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County-Level Variation in Hepatitis C Virus Mortality and Trends in the United States, 2005-2017

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BACKGROUND AND AIMS: Since 2013, the national hepatitis C virus (HCV) death rate has steadily declined, but this decline has not been quantified or described on a local level.

APPROACH AND RESULTS: We estimated county-level HCV death rates and assessed trends in HCV mortality from 2005 to 2013 and from 2013 to 2017. We used mortality data from the National Vital Statistics System and used a Bayesian multivariate space–time conditional autoregressive model to estimate age-standardized HCV death rates from 2005 through 2017 for 3,115 U.S. counties. Additionally, we estimated county-level, age-standardized rates for persons <40 and 40+ years of age. We used log-linear regression models to estimate the average annual percent change in HCV mortality during periods of interest and compared county-level trends with national trends. Nationally, the age-adjusted HCV death rate peaked in 2013 at 5.20 HCV deaths per 100,000 persons (95% credible interval [CI], 5.12, 5.26) before decreasing to 4.34 per 100,000 persons (95% CI, 4.28, 4.41) in 2017 (average annual percent change = −4.69; 95% CI, −5.01, −4.33). County-level rates revealed heterogeneity in HCV mortality (2017 median rate = 3.6; interdecile range, 2.19, 6.77), with the highest rates being concentrated in the West, Southwest, Appalachia, and northern Florida. Between 2013 and 2017, HCV mortality decreased in 80.0% (n = 2,274) of all U.S. counties with a reliable trend estimate, with 25.8% (n = 803) of all counties experiencing a decrease larger than the national decline.

CONCLUSIONS: Although many counties have experienced a shift in HCV mortality trends since 2013, the magnitude and composition of that shift have varied by place. These data provide a better understanding of geographic differences in HCV mortality and can be used by local jurisdictions to evaluate HCV mortality in their areas relative to surrounding areas and the nation. (Hepatology 2021;74:582-590).

In the United States, infection with hepatitis C virus (HCV) is the leading cause of morbidity and mortality from liver disease and was listed as an underlying or contributing cause of death in over 15,000 deaths in 2018.[1] From 1999 to 2013, the national HCV-associated death rate increased each year,[2] and by 2013, the annual number of deaths attributable to HCV infection outnumbered deaths from all other notifiable infectious diseases combined.[3] Although data from the National Vital Statistics System indicate that the national HCV death rate has declined since 2013,[4] there has not been a trend analysis that quantifies change in HCV mortality since 2013, to our knowledge.

In recent years, there have been shifts in the epidemiological nature of the HCV epidemic, advancement in treatment options, and changes in public health strategies, all of which are likely to impact HCV mortality. Although HCV infections are still disproportionately concentrated among adults born between

Abbreviations: CDC, Centers for Disease Control and Prevention; CI, credible interval; HCV, hepatitis C virus; MCMC, Markov chain Monte Carlo.

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1945 and 1965,[5] rising acute HCV incidence rates among adults <40 years of age[6] have led to the emergence of a bimodal epidemic by age group. Despite the substantial prevalent burden and recent rise in HCV incidence rates, the availability of accurate diagnostic testing and curative therapy has the public health community targeting the elimination of HCV infection as a public health problem in the United States.[7,8] In the United States, strategic plans by Centers for Disease Control and Prevention (CDC)[9] and the Department of Health and Human Services[10] have specifically identified reductions in the national HCV death rate as an indicator to monitor progress toward achieving these goals. For example, CDC's Viral Hepatitis National Progress Report 2020 Goal was to reduce the national age-adjusted HCV death rate below 4.17 per 100,000 persons[4] by 2020.

Although there is evidence the epidemiology of hepatitis C differs by location, small-area spatial differences in HCV mortality are not well described.[11] Of the estimated 2.4 million adults who were living with a chronic HCV infection during 2013-2016,[12] over half lived in just nine states.[13] Analysis of newly reported acute and chronic HCV cases from surveillance data has shown dramatic regional differences in HCV incidence trends.[14] To our knowledge, HCV-related death rates and mortality trends have not been systematically characterized on a local level. Previous research on small-area stroke[15] and heart disease mortality[16,17] has demonstrated that merely describing changes in national death rates may conceal important trends occurring at the local level. Furthermore, many public health initiatives are implemented at the county or local level, and describing geographic disparities in HCV mortality can help inform the use of available interventions.

This analysis had two primary objectives. First, we aimed to estimate annual county-level HCV death rates between 2005 and 2017. Second, to better understand local changes in HCV mortality, we assessed county-level trends from 2005 to 2013 and from 2013 to 2017.

Participants and Methods

DATA SOURCE

Data are from the National Vital Statistics System Detailed Multiple Cause of Death microdata files.[18] All data were obtained under a data use agreement with the National Center for Health Statistics, and analysis was conducted before 2018 data were released.[19] Using codes from the *International Classification of Diseases, Tenth Revision* (ICD-10),[20] we identified the annual number of deaths that listed HCV (ICD-10 codes B17.1 and B18.2) as a "multiple cause of death" in the record axis fields for each county and demographic group of interest during the period from 2000 to 2017. Annual county-level deaths were tabulated for all 36 combinations of the following demographic groups: race (Black, White, other), sex (male, female), and age (0-19 years, 20-29 years, 30-39 years, 40-49 years, 50-59 years, and 60+ years).[21] We used National Center for Health Statistics bridged-race, annual, county-level population estimates[22] for population denominators in all death rates. Because of changes in county definitions over this time period (i.e., the creation and consolidation of counties), we combined counties to create a common set of 3,115 counties in this analysis. Institutional review board approval was not required because this analysis only

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used publicly available, restricted-use, county-level data.

ESTIMATING DEATH RATES AND PERCENT CHANGE

We used a Bayesian multivariate space–time conditional autoregressive model to model the annual number of HCV deaths for each group in each county. The details of this model, which has primarily been used to estimate stroke[15] and heart disease death rates,[16,23] have been described.[24] Briefly, it is a conditional autoregressive model for spatially referenced count data that incorporates correlations across space, time, and demographic groups. By iteratively estimating parameters and shrinking the random effects for each county toward values for neighboring counties (defined using first-order queen contiguity) and years, the Bayesian model produces estimates that are more precise than those that would be produced from other small-area analysis methods that do not incorporate information from neighboring counties.[25] Each model was fit with a Markov chain Monte Carlo (MCMC) algorithm using user-developed code in R version 3.5.0 (R Foundation for Statistical Computing).

We aggregated the modeled counts to estimate the overall and age-stratified (<40 years and 40+ years) county-level HCV death rates for the years 2005 through 2017. Although we incorporated data from 2000 to 2017, we limited results to years after 2005 because HCV infections are disproportionately concentrated among persons born between 1945 and 1965,[5] and all persons in this high-burden cohort were 40+ years of age from 2005 onward. We estimated county-level rates using the medians of the posterior MCMC distributions, and the 2.5th and 97.5th percentiles were used to calculate 95% credible intervals (CIs). Additionally, county-level counts were aggregated to estimate national HCV death rates for each year. To facilitate comparison across place and time, all estimated rates were standardized to the age distribution of the 2000 U.S. standard population.[26]

To calculate trends, we included the estimated county rates for all years of interest in separate log-linear regression models for each MCMC iteration and each county. The average annual percent change was estimated as the median trend of all MCMC iterations within each county, and the corresponding 95% CI was calculated using the 2.5th- and 97.5th-percentile values. National data has shown that HCV death rates across the country were increasing before 2013 and have declined each year thereafter.[4] Therefore, we estimated national and county-level HCV mortality trends for 2005-2013 and 2013-2017. Furthermore, we compared county-level trends from 2013 to 2017 with the estimated national decline during that time period and categorized counties into the following four groups: decrease faster than the national trend (i.e., the average annual percent change is below the lower bound of the national 95% CI), decrease similar to the national trend (i.e., the average annual percent change is within the 95% CI of national decline), decrease slower than the national trend (i.e., the average annual percent change is between the upper bound of the 95% CI of the national decline and zero), and increase (i.e., the average annual percent change is greater than zero). By using the posterior distributions to calculate the percent change and compare it against the national average, we were able to account for the uncertainty in the underlying rates.

To assess spatiotemporal trends in HCV mortality, we mapped overall and age-stratified (<40 years and 40+ years) 2017 HCV death rates by quintiles. Additionally, we mapped the overall county-level average annual percent change in HCV death rates from 2005 to 2013 and from 2013 to 2017 as well as the HCV mortality trends relative to the national decline from 2013 to 2017.

DATA SUPPRESSION

Any county-level rate that had a CI width larger than the point estimate was considered unreliable.[27] If a county had one or more unreliable HCV death-rate values between 2005 and 2017, estimated rates and trends for that county were not reported. Additionally, if a county had one or more unreliable death-rate values for either age group in 2017, all age-stratified rates were suppressed for that county. To protect privacy, National Center for Health Statistics data-suppression standards require the suppression of any tabulated crude counts that total less than 10. In this work, we do not report crude counts and only report modeled estimates so that individuals are not identifiable in these data. These criteria resulted in reliable rates for a common set of counties for all years of overall rates (n = 2,839, 91.1% of all counties) and a common set of counties for all age-stratified 2017 rates (n = 2,570, 82.5%).

Results

In 2017, the estimated national age-adjusted HCV death rate was 4.34 per 100,000 persons (95% CI, 4.28, 4.41; Table 1). From 2005 to 2017, the overall national HCV death rate was highest in 2013 at 5.20 HCV deaths per 100,000 persons (95% CI, 5.12, 5.26). On average, national HCV mortality increased by 3.17% each year (95% CI, 3.00, 3.34) from 2005 to 2013 before decreasing 4.69% each year (4.33, 5.01) from 2013 to 2017. For all years, the HCV death rate was much higher among adults of 40+ years of age (9.77 per 100,000 persons in 2017; 95% CI, 9.65, 9.94) compared with persons<40 years of age (0.23 per 100,000 persons; 95% CI, 0.22, 0.24).

COUNTY-LEVEL HCV DEATH RATES AND TRENDS

The overall median county-level HCV death rate was lower than the national average (2017 median rate = 3.66; interdecile range, 2.19, 6.77). In 2017, 61.0% (n = 1,732) of counties with reliable rate estimates had an age-adjusted HCV death rate lower than the National Progress Report 2020 Goal of 4.17 per 100,000 persons[4] (Supporting Table S1). The spatial pattern of HCV death rates in 2017 indicated that the highest rates are primarily concentrated in the West, Southwest, Appalachia, and northern Florida (Fig. 1). Stratifying the 2017 HCV death rates by age group reveals the emergence of some key spatial trends. The highest burden of HCV death rates among persons <40 years of age occurred in New Mexico, Oklahoma, and Appalachia, primarily in a geographic band that stretches from Tennessee through Pennsylvania (Fig. 2). In contrast, the highest burden of HCV deaths among adults who were 40+ years of age were concentrated along the west coast in and in the Southwest.

Of the 2,839 counties with reliable rate estimates for all years, HCV mortality increased in 95.3% (n = 2,705) of counties from 2005 to 2013. Counties that did not experience an increase in HCV death rates during this time frame were primarily centered around urban areas, such as St. Louis; New Orleans; Miami; Washington, DC; and New York City

TABLE 1. Estimated Age-Standardized National and County-Level Hepatitis C Death Rates and Percent Change, United States, 2005-2017

	National		County-Level	
	Rate or Change	95% CI	Median	IDR
Rate				
All ages				
2005 rate (per 100,000)	3.83	3.77, 3.89	2.93	1.75, 5.03
2013 rate (per 100,000)	5.20	5.12, 5.26	4.12	2.52, 7.40
2017 rate (per 100,000)	4.34	4.28, 4.41	3.66	2.19, 6.77
<40 years old				
2005 rate (per 100,000)	0.27	0.26, 0.27	0.24	0.19, 0.33
2013 rate (per 100,000)	0.18	0.17, 0.19	0.19	0.15, 0.25
2017 rate (per 100,000)	0.23	0.22, 0.24	0.24	0.18, 0.36
40+ years old				
2005 rate (per 100,000)	8.56	8.40, 8.68	6.49	3.80, 11.27
2013 rate (per 100,000)	11.84	11.65, 11.98	9.33	5.65, 16.83
2017 rate (per 100,000)	9.77	9.65, 9.94	8.19	4.80, 15.35
Trends (all ages)				
AAPC				
2005 to 2013	+3.17	+3.00, +3.34	+4.11	+0.97, +7.19
2013 to 2017	–4.69	–5.01, –4.33	–3.09	–7.36, +1.92
Absolute change (per 100,000 persons)				
2005 to 2013	+1.37	+1.26, +1.46	+1.13	+0.38, +2.85
2013 to 2017	–0.86	–0.93, –0.76	–0.40	–1.30, +0.37

Abbreviations: AAPC, average annual percent change; IDR, interdecile range (10th and 90th percentiles).

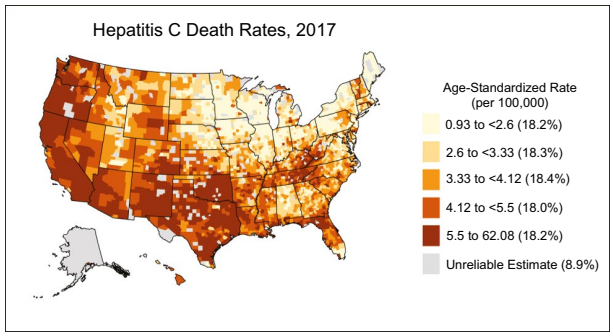

FIG. 1. Age-standardized HCV death rates, by U.S. county, 2017. Any counties that have at least one unreliable rate estimate between 2005 and 2017 are suppressed as unreliable.

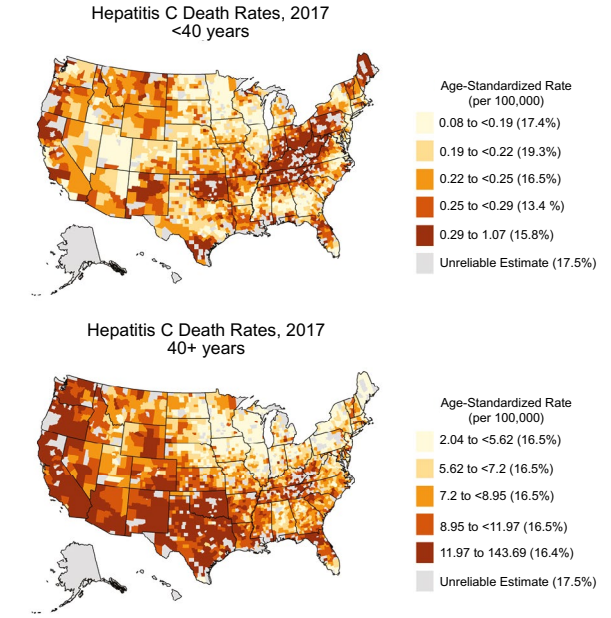

FIG. 2. Age-standardized HCV death rates by age group, U.S. counties, 2017. Any counties that have an unreliable 2017 rate for either age group are suppressed as unreliable in both panels. All rates are age-adjusted to the 2000 U.S. standard population. Scales for each map differ.

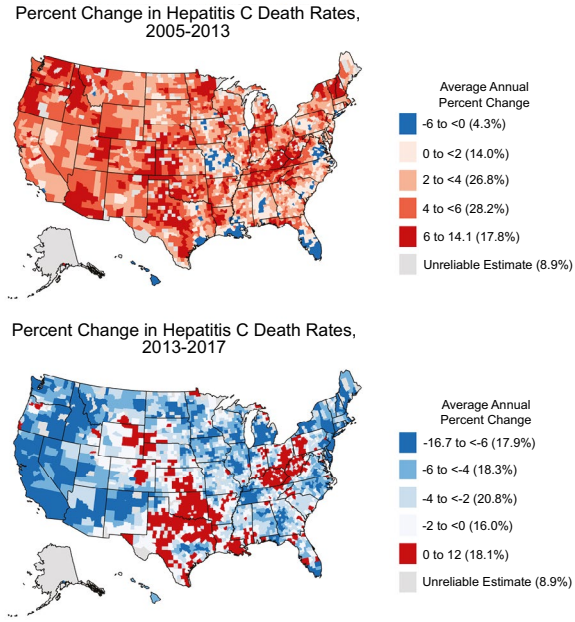

FIG. 3. Average annual percent change in HCV death rates, all ages, by U.S. county. Any counties that have at least one unreliable rate estimate between 2005 and 2017 are suppressed as unreliable. All rates are age-adjusted to the 2000 U.S. standard population. Scales for each map differ.

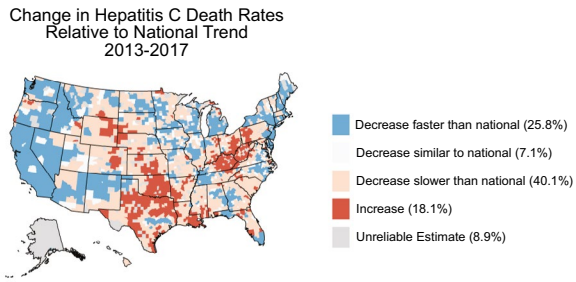

FIG. 4. Change in county-level HCV death rates relative to the national trend, 2013-2017. Counties that have an estimated average annual percent change that is within the 95% CI of the estimated national average annual percent change (−5.01% to −4.33%) are categorized as decreasing at a pace similar to that of the national trend. To present a consistent set of counties, any counties that have at least one unreliable rate estimate between 2000 and 2017 are suppressed as unreliable. All rates are age-adjusted to the 2000 U.S. standard population. Values inside parentheses indicate the percent of counties that are included in each category.

(Fig. 3). In contrast, 80.0% (n = 2,274) of counties with a reliable trend estimate experienced a decrease in HCV mortality between 2013 and 2017. A total of 803 counties (25.8%) had a decline in HCV mortality that was faster than the national decline (average annual percent change between 4.33% and 5.01%) during this time period (Fig. 4). Many of these counties were located in the Plains states, in Michigan and Wisconsin, and in the Northeast. Counties that had an increase in HCV mortality during this time frame were concentrated in Oklahoma, Texas, and

parts of Appalachia, stretching from Kentucky up through western Pennsylvania. The majority of urban areas that experienced a decrease in HCV mortality from 2005 to 2013 continued that trend from 2013 to 2017. The notable exceptions are the counties around New Orleans, in which HCV death rates increased between 2013 and 2017.

Figure 5 displays a hexamap of the estimated national HCV death rates per 100,000 persons to visualize age–period–cohort trends.[28] The figure contains three axes representative of age (in single years), birth cohort, and year. The highest HCV death rates are concentrated among persons born between 1945 and 1960.

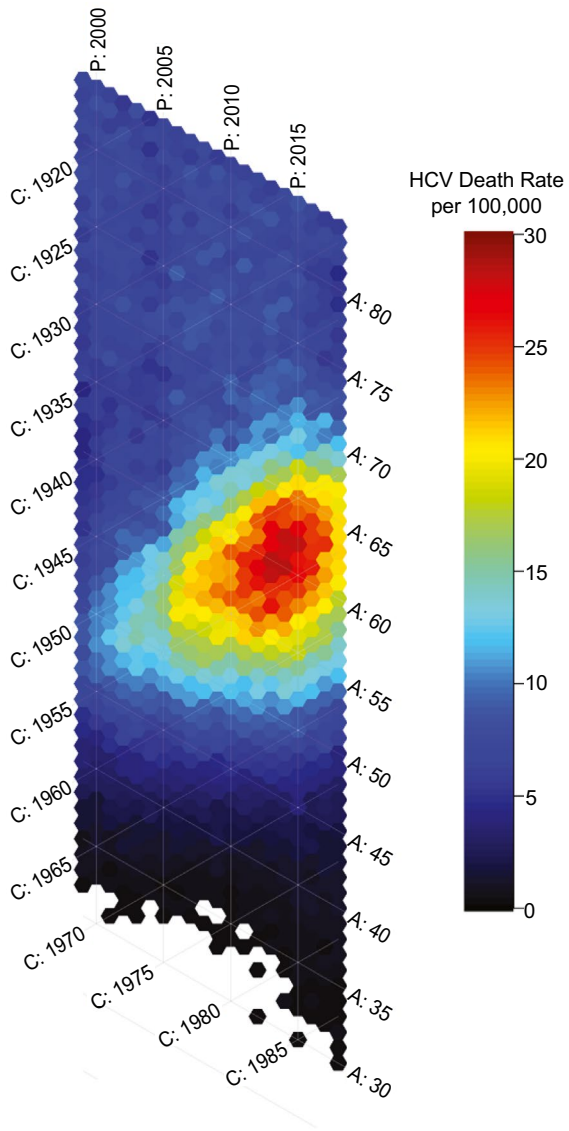

FIG. 5. Hexamap of birth-year cohort patterns in HCV death rates, United States, 1999-2018. Abbreviations: A, age; C, birth-year cohort; P, period (i.e., year).

Discussion

These results illustrate a widespread shift in HCV mortality trends since 2013, but the magnitude and composition of that shift have occurred differently by place and age group. Before 2013, increases in HCV death rates were widespread throughout the country. Although national HCV mortality trends reversed in 2013, there is much more heterogeneity in recent trends at the county level. Since 2013, decreasing national trends have been driven primarily by large, decreasing HCV death rates in the West, Southwest, and Northeast. However, roughly one in five counties have experienced an increase in HCV death rates during this same time period, and these counties are disproportionally concentrated in Texas, Oklahoma, Appalachia, and the area surrounding New Orleans.

There are a few possible explanations for the reversal of HCV mortality trends since 2013. First, as a result of elevated underlying prevalence and years of targeted screening, the majority of diagnosed chronic HCV infections are among adults born between 1945 and 1965.[5] Additionally, from 2013 to 2016, only 62% of persons with HCV infection in this age group were aware of their infection, indicating there are many more undiagnosed infections.[29] As members of this birth cohort aged and the severity of their infections progressed, HCV death rates were expected to increase. Accordingly, after a large proportion of this high-burden birth cohort dies, overall HCV death rates are expected to fall. The pattern seen in Fig. 5 illustrates this birth-cohort effect. Second, since the introduction of curative treatment in the form of direct-acting antiviral (DAA) agents in 2011, there is some evidence that mortality due to HCV-related cirrhosis has been decreasing on the national level.[30] Given that DAAs can cure approximately 90% of persons with an HCV infection within 8-12 weeks with a well-tolerated oral therapy regimen, their introduction would be expected to lower HCV-related mortality.[31] However, access to treatment is not widespread,[32] and the short time frame makes it difficult to attribute county-level declines in HCV mortality to successful treatment initiatives. It is important to

note that earlier this year, both the CDC[32] and the U.S. Preventive Services Task Force[33] updated their respective screening guidelines to recommend HCV screening at least once in a lifetime for all adults 18 years of age or older,[32] and it is unclear how this will impact current HCV mortality trends. Although adherence to guidelines should theoretically result in the identification of additional HCV infections, which could potentially increase HCV death rates, it should also result in additional persons receiving therapy, which could decrease HCV mortality. The continued monitoring of trends in county-level HCV death rates can provide additional insight on the impact new guidelines may have on mortality.

In addition to understanding trends in HCV mortality, the spatial distribution of age-specific HCV death rates provides additional cross-sectional insight on the current HCV epidemic. HCV death rates are much higher in adults 40+ years of age throughout the time frame of interest, which aligns with expectations for two reasons. First, for all years of study in this analysis, the well-described, high-burden birth cohort (born between 1945 and 1965) is included in the older age group. Second, the progression of chronic liver disease caused by HCV infection develops slowly, and significant liver fibrosis does not usually occur before 20 years of age.[32] Although the magnitude and variability in county-level HCV death rates is much smaller among persons <40 years of age, the spatial pattern provides additional emphasis areas of concern for increasing HCV incidence rates among young adults. Counties in the highest quintile of HCV death rates among persons <40 are disproportionately concentrated in Appalachia (from Tennessee up through Pennsylvania) and Oklahoma, which are areas that have been known to be impacted by increases in injection drug use as a result of the opioid crisis and rising viral hepatitis incidence rates.[14,34,35]

The combined interpretation of cross-sectional death rates and temporal trends provides geographic context to the current bimodal nature of the HCV epidemic. As previously noted, in 2017, the highest HCV death rates were concentrated in the West, Southwest, Appalachia, and northern Florida, but age-stratification and trend analysis reveal differences between these regions. For example, high overall county-level HCV death rates in the West and Southwest have primarily been driven by high rates among older (40+ years) adults, and these rates are declining. This is in contrast to many of the counties in Appalachia, in which the overall HCV death rate is increasing and seems to be driven by high HCV mortality among persons aged <40 years. Finally, there are select counties around Oklahoma and northern New Mexico in which high HCV mortality is occurring in older adults and emerging among persons under 40 years. This emergence of HCV mortality among adults <40 provides additional support for the expansion of HCV screening recommendations to include adults of all ages.[32]

Importantly, these results provide an additional granular data point that can be used to better understand the distribution of viral hepatitis infection in general. Systematic, accurate, and timely measurements of incidence, prevalence, and mortality are essential for describing the epidemiological burden of any health condition, but these indicators are not consistently available on a small geographic scale for viral hepatitis. State health departments are responsible for identifying and reporting incident HCV cases, but many states lack adequate funding, and surveillance practices are inconsistent across jurisdictions.[36] Nationally representative survey data have been used in small-area estimation models to estimate state-level HCV prevalence,[13] but updates to those estimates are reliant on model assumptions, and long delays between survey cycles limit utility. Although these results do not replace the need for a comprehensive and cohesive viral hepatitis surveillance system, these granular and temporal data on HCV mortality provide an important metric for understanding the evolution of the HCV epidemic.

In addition to using the HCV-related death rate as a key indicator in monitoring the progress of national viral hepatitis action plans,[9,10] local jurisdictions can use these data to evaluate HCV mortality in their area relative to surrounding areas and the nation as a whole. A better understanding of where high HCV mortality is occurring can inform the allocation of public health resources and interventions that aim to reduce HCV mortality or infection. For example, providing HCV screening along with medication-assisted treatment and syringe-service programs has been shown to be a cost-effective strategy in reducing HCV infection.[37] As the HCV epidemic continues to evolve and injection drug use continues to drive HCV transmission, these data can help inform decisions about where syringe-service programs, or any other interventions

that increase access to HCV screening or linkage to care, should be located.

LIMITATIONS

The main limitation of this study is the potential for misclassification of HCV-related deaths through the use of death certificate data. Although deaths that include an HCV death code are not expected to be misclassified, viral hepatitis is often undiagnosed and underreported as cause of death on death certificates.[38] The degree to which HCV is undiagnosed and underreported on death certificates may differ across jurisdictions, which would impact county-level results. However, this method of death classification has been constant over time, and changes in underreporting would be unlikely to explain temporal trends. As universal HCV screening recommendations are implemented, the underdiagnosis of HCV is expected to decrease in future years. Finally, these estimated HCV death rates have not been compared with jurisdiction-based data. Although these comparison data are limited, a formal comparison would further validate these results.

Additionally, data in the National Vital Statistics System includes all recorded deaths in the United States, which reduces concerns about selection bias or generalizability. Age-standardized death rates may not be equivalent to actual observed death rates, but age standardization was appropriate in this analysis for comparisons across the population and time as the age distribution of the population changes. Finally, previous work has indicated that race/ethnicity and sex disparities in chronic HCV prevalence differ on the state level,[39] and there may also be demographic disparities in county-level mortality trends. Future research should explore and quantify demographic disparities in these spatiotemporal trends.

In conclusion, hepatitis C death rates have been declining since 2013, but the direction and magnitude of that trend is not consistent by place or age group. Efforts to continue the national decline in HCV mortality will require innovative approaches that increase access to testing and care for persons living with HCV infection, particularly in counties in which HCV death rates continue to remain high.

Author Contributions: E.H. contributed to the conception, design, acquisition of data, analysis, interpretation of results and led the writing of the manuscript. S.S. contributed to the conceptualization of the analysis, interpretation of results and revised manuscript drafts. A.V. contributed to the methodology development, interpretation of results and revised the manuscript. H.B., B.L. and E.R. contributed to the interpretation and implication of results and revised the manuscript. P.S. secured the funding, contributed to the conceptualization and interpretation of results and revised the manuscript.

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Supporting Information

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