained significant. The adjusted relative odds of HCV-related death were consistently and significantly higher for all racial or ethnic groups than for non-Hispanic white persons and highest for Hispanic decedents.

The adjusted relative odds of HCV-related death were higher for male decedents than female decedents in all models. However, decedents who completed college or obtained a graduate degree were 40% less likely to have HCV infection reported at death than decedents who did not complete high school. These odds were higher in divorced decedents, whereas widowed decedents had slightly lower odds than married decedents.

All 4 of the comorbid conditions that we evaluated were significantly associated with a listing of HCV infection as a cause of death (**Table 2**). Chronic liver disease (adjusted OR, 32.1 [CI, 31.0 to 33.3]) and HBV co-infection (adjusted OR, 29.9 [CI, 26.5 to 33.6]) were the most strongly associated, followed by alcohol-related conditions (adjusted OR, 4.6 [CI, 4.4 to 4.8]) and HIV infection (adjusted OR, 1.8 [CI, 1.6 to 2.0]).

Discussion

This analysis shows the rapidly increasing number of deaths among HCV-infected persons, which now surpass deaths among HIV-infected persons. In addition, the relatively young age of most HCV-infected persons who are dying (that is, 45 to 64 years of age) portends a large and ever-increasing health care burden (18) from what the current U.S. Assistant Secretary of Health has dubbed the "silent epidemic" (19).

In fact, our analysis may underestimate the relative effect of viral hepatitis, because many fewer decedents at the time of death would have been diagnosed with HCV (approximately 40% to 50% of all HCV-infected persons) (20, 21) or HBV (variously estimated at 40% to 75%) (9, 20, 22) than with HIV (80% or more) (23). Given the approximately 3 million HCV-infected persons in the United States (10), the increase in deaths after 2 or 3 decades of infection may not be unexpected, as has been predicted previously (5, 6). However, few diseases of such morbidity and mortality in the United States have received so little public attention and funding as chronic viral hepatitis (24).

Recent marked decreases in HCV incident infections (7) may distract from the impending problem of persons with chronic viral hepatitis infections in the United States (10) as they age and need services ranging from antiviral therapy to liver transplantation. The health and economic burden from this coming wave of health care needs will be large and, as these data show, will disproportionately affect persons aged 45 to 64 years (6, 18).

Hepatitis C virus infection is often asymptomatic or causes nonspecific symptoms (depression, arthralgia, and fatigue) for decades (25, 26). Therefore, the current goals of secondary prevention and control of this condition are based on screening persons at risk and identifying affected persons and referring them to care. However, because we found that almost 75% of HCV-related deaths occurred in persons aged 45 to 64 years, screening efforts that target middle-aged persons may be profitable.

The limitations of analyses of death certificates, which are often completed by someone other than the primary physician, include the incomplete ascertainment of cases, misclassification (27), and missing causes of death. Such problems may be mitigated when analyzing trends (28), such as those of HBV, HCV, and HIV (29), in which biases have been assumed to be relatively constant over the years of analysis.

No data suggest that the ability to detect HCV-related deaths has substantially changed during the period of interest (bias of ascertainment). To the contrary, recommended screening (30) of persons at risk for HCV, such as injection drug users and incarcerated persons, has been notably unsuccessful, as few have been screened for risk and are still usually tested only when they have symptoms, such as jaundice (22, 31). Few physicians ask about the major risk factor for HCV (32), injection-drug use, and few interviewees wish to admit to this behavior (33). Therefore, HCV infection and HCV-related chronic liver disease have remained consistently poorly ascertained and, thus, underreported in death certificates.

Assignment of the attributable fraction of a person's death to infection with one of these viruses is also of concern. For example, analyses of HBV and HCV infections often focus, as a conservative assumption, on end-stage liver disease and hepatocellular carcinoma as causes of death among HCV-

or HBV-infected persons (18), whereas all-cause mortality is approximately double in HCV-infected persons than those without HCV infection (34–36). Conversely, there is a tendency to attribute almost all deaths among HIV-infected persons to HIV (36).

Systematic biases also are present against ascertaining co-infections with HCV in death certificates of HIV-infected persons. In our analysis, which examined all "underlying" or "multiple" causes of death, 89% of deaths among HIV-infected persons were attributed to HIV as the "underlying condition." However, only 44% of deaths among HCV-infected persons were attributed to HCV.

The ICD-10 rules for selecting underlying cause of death state that if the underlying cause of death is any of several infectious diseases (including viral hepatitis) and HIV infection is also mentioned anywhere on the death certificate, then HIV must be selected as the underlying cause of death in the record axis instead of the other condition (37). According to the description in the Methods section, consolidating or reducing the number of diagnoses from the entity into the record axis gives HIV priority as a diagnosis over HBV or HCV infections. Indeed, although we analyzed the "cleaner" record axis, we noted a decrease in HBV and HCV in records that also listed HIV as the underlying cause of death when examining the record rather than the entity axis. Another important trend has been that, in the modern era of effective antiretroviral therapies, the greatest non-AIDS cause of death among HIV-infected persons has been liver disease that is usually secondary to HCV or HBV infection (29, 37).

In summary, even if one cannot easily assign a cause of death among persons with HBV, HCV, or HIV infection, approximately 16 000 deaths among HCV- and HBV-infected persons were registered in 2007, and this figure must represent only a fraction of a larger burden of morbidity and mortality from viral hepatitis.

Our report confirms the rapid growth in viral hepatitis–associated deaths as the baby-boomer generation ages. A recent Institute of Medicine report (24) identified multiple barriers and inadequate public resources to support the prevention, care, and monitoring needed for the public health problem of viral hepatitis. This report focused on low awareness and knowledge of viral hepatitis among the public and health care providers. This factor contributes to inadequate investments in prevention and care services, resulting in missed opportunities to prevent transmission and disease. Recent licensure of point-of-care tests for HCV and several new and more effective therapies for HCV that are in advanced stages of clinical trials increase the opportunities to screen and intervene early and prevent HCV-associated deaths. The Institute of Medicine called for an intensified, coordinated national effort to improve the prevention of new cases and the detection and treatment of discovered persons with this condition.

On the basis of this analysis of multiple causes of death, the increasing trend in viral hepatitis–associated deaths sharply contrasts with the decreasing trend in HIV-related deaths. The decrease in deaths from HIV infection in the past decades reflects the availability and utilization of highly effective therapies, as well as effective national implementation of programs for prevention and care. The experience with HIV mortality reduction suggests that a similar approach to HBV and HCV prevention might lead to similar reductions in mortality from viral hepatitis over time. Continuing the downward trend in HIV mortality while at the same time pursuing similar reductions in mortality from viral hepatitis are complementary goals that are consistent with recommendations made by the Institute of Medicine (24) and the U.S. Department of Health and Human Services (19, 38).

From the Centers for Disease Control and Prevention, Atlanta, Georgia.

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Requests for Single Reprints: Kathleen N. Ly, MPH, Division of Viral Hepatitis, Centers for Disease Control and Prevention, 1600 Clifton Road NE, Mailstop G-37, Atlanta, GA 30333; e-mail, kathleenly@cdc.gov.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Ms. Ly and Drs. Xing, Klevens, Jiles, Ward, and Holmberg: Division of Viral Hepatitis, Centers for Disease Control and Prevention, 1600 Clifton Road NE, Mailstop G-37, Atlanta, GA 30333.

Author Contributions: Conception and design: K.N. Ly, J. Xing, R.M. Klevens, R.B. Jiles, J.W. Ward, S.D. Holmberg.
Analysis and interpretation of the data: K.N. Ly, J. Xing, S.D. Holmberg.
Drafting of the article: K.N. Ly, R.M. Klevens, J.W. Ward, S.D. Holmberg.
Critical revision of the article for important intellectual content: K.N. Ly, R.M. Klevens, J.W. Ward, S.D. Holmberg.
Final approval of the article: R.M. Klevens, R.B. Jiles, J.W. Ward, S.D. Holmberg.
Statistical expertise: J. Xing.
Obtaining of funding: R.B. Jiles, J.W. Ward, S.D. Holmberg.
Administrative, technical, or logistic support: R.B. Jiles, S.D. Holmberg.