Incidence of Hepatitis A in the United States in the Era of Vaccination

Annemarie Wasley, ScD
Taraz Samandari, MD, PhD
Beth P. Bell, MD, MPH

In the United States, an average of 26,000 hepatitis A cases were reported annually to public health agencies during the 1980s and 1990s, representing an estimated 270,000 infections per year when anicteric disease and asymptomatic infections are taken into account. More than half of the estimated infections occurred among children. In 1995, highly effective hepatitis A vaccines became available in the United States for use among persons aged 2 years or older, providing an opportunity to substantially reduce hepatitis A incidence.

In 1996, the Advisory Committee on Immunization Practices recommended targeted hepatitis A vaccination of selected high-risk populations, such as men who have sex with men, users of illicit drugs, and travelers to endemic countries. Routine vaccination was recommended for children living in communities with the highest hepatitis A rates, such as Native American communities. In 1999, the Advisory Committee on Immunization Practices expanded its recommendations for routine vaccination of children to include children living in states that had consistently elevated hepatitis A rates and a distinctive pattern of hepatitis A epidemiology. The average rate during the previous 11-year (1987-1997) baseline period was used to identify states targeted for childhood vaccination, which included approximately one third of the US population but from which more than half of hepatitis A cases were reported.

We present an analysis of data from national hepatitis A surveillance that describes fundamental changes in the incidence and epidemiology of hepatitis A in the United States following implementation of recommendations for hepatitis A vaccination of children.

See also pp 202 and 246.
METHODS
The incidence of hepatitis A by age, race/ethnicity, state, and year was determined per 100,000 population using data on hepatitis A cases reported through the National Notifiable Diseases Surveillance System (NNDSS). NNDSS is a passive national surveillance system through which states voluntarily report more than 50 nationally notifiable diseases. Hepatitis A has been a nationally notifiable condition since 1966. A reportable case is defined as an acute illness with discrete onset of symptoms and jaundice and/or elevated serum aminotransferase levels in a person who tests positive for IgM antibody to hepatitis A virus or who is a contact of a laboratory-confirmed case. Hepatitis A is reportable by law to the relevant public health authority in all jurisdictions that report to NNDSS.

NNDSS case reports are submitted weekly to the Centers for Disease Control and Prevention (CDC) by state health departments and summarize the results of case investigations conducted by local and state health department personnel. Before reporting a case, investigators determine if the criteria of the case definition have been met. The information to complete these investigations is collected through communication with the patient and/or the health care practitioner. Other information routinely collected and reported includes where the case was reported (state and county) and the basic demographic characteristics (age, sex, race, and ethnicity) of the patient. In NNDSS, race and ethnicity are reported using 5 categories of race and 2 categories of ethnicity as recommended by the White House Office of Management and Budget. Classification of cases with regard to race and ethnicity is made according to the patient’s self-report or as reported by the health care clinician in the patient’s medical record. Race/ethnicity are assessed for viral hepatitis and other nationally notifiable diseases to identify racial disparities in the incidence of disease and to develop effective disease prevention strategies.

The data analyzed here are collected as part of the routine disease control activities of state health departments and have been determined to be exempt from institutional review board review. Informed consent is not required for investigation of cases of nationally notifiable diseases.

Population estimates by state for 1966 to 2003 and more detailed state-level estimates by age, sex, race, and ethnicity for 1990 to 2003 were obtained from the US Census Bureau. To assess how current rates compare with those observed in previous disease cycles, national and regional rates in 2003 were compared with those reported during peak and valley years that have occurred since 1966. These current rates were also compared with the average (defined as the arithmetic mean) rates during 1987 through 1997, the baseline period used to develop geographically based recommendations for vaccination. It was recommended that routine vaccination of children be implemented in 11 states with hepatitis A rates during the 1987 to 1997 baseline period that were 20 or more cases per 100,000 (Alaska, Arizona, California, Idaho, Nevada, New Mexico, Oregon, South Dakota, Utah, Washington) and that it be considered in an additional 6 states with rates less than 20 per 100,000 but with rates of 10 or more per 100,000 during this period (Arkansas, Colorado, Missouri, Montana, Texas, Wyoming). Rates in these 17 states (vaccinating states) were compared with those in the remaining states where there is no recommendation for statewide vaccination of children (nonvaccinating states). Overall hepatitis A rates in 2003 were compared with equivalent rates during the baseline period (1987-1997) but in evaluating changes in age-, race- and ethnicity-specific rates, a modified baseline (1990-1997) was used because detailed demographic information was unavailable for cases reported before 1990.

Rates in 2003 were compared with appropriate baseline and annual rates by the calculation of a normal z statistic. A P value <.001 was chosen for assessing the statistical significance of these changes because, as a result of the large denominators in these comparisons, even small differences in rates were statistically different at the more typically used cutoff of P = .01. We chose to use a more conservative definition of statistical significance to better highlight differences of potential public health importance. To facilitate the interpretation and comparison of changing rates in different groups, these changes were evaluated not only as absolute differences in rates over time, but also as percent declines normalized to the baseline rate. To compare percent declines, a z statistic comparing the ratio of 1 pair of rates with the other pair was calculated. Statistical analysis was facilitated by using Microsoft Excel (Microsoft Corp, Redmond, Wash).

RESULTS
National Trends in Hepatitis A Incidence
During the 35 years from 1966 through 1995, there were 2 cycles of hepatitis A incidence with peaks occurring in 1971 (59,000 cases; 29/100,000) and 1989 (36,000 cases; 14/100,000) and corresponding nadirs in 1983 (22,000 cases; 9.2/100,000) and 1992 (23,000 cases; 9.1/100,000) (FIGURE 1). Following the nadirs in 1992, rates increased through 1995 (31,582 reported cases; 12.0/100,000), and then declined steadily. The 2003 rate of 2.6 per 100,000 (7653 reported cases) is the lowest ever recorded, and is 71% lower than either previously recorded nadir (P<.001).

The percent difference between peaks and nadirs for the 2 earlier cycles was 68% (1971-1983) and 40% (1989-1992). From 1995 through 2003, rates declined by 78% with 90% of that decline occurring since 1997. During 1998 through 2003, rates dropped by an average of 21% per year (with declines exceeding 20% during 4 of those years). Since 1966, there were 2 other years (1974 and 1991) when annual declines relative to the previous year exceeded 20%.

Relative to the average rate during the modified baseline period (1990-1997), the rate in 2003 represented a
76% decline overall, with significant declines in all age groups (Table). By 2003, rates among children aged 2 to 9 years had declined by 89% and those among children aged 10 to 18 years by 84%. Although rates among persons 19 years of age or more also declined significantly by 69%, the percent decline among children was significantly greater than for adults. The percentage of all cases occurring among children 2 through 18 years of age, who account for 24% of the US population, declined from 35% to 19%.

Mapping hepatitis A rates by county illustrates how the geographic pattern of incidence changed from the baseline period (Figure 2). Of 3145 US counties, 694 (22%) reported average rates of 10 or more cases per 100,000 during baseline (1987-1997); the highest average county rate was 738 per 100,000. By 2003, there were 119 (3.8%) counties with average rates of 10 or more cases per 100,000. The highest rate of 256 reported cases per 100,000 was in a Pennsylvania county where more than 500 cases associated with a large foodborne outbreak were reported.

### Trends in Vaccinating States

In the 17 vaccinating states, incidence rates during 2000 through 2003 were 7.2, 3.8, 3.3, and 2.5 per 100,000, respectively (Figure 3). The 2003 rate was 88.2% lower than the baseline rate of 21.1 (P < .001) (Table). Nine of the 10 states with the greatest declines in rates from baseline to 2003 were vaccinating states, and the proportion of hepatitis A cases originating from vaccinating states, the populations of which account for 33% of the US population, declined from 65% (baseline) to 33% (2003). At baseline, 560 (81%) of 694 counties with rates above the national average for that period (10/100,000) were located in these states; in 2003, only 38 (47%) of the 119 counties with rates at or above that level were in these states.

### Table. Hepatitis A Incidence by Demographic Characteristics: Overall and by Region, 1990-1997 and 2003 *

<table>
<thead>
<tr>
<th></th>
<th>All States</th>
<th>Childhood Vaccination Recommended or Considered (Vaccinating States)</th>
<th>No Childhood Vaccination Recommendation (Nonvaccinating States)</th>
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<td>Baseline, 1990-1997</td>
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<td>Baseline, 1990-1997</td>
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</table>

*Incidence rates for baseline period and 2003 are per 100,000 persons.
During the baseline period, the highest age-specific rates in these 17 vaccinating states occurred among children aged 2 to 9 years (Table). Incidence rates subsequently declined significantly in all age groups (Figure 3) (Table), but the declines among children, especially those aged 2 to 9 years, were greater than among older age groups. In 2003, age-specific incidence rates were significantly lower among children aged 2 to 9 years, compared with children aged 10 to 18 years or with adults (Table). A total of 78% of reported cases occurred among adults in 2003, compared with 60% at baseline.

Relative to the baseline, incidence in males and females declined 89% and 87%, respectively. Rates among men, historically higher than among women, were not statistically different in 2003 (2.6 vs 2.4/100,000, respectively) (Table) (FIGURE 4).

In vaccinating states, rates declined significantly in all racial/ethnic groups (Table). During the baseline period, incidence rates among Native Americans were 6 to 17 times higher than among other racial/ethnic groups. By 2003, incidence among Native Americans declined by 98.8% and was not significantly different from that of any other racial/ethnic group. Cases among Native Americans accounted for 1.1% of all cases reported in 2003 compared with 8.5% at baseline. The incidence rate among Hispanics was 3 to 6 times higher at baseline than among all non-Hispanic racial/ethnic groups except Native Americans. Although the rate in Hispanics declined significantly, in 2003 it remained significantly higher than any other racial/ethnic group, including Native Americans. Cases among Hispanics, which accounted for 30% of all cases in the vaccinating states at baseline, accounted for 35% of cases in 2003.

**Comparison of Trends in Vaccinating and Nonvaccinating States**

At baseline, the overall rate in vaccinating states was almost 4 times higher than in nonvaccinating states, but by 2003, the rate in vaccinating states was not significantly different from the rate in nonvaccinating states (Table). 2001 was the first year since surveillance for hepatitis A began in 1966 that the overall rate was not significantly higher in vaccinating states (Figure 1). Before 2000, there was only 1 year (1970) in which the difference was less than 50% (vaccinating states, 36/100,000; nonvaccinating states, 25/100,000). One third of US counties are located in the vaccinating states. In 2003, 32% of counties with rates above 10 per 100,000 were located in vaccinating states (Figure 2), significantly lower ($P<.001$) compared with 55% (1983) and 62% (1992), respectively, during the previous 2 nadirs in hepatitis A incidence.

Among adults, baseline rates were more than 3 times higher in vaccinating than nonvaccinating states but by 2003, the rate among adults in vaccinating states was not statistically different from that in nonvaccinating states.
In 2003, the highest age- and sex-specific rate occurred among adult men aged 25 through 29 years in nonvaccinating states (Figure 4). Among children, age-specific rates at baseline were 3.5 to 5.5 times higher in vaccinating than nonvaccinating states, with the largest difference among children aged 2 to 9 years (Table) (Figure 4). The 2003 age-specific rates among children aged younger than 2 years, 2 to 9 years, and 10 through 18 years reflect significantly larger declines in vaccinating (90.6%-95.6%) than in nonvaccinating states (59.1%-69.6%). The 2003 rates among these age groups in vaccinating states were not statistically different from those in nonvaccinating states (Table) (Figure 4). These shifts were reflected in the distribution of reported cases. At baseline, 72% of all reported cases in 2- to 18-year-olds occurred in vaccinating states (although only 35% of the children in this age group lived in those states); by 2003, this percentage had dropped to 37%.

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Baseline rates were 2 to 3 times higher among all racial/ethnic groups except Asian Pacific Islanders in vaccinating than nonvaccinating states. Rates among Native Americans and Asian Pacific Islanders declined similarly in vaccinating and nonvaccinating states (Table), but among non-Hispanic whites and non-Hispanic blacks the decline in rates was significantly higher in vaccinating states.
Among Hispanics, baseline rates were nearly 4 times higher in vaccinating than nonvaccinating states, but in 2003 were significantly lower in vaccinating states, reflecting a larger decline. By 2003, rates among all racial/ethnic groups in vaccinating states were similar to or lower than those in nonvaccinating states (Table).

COMMENT

This report describes a dramatic decline in hepatitis A incidence rates in the United States. The 2003 rate was the lowest recorded in 40 years of surveillance, and the provisional 2004 rate of 1.9 reported cases per 100,000 represents yet a further decrease. This decline coincided with implementation of recommendations for routine hepatitis A vaccination of children, and was most striking in the parts of the country and age groups covered by the recommendations. The greater declines in hepatitis A incidence rates in children have resulted in a shift in the age profile of reported cases. The highest rates, which previously were among children, now occur among adults, with the largest proportion of cases among adults in historically low-rate states.

Fundamental shifts in the epidemiologic patterns of hepatitis A have accompanied the decline in disease rates. The large community-wide outbreaks that accounted for the majority of cases during the past several decades, driven primarily by infections among children and transmission in households and extended family settings, have virtually disappeared. This is reflected in a shift in the distribution of reported potential sources of infection, with a declining proportion reporting exposure in child day care centers.

Because of high disease rates among Native American populations, routine hepatitis A vaccination was recommended for Native American communities several years before state-wide recommendations were developed. Widespread hepatitis A vaccination of children in these communities, many of which are geographically and racially well-defined, produced high coverage levels. Hepatitis A rates among Native Americans began declining sharply in 1995 and have been below the national average since 2000, eliminating a large racial disparity in hepatitis A-associated disease burden.

Determining the role that vaccination has played in the observed changes in hepatitis A epidemiology is complicated by the historical pattern of hepatitis A incidence, which varies cyclically and peaks approximately every 10 to 15 years. Certainly, the observed decline is not entirely attributable to vaccination. Indeed, mathematical models of hepatitis A incidence predicted a 4.5% yearly decline among susceptible persons over 7 decades before the availability of vaccines, and that 39% of the potential cases in 2001 were prevented by vaccination. With use of any new vaccine, dynamic modeling theory predicts that the eventual steady state incidence rate, while lower than during the prevaccination era, will be higher than the nadir that occurs shortly after vaccine introduction.

While available data do not allow for quantifying the relative contribution of vaccination and temporal trends to the observed declines in incidence, these declines, particularly since 1999, have been unprecedented in magnitude and greater in areas in which vaccination of children is occurring. In reality, in view of the number of years from valley to peak in previous cycles, it might be argued that in the absence of any intervention, the incidence after 1995 would have been expected to continue to rise for several additional years. It is possible that targeted vaccination programs initiated in 1996 and involving children living in communities with the highest rates, especially Native American communities, might have played a role in the moderate decline in rates that occurred in 1996 and 1997. Further, the epidemiologic situation we describe does not represent maintenance of previous characteristics that have been reset at a lower incidence rate. Rather, declines have been accompanied by fundamental changes in the epidemiology of hepatitis A, such as shifts in the relative distribution of cases by age and geographic region, which are consistent with the expected effects of this intervention and were not observed during previous nadirs in the natural disease cycle.

Comprehensive information on hepatitis A vaccination coverage could provide a useful context in which to interpret the key findings presented in this report. Unfortunately, only very limited data are available. Vaccination coverage among adults is not assessed systematically. However, available information indicates that hepatitis A vaccination coverage of adults in high-risk groups, although recommended since 1996, is low. The only nationwide estimate of coverage among children comes from the National Immunization Survey, a nationwide survey that provides annual estimates of vaccination coverage among 19- through 35-month-old children in 50 states and 28 selected urban areas. In 2003, when hepatitis A vaccine was first included in the National Immunization Survey, first-dose coverage among children 24 through 35 months old was 50% in the 11 states in which routine vaccination is recommended, and 25% in the 6 states where routine vaccination is to be considered. By comparison, coverage in this age group in the remaining states was 1%. According to a 2005 written communication from CDC health scientist Diana Bartlett, MPH, limited coverage data among somewhat older children, available from vaccine registries of selected populations in 5 states included in the recommendations, indicated that of the second quarter of 2004, 44% to 81% of children aged 3 to 5 years had received 1 or more doses of hepatitis A vaccine.

The 2003 National Immunization Survey data suggest that at least some vaccination efforts to date may have been targeted to children at highest risk. For example, although the overall state-wide vaccination coverage level in Texas was 32%, coverage in counties bordering Mexico with the highest incidence rates in the prevaccine era was considerably higher, reaching 70% in some
 counties. In a multivariate model, factors that were associated with receiving hepatitis A vaccine included residence in a vaccinating state, living in an urban area, being either Hispanic or Native American (compared with non-Hispanic white race/ethnicity), and having a mother with less than a high school education (compared with having graduated from high school). Targeting these groups might have increased the impact of limited vaccination efforts.

Trends in vaccination coverage are difficult to measure because before 2003, comprehensive vaccination coverage data were not collected in any routine or systematic way. Records of yearly pediatric doses distributed in the public sector offer a rough indication. Before 1998, less than 400 000 doses had been distributed. In 1998, almost 600 000 doses were distributed, more than doubling in 1999 to almost 1.5 million, and continuing to rise in 2000 to approximately 2.9 million. During 2001 through 2003, approximately 3 to 3.5 million doses were distributed each year, over 95% to vaccinating states.

This available information on vaccine use indicates that the observed declines in rates among children appear to have been achieved with modest levels of vaccination coverage, supporting the hypothesis of a strong herd immunity effect. Declines in rates among adults in vaccinating states were larger than in nonvaccinating states, suggesting that vaccination of children also might have reduced transmission in other age groups through herd immunity. Additional evidence of such an effect was seen in a demonstration project where vaccination of children (approximately 66% coverage with at least 1 vaccine dose) resulted in a substantial reduction in disease rates in adults. Similar findings have been reported from other countries in which routine hepatitis A vaccination of infants or children has been implemented, including Israel and parts of Italy and Spain. A recent article that presented the results of modeling the relationship between hepatitis A incidence and vaccine coverage also found a strong herd immunity effect, accounting for more than one third of the estimated number of cases prevented by vaccination.

Although vaccination of children can result in fewer adult cases associated with contact with children, transmission among selected groups of adults can be sustained in the absence of transmission among children. Thus, cases increasingly are concentrated among adults in identified high-risk groups, such as international travelers, users of illegal drugs, and men who have sex with men. The relatively high disease rates among adult men younger than 40 years are a manifestation of this phenomenon.

We compared rates from 2003 with the averages during the 1987 through 1997 baseline period that was the basis of the recommendations for use of hepatitis A vaccine per the Advisory Committee on Immunization Practices. Because hepatitis A incidence has varied cyclically with periodic nationwide increases, the years 1987-1997 were chosen as a baseline that reflected neither a peak nor a valley in the incidence rate and provided a representative picture of hepatitis A incidence during the prevaccine era. We compared the baseline rates with those in the most recent year rather than with the averages from multiple years because implementation of the vaccination recommendations has occurred in stages and is still expanding, thus, there is no well-defined postvaccination period. In describing postvaccine era changes, the use of any group of years since the recommendations were made (rather than the most recent year) as an end point reflects the average changes during the entire time period, a time during which vaccine coverage has been consistently increasing and rates consistently declining. Thus, while the overall conclusions are the same regardless of whether the end point used is 2003 or a group of recent years, given the dynamic situation, the analysis comparing the baseline rate with 2003 more completely and accurately describes the magnitude of the changes to date.

Our analyses used passive surveillance data reported through NNDSS, which collects information on symptomatic, serologically confirmed hepatitis A cases, and has a number of previously described limitations. These reports represent only a portion of all infections, because asymptomatic infections and some symptomatic cases are not reported. Studies have estimated that for each hepatitis A case reported to NNDSS, there are 2 to 3 that meet the case definition that are not reported. Completeness of the data reported, such as demographic characteristics, also can vary. However, available information indicates that in general, data quality from vaccinating states is better than from nonvaccinating states and there has been no evidence of systematic changes in these reporting patterns since 1990, the first year in which detailed demographic data by case were reported. For example, information on age and race/ethnicity is missing from a smaller proportion of reports from vaccinating states compared with nonvaccinating states (eg, 98.5% of case reports from vaccinating states include age vs 97.5% from nonvaccinating states). This differential in completeness of reports would have the effect of underestimating differences between regions. Further, the national trends reported here were also reflected in the Sentinel Counties Study of Acute Viral Hepatitis, a long-standing CDC-sponsored study (since the early 1980s) in 6 US counties where the accuracy and completeness of reporting have been assessed and are known to be high. Hepatitis A incidence rates in the Sentinel Counties Study declined from an average of 15.3 per 100 000 in 1987 through 1997 to 1.2 cases per 100 000 in 2003, and the incidence curve closely mirrors national trends. Thus, while use of NNDSS data may have resulted in imprecision in incidence estimates, we believe these data accurately reflect trends in incidence, both overall and among regions.

In summary, we report early apparent impact of implementation of a
novel, and to our knowledge, unique vaccination strategy. This strategy is based on distinctive features of hepatitis A epidemiology, including the geographic clustering of areas with consistently elevated rates, the important role of children in sustaining transmission, and the hypothesized large effect of herd immunity. These features lent themselves to a geographically focused strategy using a vaccine that could not be readily integrated into the routine vaccination schedule, and maximized the impact of limited vaccination. The changes we describe represent a transformation in hepatitis A epidemiology in the United States. However, because hepatitis A incidence has historically exhibited a pattern of periodic increases, further monitoring is needed to determine the extent to which the declines that have occurred will be sustained and are attributable to vaccination. In addition, more data on vaccine coverage levels are needed to better describe the relationship between hepatitis A vaccination use and disease rates.

Sustaining and further reducing hepatitis A incidence can be achieved by improving vaccination coverage in groups for which it is currently recommended, including children living in the historically higher-rate states and children and adults in high-risk groups. Elimination of hepatitis A virus transmission will require expansion of existing recommendations to include routine vaccination of all US children.

Author Contributions: Dr Wasley had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Wasley, Samandari, Bell.

Acquisition of data: Wasley, Samandari.

Analysis and interpretation of data: Wasley, Samandari, Bell.

Drafting of the manuscript: Wasley, Samandari, Bell.

Critical revision of the manuscript for important intellectual content: Wasley, Samandari, Bell.

Statistical analysis: Wasley, Samandari, Bell.

Study supervision: Bell.

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REFERENCES


