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Evolving Characteristics of Decedents With Hepatitis A Listed as a Cause of Death, United States, 2011–2021

Megan G. Hofmeister,

Kathleen N. Ly,

Shaoman Yin,

Philip R. Spradling

Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Abstract

Hepatitis A is a vaccine-preventable disease that typically causes mild illness. Hepatitis A outbreaks associated with person-to-person transmission have been widespread in the United States since 2016. We used public-use US Multiple Cause of Death data to compare characteristics and listed comorbidities among decedents with hepatitis A-listed deaths during non-outbreak (2011–2015) and outbreak (2017–2021) periods and assessed the median age at death among decedents with and without hepatitis A-listed deaths during the outbreak period. From the non-outbreak period to the outbreak period, hepatitis A-listed deaths more than doubled (from 369 to 801), while the hepatitis A-listed age-adjusted mortality rate increased 150% ($p < 0.001$). When compared with the non-outbreak period, hepatitis A-listed decedents during the outbreak period were more frequently male, aged 18–49 years, non-Hispanic White, died in an inpatient setting, and had hepatitis A listed as their underlying cause of death. The median age at death for hepatitis A-listed decedents was significantly younger during the outbreak period overall and among females (62 and 66 years, respectively) compared with the non-outbreak period (64 and 72 years, respectively, $p < 0.001$). During the outbreak period, median age at death for hepatitis A-listed decedents was 14 years younger than decedents without hepatitis A listed. Compared with the general US population, decedents with hepatitis A listed on the death certificate died at younger ages during 2017–2021. Efforts are needed to improve hepatitis A vaccination coverage among adults recommended for hepatitis A vaccination to prevent additional premature hepatitis A deaths.

This article is a U.S. Government work and is in the public domain in the USA.

Correspondence: Megan G. Hofmeister (lxn7@cdc.gov).

Conflicts of Interest

The authors declare no conflicts of interest.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Keywords

cause of death; hepatitis A virus; infectious disease outbreak; mortality; vaccine-preventable disease

Hepatitis A virus (HAV) infection is transmitted by the faecal–oral route and usually causes mild, self-limited illness. Serious complications, including death, are uncommon [1, 2]. During 2001 through 2016, the overall hepatitis A case-fatality ratio according to US national surveillance data was <1% annually [3]. Based on US Multiple Cause of Death (MCOd) data, from 1999 to 2011, the mean age at death among decedents with listed HAV infection increased in the United States from 61.0 to 69.8 years [4].

Since 2016, 37 US states have experienced hepatitis A outbreaks associated with person-to-person transmission that were unprecedented in the hepatitis A vaccine era [5, 6]. HAV spread primarily through close contact among persons who use drugs and persons experiencing homelessness [6–9]. Between July 1, 2016, and January 12, 2024, 37 states reported >44,900 outbreak-associated cases, >27,450 hospitalisations, and 424 deaths [5]. During these outbreaks, several states reported hepatitis A-related case-fatality ratios of approximately 3%—at least three times higher than case-fatality ratios historically associated with hepatitis A in the United States [5, 10, 11]. Additionally, a shift towards younger age at death among decedents with hepatitis A listed as a cause of death was observed from US MCOd data in annual national viral hepatitis statistics during the outbreak period [3].

Given the high reported hepatitis A case-fatality ratios and apparent shift towards younger age at death in the outbreaks associated with person-to-person transmission, we sought to compare sociodemographic characteristics and underlying cause of death among decedents with hepatitis A-listed deaths during non-outbreak (2011–2015) and outbreak periods (2017–2021) and assess the median age at death among decedents with and without hepatitis A-listed deaths during the outbreak period.

1 | Materials and Methods

1.1 | Data Source and Definitions

We used public-use US MCOd data from the National Center for Health Statistics' (NCHS) National Vital Statistics System for this analysis [12]. We defined 2011–2015 as the non-outbreak period (the period during which widespread hepatitis A outbreaks associated with person-to-person transmission did not occur) and data during 2017–2021 as the outbreak period (the period during which widespread hepatitis A outbreaks associated with person-to-person transmission did occur). Although the initial hepatitis A outbreaks associated with person-to-person transmission started in two jurisdictions in late 2016, we excluded 2016 data from the analysis to better delineate between the non-outbreak and outbreak periods as only four outbreak-related hepatitis A deaths were reported by state health departments in 2016 [13].

We defined hepatitis A-listed deaths using *International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10)* codes [14]. If ICD-10 codes B15.0 or B15.9 were listed as the underlying cause of death or a contributing cause of death in the MCODE record axis fields, we considered deaths to be hepatitis A-listed. ICD-10 codes for additional underlying cause of death and coinfection categories assessed in the analysis are found in Table S1.

1.2 | Statistical Analysis

We counted hepatitis A-listed deaths by year during the outbreak period, and by aggregating data into two 5-year non-outbreak and outbreak periods. We calculated cumulative 5-year mortality rates per 100,000 population for the total and by age group, sex and race/ethnicity by dividing the number of hepatitis A-listed deaths in a time period by the equivalent cumulative 5-year US Census population. Rates for the total and by sex and race/ethnicity were adjusted to the age distribution of the 2000 US standard population using the direct method [15]. We determined whether there were differences between non-outbreak vs. outbreak periods by describing the distribution, median age and age-adjusted mortality rate of hepatitis A-listed deaths by sociodemographic characteristics, place of death, listed coinfection with hepatitis B virus (HBV)/hepatitis C virus (HCV)/HIV, and underlying cause of death categories. During the outbreak period, we assessed differences in the median age of decedents with and without hepatitis A listed as a cause of death overall and by underlying cause of death categories.

We adhered to NCHS's data presentation standards regarding stability and reliability of proportions and rates, and therefore indicated that the estimates were unreliable when the numerator was <20 deaths [16]. The analysis was conducted using SAS (version 9.4; SAS Institute). This analysis used publicly available data without personal identifiers and did not require institutional review board approval.

2 | Results

There were 369 and 801 decedents in the United States with hepatitis A listed as a cause of death during the non-outbreak and outbreak periods respectively (Table 1). Hepatitis A-listed deaths were more common among men than women during both the non-outbreak (57.7% vs. 42.3%) and outbreak periods (68.2% vs. 31.8%). The ≥70-year-old age category accounted for the highest percentage of hepatitis A-listed deaths by age group during the non-outbreak period (38.2%) and outbreak period (31.3%). Similarly, hepatitis A-listed deaths were most common among non-Hispanic White persons during both the non-outbreak period (69.0%) and the outbreak period (84.6%). The proportion of hepatitis A-listed deaths that occurred in inpatient hospital settings increased from 45.8% during the non-outbreak period to 60.4% during the outbreak period. Coinfection with HBV, HCV or HIV was less frequently reported among hepatitis A-listed deaths during the outbreak period (28.3%) than during the non-outbreak period (38.8%).

The age-adjusted hepatitis A mortality rate increased 150%, from 0.02 (95% CI, 0.02–0.02) deaths per 100,000 population during the non-outbreak period to 0.05 (95% CI, 0.05–0.06) deaths per 100,000 population during the outbreak period ($p < 0.001$) (Table 2). Compared

with the non-outbreak period, the age-adjusted mortality rate increased among men by 300% ($p < 0.001$) and among women by 50% ($p < 0.001$) in the outbreak period. Similarly, the age-adjusted hepatitis A mortality rate increased significantly ($p < 0.001$) over time for all age categories ≥ 18 years old, with the largest change in rate occurring among 40–49-year olds (250%) and the smallest change in rate occurring among ≥ 70 -year olds (89%). The age-adjusted mortality rate increased 150% for non-Hispanic White persons ($p < 0.001$) from the non-outbreak period to the outbreak period, remained steady for non-Hispanic Black ($p = 0.646$) and Hispanic ($p = 0.373$) persons, and declined 33% for Asian and Pacific Islander persons ($p = 0.259$).

Among decedents with hepatitis A listed, the proportion of decedents with hepatitis A recorded as the underlying cause (rather than the contributing cause) increased from 33.1% during the non-outbreak period to 48.2% during the outbreak-period (Table 1). When hepatitis A was listed as a contributing cause of death, rather than as the underlying cause of death, mental and behavioural disorders were more frequently listed as an underlying cause of death in the outbreak period (4.6%) than during the non-outbreak period (1.6%; $p = 0.044$). There were no other significant differences in underlying cause of death between the two periods. However, the mental and behavioural disorder estimates are considered unreliable based on NCHS standards because the death count was < 20 in both the non-outbreak and outbreak periods.

The median (interquartile range [IQR]) age at death for hepatitis A-listed decedents was significantly younger during the outbreak period (62 years [IQR 53–73]) than during the non-outbreak period (64 years [IQR 56–77], $p < 0.001$) (Table 3). The median age at hepatitis A-listed death was 61 years for males in both periods, but decreased significantly for females from 72 years (IQR 58–83) during the non-outbreak period to 66 years (IQR 53–77) during the outbreak period ($p < 0.001$). Non-Hispanic White persons had a significantly younger median age at death during the outbreak period (61 years [IQR 53–72]) than during the non-outbreak period (66 years [IQR 57–80], $p < 0.001$).

The median (IQR) age at death among decedents with hepatitis A listed as the underlying cause of death declined significantly from the non-outbreak period (70 years [IQR 59–82]) to the outbreak period (61 years [IQR 52–73], $p < 0.001$) (Table 3). When hepatitis A was listed as a contributing cause of death, rather than as the underlying cause, the median age at death significantly ($p < 0.05$) decreased by at least 5 years from the non-outbreak period to the outbreak period among the following underlying causes of death: hepatitis C; HBV, HCV or HIV coinfection; and mental and behavioural disorders. The predominant mental and behavioural disorder underlying the cause of death codes that were observed shifted from those related to dementia during the non-outbreak period to those related to drug and alcohol use during the outbreak period.

The median age at hepatitis A-listed death in the United States during the outbreak period was 62 (IQR 53–73) years, which was significantly younger than the median age at death among decedents without hepatitis A listed as a COD (76 years [IQR 64–86], $p < 0.001$) (Table 4). Hepatitis A-listed decedents had younger median age at death compared with decedents without hepatitis A listed as a cause of death for all underlying cause of death

categories examined except for the injury, trauma and poisoning category. The difference was statistically significant ($p < 0.05$) for the following underlying cause of death categories: hepatitis B; hepatitis C; HBV, HCV or HIV coinfection; liver cancer; mental and behavioural disorders; diseases of the circulatory, respiratory, digestive (non-liver) systems; diseases of the liver, non-alcohol-related; and 'other' underlying cause of death.

During the outbreak period, the highest number (225) and age-adjusted rate (0.06 [95% CI, 0.05–0.07] deaths per 100,000 population) of hepatitis A-listed deaths occurred in 2019, while the lowest number (91) and rate (0.02 [95% CI, 0.02–0.03] deaths per 100,000 population) occurred in 2017 (Table 5). The age-adjusted mortality rate during the outbreak period also peaked in 2019 for several subpopulations, including males, decedents aged ≥ 40 years, and non-Hispanic White decedents. During each year of the outbreak period, the age-adjusted mortality rate among men was over two times the rate among women. In general, during each outbreak year, the proportion and rate of hepatitis A-listed deaths increased with increasingly older age group categories. Decedents aged ≥ 70 years accounted for the highest proportion and mortality rate of hepatitis A-listed deaths by age group for each of the outbreak years except 2019, when decedents aged 60–69 years accounted for the highest proportion and an equal mortality rate. Decedents aged < 40 years accounted for $< 10\%$ of hepatitis A-listed deaths in each of the outbreak years. Non-Hispanic White decedents accounted for $> 75\%$ of hepatitis A-listed deaths annually during 2017–2021.

3 | Discussion

In this cross-sectional analysis of hepatitis A-listed deaths in the United States during non-outbreak and outbreak periods, we found that decedents with hepatitis A-listed on the death certificate were most commonly men, aged ≥ 60 years, and non-Hispanic White during both the non-outbreak (2011–2015) and outbreak (2017–2021) periods. Overall, the hepatitis A-listed age-adjusted mortality rate increased 150% and the number of deaths more than doubled from the non-outbreak period to the outbreak period. The median age at death for hepatitis A-listed decedents was significantly younger during the outbreak period (62 years) compared with both the median age at death for hepatitis A-listed decedents during the non-outbreak period (64 years) and for decedents without hepatitis A listed as a cause of death during the outbreak period (76 years).

Our analysis reinforces results from prior studies that older age is associated with hepatitis A mortality [4, 17–20]. During both the non-outbreak and outbreak periods, the ≥ 70 -year-old age category accounted for the highest percentage of hepatitis A-listed deaths and the highest mortality rates overall. Because of changes in the epidemiology of hepatitis A in the United States after the introduction of hepatitis A vaccines in 1996 and universal childhood vaccination in 2006, susceptibility to HAV infection in older adult age groups (that are at increased risk for serious consequences of HAV infection, including death) has increased over time [9]. The association of older age with hepatitis A mortality is observed in the US MCOD data—for the entire analysis period, the hepatitis A mortality rate increased by increasing age category among all adults. During the outbreak period of 2017–2021, approximately 58% of hepatitis A-listed decedents were aged ≥ 60 years despite a report

indicating that <10% of all hepatitis A patients linked to the recent outbreaks associated with person-to-person transmission during 2016–2020 were aged ≥ 60 years [6].

With the exception of age, the characteristics of hepatitis A-listed decedents during the outbreak period generally reflected the characteristics of outbreak-associated hepatitis A cases involved in the recent hepatitis A outbreaks associated with person-to-person transmission. Sixty-two per cent of outbreak-associated cases were male, compared to 68% of hepatitis A-listed decedents; 81% of outbreak-associated cases were White (ethnicity not available) while 85% of hepatitis A-listed decedents were non-Hispanic White; and 31% of outbreak-associated cases were coinfecting with HBV or HCV, compared with 28% of hepatitis A-listed decedents with HBV, HCV or HIV coinfection listed as a cause of death [6]. Similarly, the highest number (225) and age-adjusted rate (0.06 [95% CI, 0.05–0.07] deaths per 100,000 population) of hepatitis A-listed deaths occurred in 2019, the same year when cases peaked during the outbreaks [3].

Our findings are subject to limitations. First, the analysis utilised MCOD data which are predicated on clinician judgement regarding the comparative role and importance that conditions played in contributing to death. Studies have demonstrated that death certificates are subject to high rates of error [21–23]. Medical record validation studies have shown that vital statistics mortality data underestimate the true mortality burden of infections generally, and viral infections causing hepatitis B and hepatitis C specifically [24–26]. A recent death certificate analysis found that hepatitis A was documented as an underlying or contributing cause of death on only 60% of death certificates from decedents whose deaths were considered hepatitis A outbreak-related by state health departments [13]. Second, racial and ethnic misclassification is common on death certificates [27], which could have led to an underestimate of hepatitis A-listed deaths among certain racial/ethnic minority groups. Third, the number of deaths used to calculate percentages and rates was small, which reduced the stability and reliability of some of these estimates when stratified by the characteristic groups examined in our analysis. Fourth, the ‘other’ underlying cause of death category included ICD-10 codes for COVID-19, which might at least partially account for the increase observed in ‘other’ listed as the underlying cause of death when hepatitis A was listed as a contributing cause of death from the non-outbreak period (prior to the COVID-19 pandemic) to the outbreak period. Finally, the US Census Bureau, in collaboration with NCHS, started transitioning from using bridged race categories to single/multiple race categories for both the MCOD data and population estimates in 2018 and was fully transitioned in 2021 for mortality rate calculations [28, 29]. Because our analysis included this transition period and bridged race and single/multiple race categories are not directly comparable, we were unable to present race/ethnicity data in a consistent manner throughout the analysis and had to adjust how race/ethnicity data were presented in the tables.

Over the course of widespread community outbreaks that occurred during 2017–2021, hepatitis A-listed decedents died at a median age that was 14 years younger than that of the general US population without hepatitis A listed as a cause of death. Hepatitis A is a vaccine-preventable disease. Safe and highly effective vaccines have been recommended in the United States since 1996 for adults at increased risk for HAV infection or severe disease

from HAV infection (e.g., people who use drugs, men who have sex with men, international travellers and people with chronic liver disease), and since 2006 for all children aged 12–23 months [30]. During the recent outbreaks, the Advisory Committee on Immunization Practices (ACIP) expanded the indications for adult hepatitis A vaccination to include people experiencing homelessness and people living with HIV [30, 31]. According to a recent National Health and Nutrition Examination Survey analysis, during 2015–March 2020, more than 60% of US-born adult participants aged ≥ 30 years were susceptible to HAV infection [9]. Given the increased susceptibility to HAV infection among adults and the higher likelihood of severe outcomes from HAV infection among older adults, efforts are needed to optimise vaccination of medically underserved populations that are currently recommended to receive hepatitis A vaccination to prevent additional premature hepatitis A deaths.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

The data that support the findings of this study are available in Multiple Cause of Death data from the National Vital Statistics System at: <https://www.cdc.gov/nchs/nvss/deaths.htm>. These data were derived from the following resources available in the public domain: <https://www.cdc.gov/nchs/nvss/deaths.htm>.

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TABLE 1 |

Comparison of sociodemographic characteristics, coinfection and underlying causes of death during 2011–2015 versus 2017–2021 among decedents with hepatitis A listed as a cause of death, United States.^a

	Non-outbreak period (2011–2015)		Outbreak period (2017–2021)	
	Number	Proportion (%)	Number	Proportion (%)
Total	369	100.0	801	100.0
Sex				
Female	156	42.3	255	31.8
Male	213	57.7	546	68.2
Age at death				
0–17	1	0.3 ^b	2	0.2 ^b
18–39	8	2.2 ^b	49	6.1
40–49	33	8.9	111	13.9
50–59	96	26.0	178	22.2
60–69	90	24.4	210	26.2
≥70	141	38.2	251	31.3
Race and ethnicity ^c				
American Indian/Alaska Native, NH	5	1.4 ^b	8	1.2 ^b
Asian/Pacific Islander, NH ^d	24	6.5	17	2.6 ^b
Black, NH	42	11.4	43	6.5
White, NH	254	69.0	560	84.6
Hispanic	43	11.7	34	5.1
Place of death				
Inpatient	169	45.8	484	60.4
Outpatient or emergency room	27	7.3	25	3.1
Decedent's home	78	21.1	130	16.2
Hospice facility	39	10.6	88	11.0
Nursing home/long term care	40	10.8	47	5.9
Other ^e	16	4.3 ^b	27	3.4
HBV, HCV or HIV coinfection				

	Non-outbreak period (2011–2015)		Outbreak period (2017–2021)	
	Number	Proportion (%)	Number	Proportion (%)
Yes	143	38.8	227	28.3
No	226	61.2	574	71.7
Hepatitis A COD status ^f				
Listed as the underlying COD	122	33.1	386	48.2
Listed as a contributing COD	247	66.9	415	51.8
Underlying COD when hepatitis A was listed as a contributing COD ^g				
Hepatitis B	2	0.8 ^b	6	1.4 ^b
Hepatitis C	15	6.1 ^b	15	3.6 ^b
Other or unspecified viral hepatitis	0	0 ^b	0	0 ^b
HIV	5	2.0 ^b	9	2.2 ^b
Hepatitis B, Hepatitis C or HIV	22	8.9	30	7.2
Cancer, excluding liver cancer	45	18.2	63	15.2
Liver cancer	20	8.1	33	8.0
Diabetes mellitus	10	4.0 ^b	12	2.9 ^b
Mental and behavioural disorders	4	1.6 ^b	19	4.6 ^b
Diseases of the circulatory system	38	15.4	53	12.8
Diseases of the respiratory system	15	6.1 ^b	20	4.8
Diseases of the digestive system, non-liver	5	2.0 ^b	10	2.4 ^b
Diseases of the liver, alcohol-related	31	12.6	60	14.5
Diseases of the liver, non-alcohol-related	22	8.9	25	6.0
Diseases of the genitourinary system	9	3.6 ^b	15	3.6 ^b
Injury, trauma, poisoning				
Any	6	2.4 ^b	18	4.3 ^b
Drug overdose	4	1.6 ^b	11	2.7 ^b
Other	20	8.1	57	13.7
COVID-19	N/A	N/A	17	4.1 ^b

Abbreviations: COD, cause of death; HBV, hepatitis B virus; HCV, hepatitis C virus; NH, non-Hispanic.

^aData source: Multiple Cause of Death data, National Vital Statistics System, CDC.

^bPer National Center for Health Statistics data presentation standards, estimated proportions are considered unreliable when the death count is <20.

^cThe bridged race variable was used during 2011–2020. For the 2017–2021 period, we excluded race/ethnicity data for decedents who died in 2021 due to the full transition to the single/multiple race variable in 2021 which is not directly comparable with the bridged race variable used throughout the remainder of the analysis period.

^dIncludes other or multiple Asian and other or multiple Pacific Islander.

^eIncludes dead on arrival.

^fICD-10 codes used to define each COD category are provided in Table S1.

^gThe denominator used to calculate the percent distribution for the underlying COD categories was 247 for the non-outbreak period and 415 for the outbreak period. Percentages sum to 100% when excluding the ‘Hepatitis B, Hepatitis C or HIV’, ‘Injury, trauma, poisoning—Drug overdose’ and ‘Other—COVID-19’ rows, which are already accounted for in other rows in the table.

TABLE 2 |

Comparison of average annual age-adjusted mortality rate by sociodemographic characteristics during 2011–2015 versus 2017–2021 among decedents with hepatitis A listed as a cause of death, United States.^a

	Non-outbreak period (2011–2015)		Outbreak period (2017–2021)		<i>p</i> ^b	Change in rate, %
	Number	Average annual age-adjusted mortality rate (95% CI) ^c	Number	Average annual age-adjusted mortality rate (95% CI) ^c		
Total	369	0.02 (0.02–0.02)	801	0.05 (0.05–0.06)	<0.001	150.0
Sex						
Female	156	0.02 (0.01–0.02)	255	0.03 (0.03–0.04)	<0.001	50.0
Male	213	0.02 (0.02–0.03)	546	0.08 (0.07–0.08)	<0.001	300.0
Age at death						
0–17	1	0.00 (0.00–0.00) ^c	2	0.00 (0.00–0.00) ^c	0.451	—
18–39	8	0.00 (0.00–0.00) ^c	49	0.01 (0.01–0.02)	<0.001	—
40–49	33	0.02 (0.01–0.02)	111	0.07 (0.06–0.08)	<0.001	250.0
50–59	96	0.04 (0.04–0.05)	178	0.10 (0.09–0.12)	<0.001	150.0
60–69	90	0.05 (0.04–0.07)	210	0.14 (0.12–0.16)	<0.001	180.0
≥70	141	0.09 (0.08–0.11)	251	0.17 (0.15–0.20)	<0.001	88.9
Race and ethnicity ^d						
American Indian/Alaska Native, NH	5	0.04 (0.01–0.11) ^c	8	0.08 (0.03–0.16) ^c	0.306	100.0
Asian/Pacific Islander, NH ^e	24	0.03 (0.02–0.05)	17	0.02 (0.01–0.03) ^c	0.259	–33.3
Black, NH	42	0.02 (0.02–0.03)	43	0.02 (0.02–0.03)	0.646	0.0
White, NH	254	0.02 (0.02–0.02)	560	0.05 (0.05–0.06)	<0.001	150.0
Hispanic	43	0.02 (0.02–0.03)	34	0.02 (0.01–0.03)	0.373	0.0

Note: –, unable to calculate change in rate given initial rate of 0.00. Bold values indicate that the *p*-value was statistically significant at the *p* < 0.05 level.

Abbreviations: CI, confidence interval; NH, non-Hispanic.

^aData source: Multiple Cause of Death data, National Vital Statistics System, CDC.

^bZ-score *p*-values were calculated to assess if the mortality rate during the outbreak (2017–2021) period was significantly different from the mortality rate during the non-outbreak (2011–2015).

^cMortality rates are per 100,000 population. Mortality rates overall and by sex and race/ethnicity were adjusted to the age distribution of the 2000 US standard population. 95% CIs are based on a *y* distribution. Per National Center for Health Statistics data presentation standards, estimated rates are considered unreliable when the death count is <20.

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The bridged race variable was used during 2011–2020. For the 2017–2021 period, we excluded race/ethnicity data for decedents who died in 2021 due to the full transition to the single/multiple race variable in 2021 which is not directly comparable with the bridged race variable used throughout the remainder of the analysis period.
p_e Includes other or multiple Asian and other or multiple Pacific Islander.

TABLE 3 |

Median age at death by sociodemographic characteristics, coinfection, and underlying causes of death during 2011–2015 versus 2017–2021 among decedents with hepatitis A listed as a cause of death, United States.^a

	Non-outbreak period (2011–2015)		Outbreak period (2017–2021)		<i>p</i> ^b
	Age at death, median (IQR)		Age at death, median (IQR)		
Total	64 (56–77)		62 (53–73)		<0.001
Sex					
Female	72 (58–83)		66 (53–77)		<0.001
Male	61 (55–70)		61 (52–71)		0.443
Race and ethnicity ^c					
American Indian/Alaska Native, NH	50 (40–58)		54 (41–68)		0.714
Asian/Pacific Islander, NH ^d	69 (62–81)		69 (63–84)		0.587
Black, NH	61 (57–71)		62 (50–72)		0.487
White, NH	66 (57–80)		61 (53–72)		<0.001
Hispanic	59 (49–70)		56 (45–68)		0.579
Place of death					
Inpatient	66 (56–80)		60 (50–70)		<0.001
Outpatient or emergency room	57 (49–63)		58 (47–66)		0.985
Decedent's home	61 (56–67)		67 (58–77)		0.023
Hospice facility	69 (60–77)		66 (57–75)		0.171
Nursing home/long term care	75 (60–86)		72 (61–86)		0.821
Other ^e	60 (51–72)		68 (49–82)		0.339
HBV, HCV or HIV coinfection					
Yes	59 (55–67)		59 (49–65)		0.006
No	69 (58–82)		65 (55–76)		<0.001
Hepatitis A COD status ^f					
Listed as the underlying COD	70 (59–82)		61 (52–73)		<0.001
Listed as a contributing COD	62 (55–72)		63 (53–73)		0.597
Underlying COD when hepatitis A was listed as a contributing COD					
Hepatitis B	66 (51–81)		49 (41–54)		0.317

	Non-outbreak period (2011–2015)		Outbreak period (2017–2021)		<i>p</i> ^b
	Age at death, median (IQR)		Age at death, median (IQR)		
Hepatitis C	60 (56–79)		55 (46–60)		0.032
Other or unspecified viral hepatitis	—		—		—
HIV	43 (42–58)		48 (44–60)		0.549
Hepatitis B, Hepatitis C or HIV	59 (54–71)		54 (44–60)		0.042
Cancer, excluding liver cancer	65 (56–78)		71 (64–77)		0.047
Liver cancer	64 (58–72)		66 (61–72)		0.620
Diabetes mellitus	62 (58–70)		67 (52–82)		0.530
Mental and behavioural disorders	87 (72–93)		49 (42–60)		0.028
Diseases of the circulatory system	65 (55–81)		66 (55–81)		0.678
Diseases of the respiratory system	66 (58–72)		66 (60–74)		0.605
Diseases of the digestive system, non-liver	59 (50–60)		59 (53–70)		0.759
Diseases of the liver, alcohol-related	56 (45–61)		56 (47–63)		0.785
Diseases of the liver, non-alcohol-related	62 (55–72)		57 (49–65)		0.175
Diseases of the genitourinary system	81 (76–88)		70 (63–82)		0.073
Injury, trauma, poisoning					
Any	58 (51–61)		54 (44–69)		0.764
Drug overdose	56 (50–62)		44 (39–60)		0.169
Other	62 (56–70)		68 (52–76)		0.557
COVID-19	N/A		69 (57–76)		N/A

Note: Bold values indicate that the *p*-value was statistically significant at the *p* < 0.05 level.

Abbreviations: COD, cause of death; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; NH, non-Hispanic.

^aData source: Multiple Cause of Death data, National Vital Statistics System, CDC.

^bDifferences in the median age at hepatitis A-listed death between non-outbreak (2011–2015) and outbreak (2017–2021) periods were assessed using the Kruskal–Wallis test.

^cThe bridged race variable was used during 2011–2020. For the 2017–2021 period, we excluded race/ethnicity data for decedents who died in 2021 due to the full transition to the single/multiple race variable in 2021 which is not directly comparable with the bridged race variable used throughout the remainder of the analysis period.

^dIncludes other or multiple Asian and other or multiple Pacific Islander.

^eIncludes dead on arrival.

^fICD-10 codes used to define each COD category are provided in Table S1.

TABLE 4 |

Median age at death among decedents with and without hepatitis A-listed deaths, United States, 2017–2021.^a

Cause of death	Decedents without hepatitis A-listed death				Decedents with hepatitis A-listed death				<i>p</i> ^b
	Number	Percent	Age at death, median (IQR)		Number	Percent	Age at death, median (IQR)		
Total	15,354,705	100	76 (64–86)		801	100	62 (53–73)		<0.001
Hepatitis A COD status									
Listed as the underlying COD	0	0	N/A		386	48.2	61 (52–73)		—
Listed as a contributing COD	0	0	N/A		415	51.8	63 (53–73)		—
Underlying COD ^c									
Hepatitis B	2182	0.0	62 (53–71)		6	0.7 ^d	49 (41–54)		0.044
Hepatitis C	18,666	0.1	62 (57–67)		15	1.9 ^d	55 (46–60)		0.001
Other or unspecified viral hepatitis	1098	0.0	64 (54–74)		0	—	—		—
HIV	26,250	0.2	55 (45–62)		9	1.1 ^d	48 (44–60)		0.611
Hepatitis B, Hepatitis C, or HIV	47,098	0.3	58 (50–65)		30	3.7	54 (44–60)		0.019
Cancer, excluding liver cancer	2,935,768	19.1	73 (64–82)		63	7.9	71 (64–77)		0.226
Liver cancer	140,854	0.9	69 (62–78)		33	4.1	66 (61–72)		0.045
Diabetes mellitus	461,627	3.0	72 (63–82)		12	1.5 ^d	67 (52–82)		0.361
Mental and behavioural disorders	689,914	4.5	87 (78–92)		19	2.4 ^d	49 (42–60)		<0.001
Diseases of the circulatory system	4,462,666	29.1	80 (68–89)		53	6.6	66 (55–81)		<0.001
Diseases of the respiratory system	1,353,661	8.8	78 (69–86)		20	2.5	66 (60–74)		0.001
Diseases of the digestive system, non-liver	282,278	1.8	78 (67–87)		10	1.2 ^d	59 (53–70)		0.001
Diseases of the liver, alcohol-related	132,071	0.9	57 (49–64)		60	7.5	56 (47–63)		0.238
Diseases of the liver, non-alcohol-related	173,682	1.1	66 (57–75)		25	3.1	57 (49–65)		0.002
Diseases of the genitourinary system	372,575	2.4	79 (69–87)		15	1.9 ^d	70 (63–82)		0.073
Injury, trauma, poisoning									
Any	1,302,977	8.5	49 (32–67)		18	2.2 ^d	54 (44–69)		0.192
Drug overdose	406,721	2.6	42 (32–54)		11	1.4 ^d	44 (39–60)		0.422
Other	2,998,436	19.5	79 (66–88)		57	7.1	68 (52–76)		<0.001
COVID-19	767,707	5.0	75 (64–84)		17	2.1 ^d	69 (57–76)		0.042

Note: Bold values indicate that the *p*-value was statistically significant at the *p* < 0.05 level.

Abbreviations: CI, confidence interval; COD, cause of death; IQR, interquartile range.

^aData source: Multiple Cause of Death data, National Vital Statistics System, CDC. The denominators used to calculate the percent distribution for the UCOD categories was 15,354,705 for decedents without hepatitis A listed deaths and 801 for decedents with hepatitis A-listed deaths.

^bDifferences in the median age at death between decedents who did not have hepatitis A listed as a COD and decedents who did have hepatitis A listed as a COD were assessed using the Kruskal–Wallis test.

^cICD-10 codes used to define each COD category are provided in Table S1.

^dPer National Center for Health Statistics data presentation standards, estimated proportions are considered unreliable when the death count is <20.

TABLE 5 |

Age-adjusted mortality rates with hepatitis A by sociodemographic characteristics, United States, 2017–2021.^{a,b}

Characteristic	2017			2018			2019			2020			2021		
	No.	%	Rate (95% CI)	No.	%	Rate (95% CI)	No.	%	Rate (95% CI)	No.	%	Rate (95% CI)	No.	%	Rate (95% CI)
Overall	91	100	0.02 (0.02–0.03)	171	100	0.05 (0.04–0.05)	225	100	0.06 (0.05–0.07)	179	100	0.04 (0.04–0.05)	135	100	0.03 (0.03–0.04)
Sex															
Female	28	30.8	0.01 (0.01–0.02)	56	32.7	0.03 (0.02–0.04)	66	29.3	0.03 (0.03–0.04)	59	33.0	0.03 (0.02–0.04)	46	34.1	0.02 (0.02–0.03)
Male	63	69.2	0.04 (0.03–0.05)	115	67.3	0.07 (0.06–0.08)	159	70.7	0.09 (0.07–0.10)	120	67.0	0.06 (0.05–0.08)	89	65.9	0.05 (0.04–0.06)
Age group															
0–17	0	0	—	2	1.2 ^c	0.00 (0.00–0.01) ^c	0	0	—	0	0	—	0	0	—
18–39	7	7.7 ^c	0.01 (0.00–0.01) ^c	14	8.2 ^c	0.01 (0.01–0.02) ^c	10	4.4 ^c	0.01 (0.00–0.02) ^c	12	6.7 ^c	0.01 (0.01–0.02) ^c	6	4.4 ^c	0.01 (0.00–0.01) ^c
40–49	6	6.6 ^c	0.01 (0.01–0.03) ^c	28	16.4	0.07 (0.05–0.10)	44	19.6	0.11 (0.08–0.15)	17	9.5 ^c	0.04 (0.02–0.07) ^c	16	11.9 ^c	0.04 (0.02–0.06) ^c
50–59	18	19.8 ^c	0.04 (0.02–0.07) ^c	39	22.8	0.09 (0.06–0.12)	53	23.6	0.13 (0.09–0.16)	41	22.9	0.10 (0.07–0.13)	27	20.0	0.06 (0.04–0.09)
60–69	24	26.4	0.07 (0.04–0.10)	36	21.1	0.10 (0.07–0.13)	61	27.1	0.16 (0.12–0.21)	53	29.6	0.14 (0.10–0.18)	36	26.7	0.09 (0.06–0.13)
≥70	36	39.6	0.11 (0.07–0.15)	52	30.4	0.15 (0.11–0.19)	57	25.3	0.16 (0.12–0.20)	56	31.3	0.15 (0.12–0.20)	50	37.0	0.13 (0.10–0.18)
Race/ethnicity ^d															
American Indian/Alaska Native, NH	0	0	—	0	0	—	3	1.3 ^c	0.12 (0.02–0.40) ^c	4	2.2 ^c	0.15 (0.04–0.44) ^c	3	2.2 ^c	0.09 (0.02–0.32) ^c
Asian/Native Hawaiian/Pacific Islander, NH ^e	7	7.9 ^c	0.04 (0.01–0.08) ^c	2	1.2 ^c	0.01 (0.00–0.04) ^c	1	0.4 ^c	0.00 (0.00–0.03) ^c	4	2.2 ^c	0.02 (0.01–0.06) ^c	7	5.2 ^c	0.03 (0.01–0.07) ^c
Black, NH	8	9.0 ^c	0.02 (0.01–0.04) ^c	8	4.7 ^c	0.02 (0.01–0.04) ^c	13	5.8 ^c	0.03 (0.02–0.05) ^c	14	7.9 ^c	0.03 (0.02–0.06) ^c	13	9.6 ^c	0.03 (0.02–0.06) ^c
Multiple race, NH	N/A	N/A	N/A	2	1.2 ^c	0.07 (0.01–0.26) ^c	2	0.9 ^c	0.04 (0.00–0.19) ^c	1	0.6 ^c	0.02 (0.00–0.16) ^c	0	0	—
White, NH	69	77.5	0.03 (0.02–0.03)	150	87.7	0.06 (0.05–0.07)	194	86.6	0.08 (0.07–0.09)	146	82.0	0.05 (0.04–0.06)	103	76.3	0.04 (0.03–0.05)

Characteristic	2017			2018			2019			2020			2021		
	No.	%	Rate (95% CI)	No.	%	Rate (95% CI)	No.	%	Rate (95% CI)	No.	%	Rate (95% CI)	No.	%	Rate (95% CI)
Hispanic	5	5.6 ^c	0.01 (0.00–0.03) ^c	9	5.3 ^c	0.02 (0.01–0.04) ^c	11	4.9 ^c	0.02 (0.01–0.05) ^c	9	5.1 ^c	0.02 (0.01–0.04) ^c	9	6.7 ^c	0.02 (0.01–0.04) ^c
Place of death															
Inpatient	59	64.8	N/A	104	60.8	N/A	149	66.2	N/A	94	52.5	N/A	78	57.8	N/A
Outpatient or emergency room	4	4.4 ^c	N/A	1	0.6 ^c	N/A	5	2.2 ^c	N/A	10	5.6 ^c	N/A	5	3.7 ^c	N/A
Decedent's home	9	9.9 ^c	N/A	26	15.2	N/A	28	12.4	N/A	40	22.3	N/A	27	20.0	N/A
Hospice facility	9	9.9 ^c	N/A	18	10.5 ^c	N/A	27	12.0	N/A	20	11.2	N/A	14	10.4 ^c	N/A
Nursing home/long term care	6	6.6 ^c	N/A	15	8.8 ^c	N/A	9	4.0 ^c	N/A	10	5.6 ^c	N/A	7	5.2 ^c	N/A
Other ^f	4	4.4 ^c	N/A	7	4.1 ^c	N/A	7	3.1 ^c	N/A	5	2.8 ^c	N/A	4	3.0 ^c	N/A

Abbreviations: CI, confidence interval; NH, non-Hispanic.

^aData source: Multiple Cause of Death data, National Vital Statistics System, CDC.

^bMortality rates overall and by sex and race/ethnicity are per 100,000 population and were adjusted to the age distribution of the 2000 US standard population. 95% CIs are based on a γ distribution. Rates where the number of deaths is <20 are considered statistically unreliable.

^cPer National Center for Health Statistics data presentation standards, estimated proportions and rates are considered unreliable when the death count is <20.

^dBridged race categories were used for 2017. Single race categories were used for 2018–2021.

^eNative Hawaiians were specifically included in the 2018–2021 single race categories, but not in the 2017 bridged race categories.

^fIncludes dead on arrival.