Hepatitis A virus (HAV) infection continues to cause significant morbidity in the United States. Annual reported incidence of hepatitis A (HA) has reached more than 35,000 cases during peak years, but the true number of annual symptomatic infections may total 90,000.1,2 HA incidence varies substantially by race/ethnicity, with higher rates reported among Latinos and American Indians/Alaska Natives than among Whites, Blacks, and Asian/Pacific Islanders.2 Clinical manifestations can include fever, jaundice, nausea, abdominal pain, fatigue, and diarrhea, although children are much less likely to experience these symptoms than adults are. Individuals aged 40 to 50 years also exhibit higher fatality rates than younger individuals do.2,3 Illness can last from weeks to months, and relapses may occur.4 HAV is normally transmitted through the fecal-oral route by person-to-person contact and by contaminated food, water, or fomites.5 A vaccine for HA was licensed for individuals older than 2 years in 1995, at which time the Advisory Committee on Immunization Practices (ACIP) released an interim vaccination recommendation for individuals traveling to areas where there is intermediate or high hepatitis A endemicity.6 These recommendations for routine vaccination were formalized in 1996 and were expanded to include children who live in communities where there are high rates of HA: men who have sex with men; drug users; and individuals who are occupationally at risk for infection, have clotting-factor disorders, or have chronic liver disease.7 In 1999, the ACIP released updated recommendations that specified the threshold level of HA incidence that warrants routine vaccination of children. These recommendations specify that any child older than 2 years who lives in a state, county, or community where the reported HA incidence rate is greater than or equal to 200 cases per 1 million persons (approximately twice the national average) should be vaccinated. The HA incidence estimates included in that report placed California in this category.2

Despite the availability of a vaccine, large numbers of HAV infections are reported annually, and HA-related deaths are occasionally reported. Few studies, however, have used vital records and multiple cause–coded (MCC) death data to estimate HA-related mortality rates. We examined HA-related mortality in California between 1989 and 2000.

METHODS

We obtained California MCC death record data for 1989 to 2000 from the California Department of Health Services Office of Vital Records. We abstracted data from death certificates for nearly all deaths that occurred in California, including the deaths of undocumented immigrants. Medical conditions listed on death certificates from 1989 to 1998 were coded in accordance with the International Classification of Diseases, 9th Revision (ICD-9),8 and conditions listed on death certificates from 1999 to 2000 were coded in accordance with the International Classification of Diseases, 10th Revision (ICD-10).9 We used the record axis of the MCC data to extract HA-related deaths, which were defined as deaths in which HA was mentioned anywhere on the death certificate (ICD-9 codes 070.0 to 070.1 and ICD-10 codes B15 to B15.9).10 We also extracted information on age, gender, race/ethnicity, and year of death. We obtained reported HA incidence data from the Division of Viral Hepatitis at the Centers for Disease Control and Prevention (CDC) to supplement the mortality data. The incidence data were composed of all HA case reports in California from 1990 to 2000 that were reported through routine surveillance and included information on age, gender, race/ethnicity, and year of occurrence.

To calculate both incidence and mortality rates, we obtained population data from the California Department of Finance. Age-adjusted rates and age-adjusted mortality rate ratios were calculated, and 95% confidence intervals (CI) were computed.11 All age-adjusted rates were standardized to the year 2000 US population. Sparse data procedures were required for the calculation of 95% CIs for both gender and race/ethnicity-specific age-adjusted mortality rate ratios. Instead of adding the traditional 0.5 to each cell for variance calculations, we redistributed fractions of cases to 0 cells on the
basis of the marginal distribution of age among gender and race/ethnicity groups. We used women as the referent group for comparisons between gender-specific mortality rates, and we used Latinos as the referent group for comparisons between race/ethnicity categories. Referent groups were the groups that had the most stable age-adjusted rate.

The distribution of other medical conditions listed on HA-related death certificates, in accordance with the ICD-9 coding scheme (1989–1998) was compared with the medical conditions listed for all other deaths. These conditions were recoded into 15 categories of medical conditions. Temporal patterns of HA-related mortality also were evaluated. We analyzed data with SAS, Version 8 (SAS Institute, Inc, Cary, NC), and Excel 2000 (Microsoft Corp, Redmond, Wash).

RESULTS

A total of 402 HA-related deaths were identified from 1989 to 2000 in California, which represented an age-adjusted rate of 1.20 deaths per 1 million person-years (95% CI = 1.08, 1.32). The overall age-adjusted HA incidence rate (reported) for California from 1990 to 2000 was 158.66 cases per 1 million person-years (95% CI = 157.36, 159.95). HA was listed as the underlying cause of death for 198 (49.3%) of the HA-related deaths. Other commonly reported underlying causes of death were liver disorders and circulatory conditions.

Mortality rates did not show a clear temporal trend during the study period (Figure 1). Mortality was highest in 1997, when there was an age-adjusted rate of 1.47 HA-related deaths per 1 million person-years (95% CI = 1.03, 1.91), and it was lowest in 2000, when there was an age-adjusted rate of 0.83 per 1 million person-years (95% CI = 0.51, 1.15). There was no consistent decline in mortality after introduction of the vaccine in 1995, although mortality rates did drop substantially from 1999 to 2000. Incidence rates varied from 1990 to 2000, with incidence peaking in 1995 at an age-adjusted rate of 200.65 cases per 1 million person-years (95% CI = 195.81, 205.49). This peak was followed by a steady decline in incidence to a low in 2000 of 83.68 cases per 1 million person-years (95% CI = 80.67, 86.70).

Other medical conditions were recorded for nearly all HA-related deaths from 1989 to 1998, and the distribution of these conditions differed between HA-related deaths and all other deaths (Table 1). Hepatitis B, unspecified viral hepatitis, hepatitis C, and liver disorders (including necrosis and cirrhosis of the liver and chronic liver disease) were substantially more common among HA-related deaths than among all other deaths. Additionally, other infections, genitourinary conditions, psychological conditions, and HIV/AIDS were all about 2 times more likely to be recorded for HA-related deaths than for all other deaths.

HA-related mortality rates increased with age (Figure 2); age-specific mortality rates ranged from 0.05 deaths per 1 million person-years for individuals aged 2 to 14 years (95% CI = 0.00, 0.10) to 5.37 per 1 million person-years for individuals aged 85 years and older (95% CI = 3.18, 7.57). Incidence peaked among individuals aged 5 to 14 years, with a rate of 286.92 cases per 1 million person-years (95% CI = 282.38, 291.47), and then declined to a low of 44.60 cases per 1 million person-years (95% CI = 40.89, 48.30) among people aged 75 to 84 years.

Observed HA-related mortality differed somewhat by race/ethnicity (Table 2). Mortality was lowest among Blacks, who had an age-adjusted rate of 1.12 deaths per 1 million person-years, and was highest among American Indians/Alaska Natives, who had an age-adjusted rate of 2.01 deaths per 1 million person-years. However, the CIs for all 5 racial/ethnic groups overlapped. Incidence also was highest among American Indians/Alaska Natives, who had an age-adjusted rate of 191.41 cases per 1 million person-years, and was lowest among Asian/Pacific Islanders, who had an age-adjusted rate of 38.06 cases per 1 million person-years (Table 2).

The age distribution of deaths also differed only slightly by race/ethnicity. Latinos had the majority of under-25 HA-related mortality; 12 of the 16 total under-25 deaths occurred among this group, 7 of which occurred among those aged 15 to 19 years. The age-mortality distribution for deaths among individuals aged 25 years and older was similar among Blacks, Latinos, Asian/Pacific Islanders, and Whites. Mortality showed a gradual increase with age for each of these groups: it peaked among decedents aged 75 years and older who were White, Latino, and Asian/Pacific Islander, and it peaked among the decedents aged 65 to 74 years who were Black. The age-mortality distribution could
TABLE 1—Comparison of Medical Conditions Recorded for HA-Related and All Other Deaths: California Multiple-Cause-of-Death Data, 1989-1998

<table>
<thead>
<tr>
<th>Condition</th>
<th>HA-Related Deaths</th>
<th>All Other Deaths</th>
<th>Ratio of Percentages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>79 (23.9)</td>
<td>3491 (0.2)</td>
<td>152.79</td>
</tr>
<tr>
<td>Unspecified viral hepatitis</td>
<td>12 (3.6)</td>
<td>1261 (0.1)</td>
<td>64.25</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>40 (12.1)</td>
<td>4772 (0.2)</td>
<td>56.60</td>
</tr>
<tr>
<td>Liver conditions</td>
<td>210 (63.4)</td>
<td>96566 (4.3)</td>
<td>14.68</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>12 (3.6)</td>
<td>13900 (0.6)</td>
<td>5.83</td>
</tr>
<tr>
<td>Digestive conditions</td>
<td>44 (13.3)</td>
<td>130395 (5.8)</td>
<td>2.28</td>
</tr>
<tr>
<td>Other infections</td>
<td>36 (10.9)</td>
<td>120846 (5.4)</td>
<td>2.01</td>
</tr>
<tr>
<td>Genitourinary conditions</td>
<td>55 (16.6)</td>
<td>192721 (8.6)</td>
<td>1.93</td>
</tr>
<tr>
<td>Psychological conditions</td>
<td>46 (13.9)</td>
<td>161615 (7.2)</td>
<td>1.92</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>15 (4.5)</td>
<td>53535 (2.4)</td>
<td>1.89</td>
</tr>
<tr>
<td>Signs, symptoms, and ill-defined conditions</td>
<td>68 (20.5)</td>
<td>496951 (22.2)</td>
<td>0.92</td>
</tr>
<tr>
<td>Circulatory conditions</td>
<td>156 (47.1)</td>
<td>1404757 (62.9)</td>
<td>0.75</td>
</tr>
<tr>
<td>Other conditions</td>
<td>76 (23.0)</td>
<td>765024 (34.2)</td>
<td>0.67</td>
</tr>
<tr>
<td>Respiratory conditions</td>
<td>53 (16.0)</td>
<td>562566 (25.2)</td>
<td>0.64</td>
</tr>
<tr>
<td>All other neoplasms</td>
<td>27 (8.2)</td>
<td>589299 (26.4)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Note: HA = hepatitis A.

*Percentages are calculated based on the total number of individuals with each condition.


DISCUSSION

The findings in our study show that, although overall mortality rates were low, HA is a preventable cause of mortality in California, and it may be a more frequent cause of death than previously recognized. HA-related mortality was higher among men, Latinos and American Indians/Alaska Natives, and older-age groups. Other conditions, including liver conditions, non-A viral hepatitis, and HIV, were more commonly recorded among HA-related deaths than among all other deaths.

Few studies have been undertaken to estimate the burden of HA mortality, and fewer have used MCC death files. The only population-based mortality estimate found in the literature, presumably based on underlying cause-of-death analysis, was presented in the 1999 ACIP HA immunization recommendations. The ACIP report included a CDC estimate of 100 deaths caused by HA each year in the United States, which represents a crude annual rate of less than 0.5 deaths per 1 million persons.² The crude rate for California in our study—1.05 deaths per 1 million persons—is consistent with California’s relatively high HA incidence, but it could indicate that HA mortality has been underestimated nationally.

HA-related mortality was substantially higher among older-age groups. HAV infections, while less frequent among older individuals, are generally more serious than among younger individuals, which is consistent with the observed increases in mortality over age.³ Although the age-mortality distribution of deaths was similar across racial/ethnic groups among individuals aged 25 years and older, the observation that 12 of the 16 total under-25 deaths were Latinos is notable. Focused vaccination efforts may be warranted for this group.

American Indians/Alaska Natives had the highest race/ethnicity-specific age-adjusted mortality rates in our study.
This is probably because of the high HA incidence rates among these groups, but it also may result from higher rates of underlying conditions, such as liver diseases and other viral hepatitis infections, that could increase the fatality risk associated with HAV infection.\textsuperscript{12–14} It also could be associated with disparities in access to health care across racial/ethnic groups, especially with regard to clinical management of fulminant hepatitis. Because of the wide confidence intervals around, and the modest differences between, race/ethnicity-specific mortality rates, it also is possible that apparent disparities in mortality are artifactual.

Relatively higher mortality among men than among women also may be explained by disparities in HA incidence. Men may be at higher risk for HAV infection because of homosexual sex practices and drug use, although the elevated mortality among men also could be the result of more severe clinical course caused by comorbidities, including liver conditions and HIV, or health-related behaviors, such as alcohol consumption.\textsuperscript{15–19}

Several medical conditions were more common among HA-related deaths than among all other deaths. Previous research has shown that chronic liver disease and viral hepatitis infections increase the severity of HA, which is consistent with the high burden of liver conditions and viral hepatitis coinfections we observed among HA-related deaths.\textsuperscript{12–14} However, a form of detection bias may have exaggerated the observed association between liver conditions and HA. HAV-infected individuals may be more likely to be tested, screened, and diagnosed with conditions such as chronic liver disease, liver cancer, or other types of viral hepatitis because of the signs and the symptoms they exhibit. More rigorous testing for liver-related conditions among individuals who have HA could create a spurious or inflated association with certain comorbidities. The association between HA and HIV/AIDS or other sexually transmitted infections (STIs) may be inflated as well because of sexual and other health-related behaviors that place an individual at risk for acquiring both HAV and STIs. Consequently, recording HIV/AIDS among HA-related deaths may be a function of common risk behaviors rather than biologic interactions between HIV and HA. Despite the potential biases in examining proportional comorbidity, it seems that other viral hepatitis infections, liver conditions, liver cancer, and perhaps HIV/AIDS are the most likely conditions to either increase susceptibility to or severity of HAV infection.

The use of underlying cause-of-death data alone may be inadequate for assessing the true impact of HA on mortality. The number of HA-related deaths we identified doubled when MCC death data were used. The primary concern with these additional deaths, however, is whether HA infection had a significant medical impact. There are 2 reasons why the 204 MCC-identified deaths do not appear to be trivial: (1) the HAV infection was clinically relevant enough for the physician to record it on the death certificate, and (2) when HA was not listed as the underlying cause of death, it was placed among the first 4 conditions listed on the death certificate in more than half of the MCC-identified deaths. If the death certificate is properly completed, these first 4 conditions include the immediate cause of death, 2 conditions causally linking the underlying cause to the immediate cause, and the underlying cause itself. These 2 reasons provide evidence that HA was clinically important among the MCC-identified deaths.

Overall, there was a lack of an obvious trend in HA-related mortality during the 12-year study period. After introduction of the vaccine in 1995, mortality rates fluctuated and then dropped between 1999 and 2000. Reported incidence made a steady decline after 1995. Despite these potentially positive observations, it is impossible to know whether the observed decreases were caused by cyclic increases and decreases in incidence that are normally observed for HA every 7 to 10 years or whether they were the result of use of the vaccine.\textsuperscript{1} Less clear reductions in mortality after 1995 could be the result of those who received vaccine being at relatively low risk for mortality. Unfortunately, little population-based information is currently available on HA vaccine coverage in California, which would have helped us interpret trends in incidence and mortality. It is important to keep in mind that the HA vaccine was introduced relatively recently, and recommendations have continued to evolve during the last decade. Increased vaccine use and the consequent decreases in incidence and mortality may become more evident as updated data are compiled over the next several years. Much of the 12 years of data in our study

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td>Age-Adjusted Rate\textsuperscript{a} (95% CI)</td>
<td>Number of Deaths</td>
<td>Age-Adjusted Rate\textsuperscript{a} (95% CI)</td>
<td>Age-Adjusted Rate Ratio (95% CI)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>177.51 (175.59, 179.43)</td>
<td>244</td>
<td>1.62 (1.14, 1.82)</td>
<td>Referent</td>
</tr>
<tr>
<td>Female</td>
<td>138.42 (136.69, 140.14)</td>
<td>158</td>
<td>0.87 (0.73, 1.00)</td>
<td>0.54 (0.44, 0.66)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latino</td>
<td>159.45 (157.11, 161.79)</td>
<td>88</td>
<td>1.45 (1.12, 1.78)</td>
<td>Referent</td>
</tr>
<tr>
<td>White</td>
<td>121.01 (119.43, 122.59)</td>
<td>255</td>
<td>1.14 (1.00, 1.29)</td>
<td>0.79 (0.60, 1.04)</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>38.06 (36.04, 40.08)</td>
<td>30</td>
<td>1.14 (0.72, 1.56)</td>
<td>0.79 (0.46, 1.34)</td>
</tr>
<tr>
<td>Black</td>
<td>83.12 (79.58, 86.67)</td>
<td>24</td>
<td>1.12 (0.66, 1.59)</td>
<td>0.78 (0.48, 1.26)</td>
</tr>
<tr>
<td>American Indian/Alaska Native\textsuperscript{b}</td>
<td>191.41 (173.49, 209.34)</td>
<td>5</td>
<td>2.01 (0.24, 3.78)</td>
<td>1.39 (0.49, 3.92)</td>
</tr>
<tr>
<td>Total</td>
<td>158.66 (157.36, 159.95)</td>
<td>402</td>
<td>1.20 (1.08, 1.32)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Note. HA = Hepatitis A; CDC = Centers for Disease Control and Prevention; CI = confidence interval.
\textsuperscript{a}Rates expressed per 1 million person-years.
\textsuperscript{b}Age-adjusted rate and rate ratio among the Native-Americans/Alaska Natives are unstable because of the small number of cases and the relatively small amount of person-time.
may ultimately be better suited to establishing baseline mortality and incidence levels for future studies that assess the impact of vaccination efforts in California since the 1999 recommendations.

**Limitations**

One of the primary limitations to our study is the potential misclassification of HA-related deaths on the death certificates. It is possible that the number of identified HA-related deaths was incorrect. This could have been caused by improper recording of causes of death on the death certificate, mistakes in coding the death certificate data, and incorrect diagnosis of HAV infection. It seems unlikely that a significant proportion of HA-related deaths were either incorrectly recorded or mis-coded for a number of reasons. First, the epidemiologic distribution of deaths with respect to race/ethnicity, age, and gender was relatively consistent with the incidence of HA. Second, the total number of deaths identified was sufficiently large, and it is unlikely that they all would have been missed. Third, the HA immunglobulin M test used for diagnosis of acute HA infection is a highly sensitive and specific test. The misdiagnosis of a small proportion of the identified deaths cannot be ruled out, however.

In addition to possible misclassification of disease status, other variables, such as age and race/ethnicity, may have been misclassified on the death certificates. Vital records data on a decedent’s race/ethnicity are classified by a third party, and population data on race/ethnicity are classified by self-identification. Consequently, mortality rates may be distorted because of differing methods of race/ethnicity classification among deaths and among the at-risk population. Beyond the misclassification of race/ethnicity, the very validity of the racial/ethnic categories that are currently used in the collection of standard mortality statistics is questionable, with little consensus as to their meaning.

The population data that we used to calculate incidence and mortality rates also were imperfect. They were derived from mathematical models that were based on national decennial census data. These models incorporate assumptions that may not be reasonable among the true population. Some groups are also systematically undercounted in the census. For instance, American Indians/Alaska Natives and Latinos may be undercounted, which would inflate the mortality rates we calculated for those groups. This problem is compounded by the fact that population adjustments for undocumented immigrants likely underestimate the size of this population, which would further inflate rates calculated for several groups, especially Latinos. Additionally, there is misclassification of race/ethnicity, age, and gender in census data, which could be nonrandom and also affect rate estimates.

Because of the relatively small number of deaths identified during the study period, mortality rates may have been distorted because of sparse data. The uncertainty generated by sparse data is reflected in the wide confidence intervals we computed for rates and rate ratios in some demographic categories. Accordingly, the rates calculated in our study should be cautiously interpreted as estimates of true HA-related mortality in California. Sparse data was a particular problem among individuals who were classified as Native American/Alaska Native, for whom a total of 5 deaths were identified. Because of the small amount of person-time among this group, the misclassification of a single death could significantly alter mortality estimates.

While estimates of HA incidence were not the primary focus of our study, it is important to note some of the limitations of these data. Underreporting of HA incidence is a major problem: only about one third of symptomatic cases are believed to be captured by existing surveillance. Misclassification and missing information on age, race/ethnicity, and gender also is present in the incidence data, which distorts group-specific incidence rates. Current HA incidence data can at best be interpreted as a rough estimate of the relative incidence of HA across groups, assuming that rates of reporting are homogenous, which may not be a realistic assumption. Because of these concerns, the incidence data must be interpreted cautiously.

**Conclusions**

The results of our study provide information on the burden of HA disease that may be of value when reassessing current vaccination recommendations. Certain groups appear to exhibit higher mortality as a result of HAV infection. Currently, the ACIP does not recommend that older individuals be vaccinated for HA, probably because of the low incidence among this group. However, the risk for HA mortality among older individuals may be high enough to justify the reevaluation of vaccine recommendations through epidemiologic and cost-effectiveness analyses. Vaccination efforts among older individuals could potentially be made more efficient by targeting older individuals who are consistently exposed to children, because younger individuals are an important mechanism by which HA is transmitted and thus persists in communities. Information on the relatively high HA-related mortality rates observed among Latinos and American Indians/Alaska Natives and the high frequency of underlying liver conditions reported among HA-related deaths should be incorporated into future HA vaccination recommendations. Although overall trends in California after introduction of the vaccine suggest a reduction in HA mortality, sustained monitoring of HA is necessary to confirm that these potentially positive results continue.
References

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