Declining Hepatitis A Mortality in the United States during the Era of Hepatitis A Vaccination

Tara M. Vogt, Matthew E. Wise, Beth P. Bell, and Lyn Finelli

1Division of Viral Hepatitis, Centers for Disease Control and Prevention, Atlanta, Georgia; 2Department of Epidemiology, University of California, Los Angeles, School of Public Health, Los Angeles, California

(See the editorial commentary by Dienstag, on pages 1220–2.)

Background. Since the mid-1990s, hepatitis A vaccine has been recommended for US children living in historically high-incidence states and for persons with other risk factors or chronic liver disease (CLD). The incidence of hepatitis A has declined dramatically during the era of vaccination, but trends in mortality are largely unknown.

Methods. US death certificates from 1990 to 2004 for which hepatitis A was listed as the underlying cause of death were analyzed. Average annual age-adjusted mortality rates during the prevaccine (1990–1995) and post–vaccination recommendation (2000–2004) periods were compared using a Mantel-Haenszel test of association. The number of deaths for which CLD was listed as a contributing cause was determined.

Results. Overall, 1436 deaths due to hepatitis A occurred, averaging 96 annually (range, 142 in 1995 to 54 in 2003). CLD contributed to nearly half of these deaths. Mortality rates paralleled incidence rates, beginning to decline in the mid-1990s and achieving low points in 2003 and 2004. Average rates were 32% lower in the post–vaccination recommendation period than in the prevaccine period (P < .01). The decline was more dramatic for states with (45%; P < .001) than without (23%; P = .002) recommendations.

Conclusions. Hepatitis A mortality rates have declined over the past decade. CLD remains an important and preventable contributing cause of death due to hepatitis A.

Infection with hepatitis A virus (HAV) can be asymptomatic or result in an acute illness characterized by flu-like symptoms and jaundice [1]. Serious complications are rare; on the basis of national surveillance data, death occurs in ∼0.3%–0.6% of persons with symptomatic hepatitis A, reaching 1.8% among those >50 years old [1].

After the US licensure of safe and effective hepatitis A vaccines in 1995–1996, the Advisory Committee on Immunization Practices (ACIP) recommended vaccination of persons at increased risk of infection, including travelers to countries of endemicity, men who have sex with men, and illicit drug users [2, 3]. Vaccination of those with chronic liver disease (CLD) was also recommended because these persons, although not at increased risk of infection, are more likely to die of hepatitis A [2–5]. The ACIP took an incremental approach to recommendations for vaccination of children. Beginning in 1996, the ACIP recommended routinely vaccinating children living in defined communities in which infection was endemic [2]. In 1999, these recommendations were expanded to include children living in 17 states with consistently elevated hepatitis A incidence rates, determined on the basis of the average incidence during the period 1987–1997 [3]. In 2006, recommendations were extended to include vaccination of all children aged 12–23 months nationwide [1].

Since 1998, national hepatitis A incidence rates have been below any previously recorded rate and have been progressively lower each year [6–8]. Analyses of national surveillance data, as well as results of mathematical models, suggest that observed declines in incidence have been due, at least in part, to implementation of childhood-vaccination recommendations [6, 9]. For example...
example, in states included in the 1999 recommendations for childhood vaccination, rates in 2003 were >85% lower than the average rate during the period immediately before these recommendations were made [6]. However, the potential impact of the implementation of vaccination recommendations on national mortality due to hepatitis A has not been evaluated [10].

Using US mortality and population data, we examined national hepatitis A mortality trends for the years 1990–2004, both overall and stratified by region according to the 1999 ACIP recommendations for routine childhood hepatitis A vaccination. We also compared trends in mortality and incidence during this time period. Finally, we evaluated trends in the prevalence of CLD among persons who died of hepatitis A during 1999–2004.

**METHODS**

*Mortality data*. We obtained multiple-cause-of-death data from the Centers for Disease Control and Prevention’s National Center for Health Statistics for deaths occurring in the United States from 1990 to 2004 [11]. Causes of death listed on death certificates were coded using the International Classification of Diseases, Ninth Revision (ICD-9), for deaths that occurred during 1990–1998 and the International Classification of Diseases, Tenth Revision (ICD-10), for deaths that occurred during 1999–2004 [12, 13]. A hepatitis A death was defined as any death for which hepatitis A was listed as the underlying cause (ICD codes 070.0, 070.1, B15.0, or B15.9).

Information on age, sex, race, Hispanic ethnicity, state of residence, and year of death was also extracted from mortality files. Hispanic ethnicity was reported by all but 3 states by 1990 and by all states by 1997 [14, 15]. Because of sparse data, race/ethnicity categories were combined and limited to non-Hispanic white, non-Hispanic black, and Hispanic. States of residence were divided into 2 groups according to the 1999 ACIP recommendations for routine statewide childhood hepatitis A vaccination; vaccination was recommended for children living in 17 states in which the average annual incidence of hepatitis A during 1987–1997 was ≥10 cases/100,000 population, and no vaccination recommendations were made for children living in other states [3].

Among hepatitis A deaths that occurred during 1999–2004 (the years during which ICD-10 codes were used), we determined the number and proportion that included a record axis code indicating that CLD was a contributing cause of death (appendix A) [16]. We limited the subanalysis to these later years to avoid biases that might be introduced with changes in the classification of CLD from ICD-9 to ICD-10.

*Incidence data*. Data on the total number of reported hepatitis A cases occurring during 1990–2004 were obtained from the National Notifiable Diseases Surveillance System [7]. Through this system, state health departments report all cases that meet both clinical (discrete onset of symptoms and jaundice or elevation of serum aminotransferase levels) and laboratory (positive test result for IgM antibody to HAV) criteria for hepatitis A [17].

**Calculation of rates and statistical comparisons.** To calculate incidence and mortality rates, we obtained bridged population estimates from the US Census Bureau and the National Center for Health Statistics [18]. Crude and age-adjusted rates per 1 million persons were calculated for each year from 1990 to 2004. We also calculated the average annual number of hepatitis A deaths and average age-adjusted mortality rate per 1 million persons during the prevaccine (1990–1995) and post–vaccination recommendation (2000–2004) periods, both unstratified and stratified by age, sex, race/ethnicity, and statewide ACIP recommendations. The years 1996–1999 were excluded because vaccination practices during this time were likely in transition. In accordance with conventions for age adjustment, rates were standardized to the age distribution of the year 2000 US population [19, 20].

Mortality rates during the earlier and later periods were calculated overall and within each strata and were statistically compared using a Mantel-Haenszel test of association [21]. Spearman correlation coefficients (p) and P values were generated to compare time trends in incidence and mortality rates. We analyzed data using Microsoft Excel 2003 (Microsoft Corporation) and SAS (version 9; SAS Institute).

**RESULTS**

*Mortality trends*. From 1990 to 2004, hepatitis A was listed as the underlying cause of death on 1436 death certificates, averaging 96 each year. The number of hepatitis A deaths peaked at 142 in 1995 and was lowest in 2003, when 54 deaths occurred (table 1). During both the earlier prevaccine period (1990–1995) and later post–vaccination recommendation period (2000–2004), average mortality rates increased with increasing age at death and were higher among men than women (table 2). Few deaths occurred in persons <20 years old (averaging 3 and 1 annually during each time period, respectively). Average rates among black and Hispanic persons were similar and were higher than those among white persons during both time periods.

Overall, average annual mortality rates were 32% lower during the post–vaccination recommendation period than the prevaccine period (P < .001) (table 2). Comparing the later to the earlier period, average annual mortality rates were 12%–63% lower among all demographic subgroups examined, achieving statistical significance in all groups except black persons and persons aged 40–59 years at death. Average annual mortality rates were 45% lower in states in which routine childhood hepatitis A vaccination was recommended (P < .001) and were 23% lower in states in which vaccination was not recommended (P = .002). The difference in mortality rates between areas with and without vaccination recommendations narrowed during the post–vaccination recommendation period (figure 1A and 1B).
Comparison with incidence trends. Increases in age-adjusted mortality rates through the mid-1990s and subsequent declines correlated with trends in overall age-adjusted incidence (figure 2) \((r = 0.65; P = .009)\). The lowest incidence and mortality rates were observed in 2004 and 2003, respectively (19 cases in 2004 and 0.18 deaths in 2003 per 1 million persons). Incidence and mortality trends were significantly correlated in states with childhood vaccination recommendations \((r = 0.68; P = .006)\) (figure 1B) but not in those without statewide recommendations \((r = 0.48; P = .07)\) (figure 1A).

Subanalysis of age at death and prevalent CLD. In a subanalysis of 511 hepatitis A deaths that occurred during 1999–2004, age at death was \(\geq 40\) years for 458 (90%) decedents; the median age at death was 63 years. A CLD-related cause of death was present on 229 (45%) of the 511 death certificates. Median age at death was 55 years (range, \(<1–95\) years) among CLD-related hepatitis A deaths and was 69 years (range, \(<1–99\) years) among non–CLD-related hepatitis A deaths. The proportion of hepatitis A death certificates that listed CLD as a contributing cause varied by age at death (29%, 33% 63%, 39%, and 30%, for those \(\geq 20, 20–39, 40–59, 60–79,\) and \(\geq 80\) years, respectively) and was highest among persons who died at age 40–59 years, corresponding to birth years 1940–1964. Hepatitis B and hepatitis C were common causes of CLD. Hepatitis B appeared on 91 (40%) death certificates, and hepatitis C appeared on 93 (41%). Most (67%) of the hepatitis C codes appeared on death certificates for persons who died at age 40–59 years.


<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A deaths, total no.</td>
<td>76</td>
<td>71</td>
<td>82</td>
<td>95</td>
<td>97</td>
<td>142</td>
<td>121</td>
<td>127</td>
<td>114</td>
<td>134</td>
<td>106</td>
<td>83</td>
<td>76</td>
<td>54</td>
<td>58</td>
</tr>
<tr>
<td>Mortality rate, per 1 million persons</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>0.30</td>
<td>0.28</td>
<td>0.32</td>
<td>0.37</td>
<td>0.37</td>
<td>0.53</td>
<td>0.46</td>
<td>0.47</td>
<td>0.41</td>
<td>0.48</td>
<td>0.38</td>
<td>0.29</td>
<td>0.26</td>
<td>0.19</td>
<td>0.20</td>
</tr>
<tr>
<td>Adjusted for age</td>
<td>0.33</td>
<td>0.30</td>
<td>0.33</td>
<td>0.38</td>
<td>0.39</td>
<td>0.55</td>
<td>0.46</td>
<td>0.47</td>
<td>0.42</td>
<td>0.49</td>
<td>0.38</td>
<td>0.29</td>
<td>0.26</td>
<td>0.18</td>
<td>0.19</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Category</th>
<th>1990–1995</th>
<th>2000–2004</th>
<th>Change in rate, %</th>
<th>(P^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>94 0.38</td>
<td>75 0.26</td>
<td>-32</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Statewide childhood vaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recommended</td>
<td>38 0.51</td>
<td>26 0.28</td>
<td>-45</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Not recommended</td>
<td>56 0.33</td>
<td>50 0.25</td>
<td>-23</td>
<td>.002</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;20) years</td>
<td>3 0.03</td>
<td>1 0.01</td>
<td>-63</td>
<td>.04</td>
</tr>
<tr>
<td>20–39 years</td>
<td>13 0.15</td>
<td>6 0.08</td>
<td>-48</td>
<td>.002</td>
</tr>
<tr>
<td>40–59 years</td>
<td>25 0.43</td>
<td>29 0.37</td>
<td>-12</td>
<td>.26</td>
</tr>
<tr>
<td>60–79 years</td>
<td>35 0.99</td>
<td>23 0.62</td>
<td>-37</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>(\geq80) years</td>
<td>19 2.55</td>
<td>16 1.60</td>
<td>-37</td>
<td>.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48 0.44</td>
<td>43 0.33</td>
<td>-26</td>
<td>.001</td>
</tr>
<tr>
<td>Female</td>
<td>46 0.33</td>
<td>32 0.20</td>
<td>-40</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>72 0.35</td>
<td>55 0.24</td>
<td>-32</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Black</td>
<td>12 0.49</td>
<td>10 0.36</td>
<td>-27</td>
<td>.06</td>
</tr>
<tr>
<td>Hispanic</td>
<td>8 0.51</td>
<td>7 0.34</td>
<td>-33</td>
<td>.01</td>
</tr>
</tbody>
</table>

\(^a\) Per 1 million persons.

\(^b\) The 2 time periods were compared and statistically evaluated by use of a Mantel-Haenszel test of association.
During 1999–2004, there was an upward trend in the proportion of hepatitis A deaths that were CLD related, from 44% in 1999 to 67% in 2004 (figure 3). This trend was observed in all age groups and in states with and without statewide childhood hepatitis A vaccination recommendations (data not shown).

DISCUSSION

We report here the results of an analysis of trends in hepatitis A mortality during a 15-year period that spans the era from before to after the availability of hepatitis A vaccine and the implementation of vaccination recommendations in the United States. We demonstrate a decline in overall age-adjusted mortality rates in the post–vaccine recommendation era, with the 2003 and 2004 rates representing the lowest observed during the study period. The comparison of trends in mortality rate in states included and not included in the 1999 recommendations for statewide hepatitis A vaccination of children [3] suggests that implementation of these recommendations resulted in reductions in mortality.

The death certificates for nearly half of the persons who died of hepatitis A during 1999–2004 included a contributing cause of death that suggested preexisting CLD, which is consistent with the results of other studies indicating more severe outcomes and higher mortality rates among persons with CLD who develop hepatitis A [2–5]. Indeed, the high prevalence of CLD among middle-aged adults who died of hepatitis A suggests that CLD may contribute considerably to premature mortality from hepatitis A. Hepatitis C–related CLD was particularly common among these persons, who were born in the 1940s through mid-1960s. The prevalence of hepatitis C–related CLD has been rising and is predicted to continue to rise in the future, primarily because of the high prevalence of chronic hepatitis C virus infection in this birth cohort [22–24].

Although hepatitis A vaccine has been recommended for persons with CLD and adults at high risk of infection (e.g., men who have sex with men and injection drug users) since 1996 [2], data (albeit limited) indicate that vaccination coverage remains low [25–28]. It has previously been demonstrated that reductions in incidence among adults can be achieved by vaccinating children [9, 29–31]. Our findings that (1) the proportion of hepatitis A deaths that were CLD-related rose during the study period and (2) hepatitis A mortality declined less dramatically in the age group/birth cohort with the highest prevalence of CLD are consistent with low vaccination coverage and a modest impact of herd immunity in this group. Given the high prevalence of hepatitis C among CLD-related hepatitis A deaths in our study and the high prevalence of injection drug use among persons with hepatitis C [32], it is possible that at least some of the persons who died of CLD-related hepatitis A acquired hepatitis A as a result of injection drug use. In community–based demonstration projects, childhood vaccination did not prevent outbreaks among adults with hepatitis A attributed to risk factors such as illicit drug use, and outbreaks in these populations continue to occur in the post–vaccination recommendation era [7, 29, 33]. Improved vaccination coverage among persons with CLD and adults with risk factors for infection would contribute to further declines in hepatitis A mortality.

Although acute liver failure following hepatitis A is uncommon, the morbidity and resulting health care–related costs are considerable [34, 35]. Reductions in morbidity associated with nonfatal acute liver failure and liver transplantation are likely to have paralleled the reductions in mortality documented in the present study. In fact, a recent analysis of data collected by the United Network for Organ Sharing and the Acute Liver Failure Study Group demonstrated significantly declining trends in the incidence of hepatitis A–related fulminant liver failure and hepatitis A–related liver transplantation [36].

The implications of our findings with respect to long-term mortality trends need to be considered in the context of the well-recognized natural variation in hepatitis A incidence and mortality. Historically, peaks in hepatitis A incidence have occurred approximately every 10–15 years and are presumably reflected in mortality patterns [3, 6]. We attempted to reduce the effect of
year-to-year variation and temporal trends by comparing average rates during the prevaccine and post-vaccination recommendation periods and by excluding from comparisons the middle time period, when vaccination practices were likely in transition. However, some of the observed decline in mortality can undoubtedly be attributed to this temporal trend, as reflected by the statistically significant declines in mortality in states in which no large-scale vaccination programs were implemented. Monitoring incidence and mortality patterns over time will help to clarify the relative contribution of natural variation versus the use of hepatitis A vaccine to reductions in hepatitis A–associated mortality.

Figure 2. Age-adjusted hepatitis A mortality and incidence rates, by year of onset/death—United States, 1990–2004. The dotted line indicates incidence, and the solid line indicates mortality.

Figure 3. No. of chronic liver disease (CLD)–related hepatitis A deaths and the proportion of hepatitis A deaths that were CLD related, by year of death—United States, 1999–2004 (n = 511). The dotted line indicates the no. of CLD-related deaths, and the solid line indicates the proportion of CLD-related hepatitis A deaths.
Our study has several strengths and limitations that are related to both the data source and analytic methodology. National death-certificate data are continuously collected, population based, and virtually complete. For these reasons, they represent a valuable source of information on mortality trends. However, death certificates can be improperly or incorrectly completed or the true cause of death could be unknown, leading to misclassification of deaths and possible distortions of mortality rates. By defining hepatitis A deaths as those with hepatitis A coded only as the underlying and not a contributing cause of death, we favored specificity over sensitivity. This could lead to an underestimate of the true hepatitis A mortality rate.

Other methodologic issues deserve mention. Demographic data in death records are obtained from a third party, so classification errors, particularly for race/ethnicity, could occur. Also, certain groups, such as Hispanics, are known to be undercounted in the census [37], which may lead to inflated mortality rates. Classifying hepatitis A deaths according to whether CLD appeared to contribute to the death required selecting cause-of-death codes that were consistent with CLD. Our selection of codes likely resulted in the inclusion of some non–CLD-related deaths and the exclusion of some true CLD-related deaths. Finally, because we restricted the CLD subanalysis to more recent deaths and the exclusion of some true CLD-related deaths, this could lead to an underestimate of the true hepatitis A mortality rate.

In summary, we report reductions in overall hepatitis A mortality in the United States during the years after implementation of recommendations for routine hepatitis A vaccination of children. These reductions were most striking among persons residing in states in which routine childhood vaccination was recommended [3] and parallel documented decreases in the incidence of hepatitis A. Further herd immunity–related decreases in incidence and mortality can be expected with the implementation of the recently published recommendations for nationwide routine vaccination of young children [1]. Ultimately, additional reductions in mortality will require improvements in vaccination coverage among adults at increased risk of HAV infection and among those with CLD. This is particularly important given the expected future increases in the prevalence of persons with hepatitis C–related CLD.

APPENDIX A

ICD-10 CODES INDICATING CLD

Acute hepatitis B: B16, B160, B161, B162, and B169.


Chronic viral hepatitis: B18, B180, B181, B182, B188, and B189.

Unspecified viral hepatitis: B19, B190, and B199.

Sequelea of viral hepatitis: B942.

Malignant neoplasm—liver and intrahepatic bile ducts: C22, C220, C222, C223, C224, C227, and C229.

Carcinoma in situ—liver, gallbladder, bile ducts, and ampulla of vater: D015.

Benign neoplasm—liver and intrahepatic bile ducts: D134.

Neoplasm of uncertain or unknown behavior—liver, gallbladder, bile ducts, and ampulla of vater: D376.

Diseases of bilirubin metabolism: E806 and E807.

Diseases of mineral metabolism: E830 and E831.

Disorders of plasma-protein metabolism: E880.

Portal vein thrombosis: I81.

Esophageal varices: I85, I85.0, and I85.9.

Alcoholic liver disease: K70, K700, K701, K702, K703, K704, and K709.

Hepatic failure not elsewhere classified: K721.

Chronic hepatitis not elsewhere classified: K73, K730, K731, K732, K738, and K739.

Fibrosis and cirrhosis of the liver: K74, K740, K741, K742, K743, K744, K745, and K746.

Other inflammatory liver disease: K75, K750, K751, K752, K753, K754, K758, and K759.

Other diseases of the liver: K76, K760, K761, K762, K763, K764, K765, K766, K767, K768, and K769.


References


