The Diverse Patterns of Hepatitis A Epidemiology in the United States—Implications for Vaccination Strategies

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Hepatitis A is the most frequently reported vaccine-preventable disease in the United States. Hepatitis A incidence and risk factors during 1983–1995 were examined among cases reported to the study's Sentinel Counties: Denver County, Colorado; Pierce County, Washington; Jefferson County, Alabama; and Pinellas County, Florida. Of 4897 serologically confirmed cases, 611 patients (13%) were hospitalized and 9 (0.2%) died. The average incidence was 14.7/100,000 (range, 0.6–100.7/100,000, depending on county and year). The frequency of reported sources of infection varied by county, but the largest single group overall (52%) did not report a source. During 3-year communitywide outbreaks in Denver (1991–1993) and Pierce (1987–1989) Counties, rates increased 4- and 13-fold, respectively, and increased in all age, racial/ethnic, and risk groups. During communitywide outbreaks, hepatitis A is not limited to specific risk groups; sustained nationwide reductions in incidence are more likely to result from routine childhood vaccination than from targeted vaccination of high-risk groups.

Despite the availability for several decades of immune globulin, a specific preventive measure, hepatitis A remains one of the most frequently reported infectious diseases in the United States. In 1996, 31,032 cases were reported to the Centers for Disease Control and Prevention's (CDC) National Notifiable Disease Surveillance System [1]; after correcting for underreporting, it is estimated that ~80,000 cases occurred (CDC, unpublished data).

CDC has conducted nationwide surveillance for acute viral hepatitis since 1966 to assess trends in incidence and potential sources of infection. However, national data are limited because of underreporting and incomplete serologic and epidemiologic evaluation of reported cases. To define more accurately the epidemiology of all types of viral hepatitis, CDC has conducted sentinel surveillance for acute viral hepatitis in four counties since October 1981. This Sentinel Counties Study of Acute Viral Hepatitis complements national surveillance systems for acute viral hepatitis, yields more complete epidemiologic information, and provides data to assist in the development of prevention strategies.

In 1995 and 1996, highly safe and effective hepatitis A vaccines were licensed in the United States. These vaccines provide long-term protection and are a powerful new tool to make a substantial impact on the burden of hepatitis A [2]. To provide epidemiologic information relevant to the development of hepatitis A vaccination strategies, we examined patterns of disease incidence and trends in sources of infection among hepatitis A cases reported to these sentinel surveillance sites during 1983–1995.

Methods

The Sentinel Counties Study is conducted in Jefferson County (Birmingham), Alabama; Denver County (Denver), Colorado; Pinellas County (St. Petersburg), Florida; and Pierce County (Tacoma), Washington [3]. The study includes all patients with acute viral hepatitis reported to each of the four county health departments who meet a case definition that includes clinical and serologic criteria. Patients are tested for all serologic markers of acute infection with known hepatitis viruses in serum specimens collected within 6 weeks of onset of illness. Only patients positive for IgM antibodies to hepatitis A virus (anti-HAV) and who have a discrete onset of a physician-diagnosed clinical illness compatible with hepatitis are included as hepatitis A cases. This report includes patients with hepatitis A reported to the four county health departments from 1 January 1983 through 31 December 1995.

To obtain epidemiologic information, each patient was interviewed by a trained study nurse, who used a standard questionnaire [4]. Patients with a history of one or more of the following potential sources of infection in the 2–6 weeks preceding onset of illness (except where indicated) were assigned to a mutually exclusive group in the following hierarchy: having household or sexual contact with a person with hepatitis A; attending or working in a day care center; having a household member who attended or worked in a day care center; male homosexual activity (in the 6 months

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before illness onset); international travel to countries of intermediate or high hepatitis A endemicity; and injecting street drugs (in the 6 months before illness onset). Patients who reported none of these potential sources of infection were considered to have no known source of infection.

Hepatitis A incidence was calculated using data from the 1980 and 1990 US census and yearly intercensal population estimates. Differences in proportions were compared by the two-tailed Mantel-Haenszel χ^2 test or Fisher's exact test. Trends were evaluated with the Mantel-Haenszel χ^2 test for trend. $P < .05$ was considered significant.

Results

Clinical characteristics. During 1983–1995, 4897 cases of hepatitis A were reported, and interviews were completed on 4433 case-patients (91%). By definition, all patients were symptomatic; 86% were jaundiced, and the median bilirubin level was 5.4 mg/dL (range, 0.1–67). In total, 611 (13%) patients were hospitalized, ranging from 74 (7%) patients <15 years old to 116 (27%) patients >44 years old. Nine patients (0.2%) died of acute hepatitis A, aged 4, 34, 37, 41, 42, 49, 61, 82, and 90 years.

Incidence. The overall average incidence was 14.7 cases/100,000 population but ranged from 0.6 to 100.7/100,000, depending on the county and year (figure 1). The cases reported from Denver ($n = 2041$) and Pierce ($n = 2242$) Counties accounted for 42% and 46%, respectively, of all cases reported during the study period. The average yearly incidence in these counties (33.4 and 30.2/100,000, respectively) was ~10-fold higher than in Pinellas and Jefferson Counties (3.8 and 2.3/100,000, respectively).

Demographic characteristics. The median age of case-patients was 26 years (range, 3 months–94 years). The largest proportion of cases and, in all counties except Denver, the highest average incidence occurred among persons 15–29 years old (table 1). In Denver County, average yearly rates were highest among children aged 5–14 years. In all counties, the average incidence among men was higher than among women but similar in boys and girls <15 years old (overall rates, 17.6/100,000 and 15.8/100,000, respectively).

Although the majority of cases occurred among whites, the average incidence was 2.5-fold higher among American Indians and persons of Hispanic ethnicity than among whites (table 1). Average rates were lowest among Asians and Pacific islanders and blacks. Of the 832 cases among Hispanic persons, 92% were reported from Denver County. Hispanics constitute 23% of the Denver County population but accounted for 41% of its cases, and this group had the highest average yearly rates compared with other racial/ethnic groups (table 1). Most cases (76%) among American Indians occurred in Pierce County, where American Indians accounted for 1% of the population but 5% of cases and had the highest average yearly rates compared with other racial/ethnic groups (table 1).

Sources of infection. Overall, the most frequently reported source of infection was a history of injecting street drugs (14%), followed by household or sexual contact with a hepatitis A patient (12%), attending or working in a day care center or having someone in the household who worked in or attended a day care center (11%), and a history of male homosexual activity (7%). Children accounted for 69% of patients reporting attending or working in a day care center and 28% of patients reporting a household member who worked in or attended a day care center.

A history of international travel accounted for 4% of cases; Mexico or Central or South America were the most common destinations (84%), followed by Asia (6%), the Middle East (3%), Europe (3%), and Africa (1%). Only 1 of the 195 travelers reported receiving immune globulin before departure. Recent international travel was reported by 7% of patients of Hispanic ethnicity, compared with 3% of whites ($P < .01$), and persons

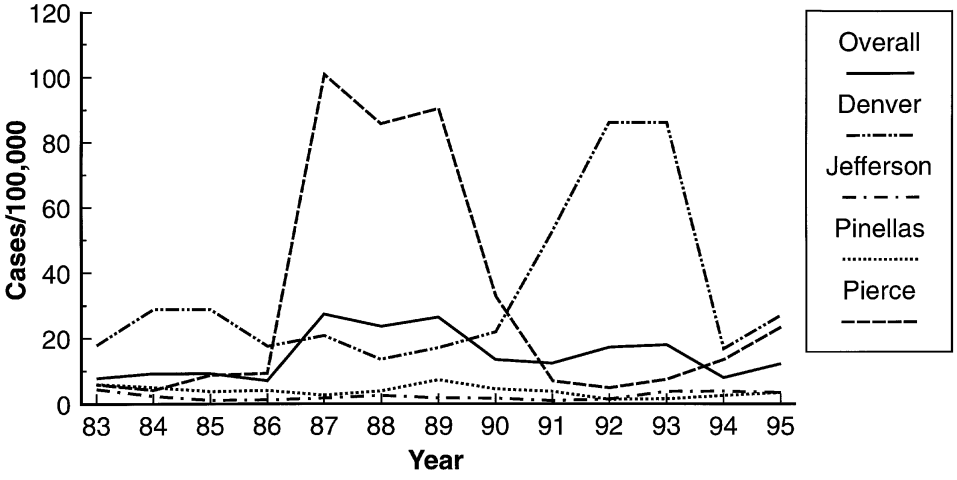

Figure 1. Hepatitis A rates, by county, Sentinel Counties, 1983–1995.

Table 1. Average incidence of hepatitis A, by age, race/ethnicity, and sex, in Sentinel Counties, Denver, Pierce, Jefferson, and Pinellas Counties, 1983–1995.

Variable	Average incidence (range) per 100,000 population				
	Total	Denver	Pierce	Jefferson	Pinellas
Age, years					
<5	9.9 (2.3–16.2)	27.6 (0.0–80.0)	10.9 (0.0–40.0)	—	—
5–14	27.3 (5.6–41.0)	78.8 (15.7–232.9)	23.8 (1.3–87.0)	2.3 (0.0–4.4)	4.3 (2.3–6.6)
15–29	29.4 (13.7–49.3)	52.9 (9.3–149.8)	53.1 (4.8–174.4)	4.2 (1.9–12.0)	7.4 (1.3–15.6)
30–44	19.9 (8.2–39.6)	30.3 (9.6–99.1)	41.5 (3.2–153.4)	2.5 (0.0–6.3)	5.3 (0.5–10.9)
>44	4.5 (1.4–6.6)	5.8 (1.4–17.5)	8.7 (0.0–19.6)	1.1 (0.0–2.3)	2.2 (0.3–4.9)
Sex					
Female	13.3 (4.8–21.8)	25.5 (9.1–66.7)	22.9 (3.1–83.5)	1.5 (0.6–3.5)	3.3 (1.1–6.0)
Male	21.8 (8.4–33.5)	41.8 (12.8–124.6)	37.5 (4.9–117.9)	3.1 (0.3–7.7)	4.6 (1.4–8.7)
Race/ethnicity					
White	15.7 (6.5–28.5)	25.6 (9.2–86.3)	30.8 (4.0–100.1)	2.6 (0.7–5.3)	3.7 (1.2–7.4)
Hispanic	38.2 (17.8–142.5)	38.2 (17.8–142.5)	61.3 (18.7–197.9)	21.2 (0.0–82.4)	—
American Indian	40.0 (7.9–267.0)	42.9 (0–179.8)	98.3 (0–526.3)	—	—
Black	11.4 (1.6–16.1)	13.9 (1.7–46.8)	22.4 (2.2–126.8)	1.1 (0.0–6.6)	4.1 (0.0–13.6)
Asian/Pacific islander	11.2 (5.7–22.6)	12.1 (0–36.3)	9.3 (0–24.1)	—	—

NOTE. —, <1 case reported per year.

of Hispanic ethnicity accounted for 35% of all travel-related cases and 41% of cases among travelers to Mexico or Central or South America.

The largest single group of patients (52%) did not report a source of infection as defined in this study. Nevertheless, 22% of these patients reported casual contact with a person with hepatitis A, 33% had a child <5 years old in the household, 6% reported injecting drugs but not during the 6 months before illness onset, and 4% reported ever having homosexual activity. Questions regarding use of noninjected street drugs were added in 1991, and 7% of patients who became ill during 1991–1995 reported snorting but not injecting street drugs in the 6 months before onset.

There were significant differences in the distribution of reported sources of infection between Denver and Pierce Counties, the counties reporting enough cases to make such comparisons (table 2). Pierce County was the only county in which injecting street drugs in the 6 months before illness onset was the most frequently reported source of infection. This behavior was reported by 22% of case-patients in Pierce County compared with 8% in Denver County ($P < .001$). The most frequently reported source of infection in Denver County was day care center–related contact, and a larger proportion of this county's cases was attributed to this exposure than in Pierce County (14% vs. 10%, $P < .01$). Male homosexual activity was reported by 11% of case-patients in Denver County, compared with 2% in Pierce County ($P < .001$).

Epidemics. In two of the Sentinel Counties, large epidemics occurred during the study period, each lasting several years. Half of the cases reported in Denver County between 1983 and 1995 occurred during an epidemic from 1991 to 1993, when average rates increased 4-fold compared with the previous 3 years (from 17.5 to 74.7/100,000) (figure 1). Similarly, the majority (69%) of the reported cases in Pierce County occurred during an epidemic during 1987–1989, when average yearly rates increased 13-fold compared with the previous 3 years (from 7.1 to 92.2/100,000) (figure 1). In Jefferson and Pinellas Counties, rates remained essentially constant during the entire study period.

The epidemics in Denver and Pierce Counties were characterized by increases in the reported number of cases in all age and racial/ethnic groups. Average rates increased 2- to 7-fold in Denver County and 4- to 31-fold in Pierce County in each age and racial/ethnic group during epidemic years compared with nonepidemic years (figure 2).

Similarly, there were increases in the number of patients re-

Table 2. Epidemiologic characteristics of patients reporting hepatitis A, by mutually exclusive groups in Sentinel Counties, Denver, Pierce, Jefferson, and Pinellas Counties, 1983–1995.

Characteristic[a]	No. of cases (%)				
	Total ($n = 4433$)	Denver ($n = 1842$)	Pierce ($n = 2078$)	Jefferson ($n = 174$)	Pinellas ($n = 339$)
Household or sexual contact with hepatitis A patient	531 (12.0)	203 (11.0)	258 (12.4)	34 (19.5)	36 (10.6)
Child/employee in day care center	182 (4.1)	106 (5.8)	64 (3.1)	6 (3.5)	6 (1.8)
Contact of day care child/employee	315 (7.1)	148 (8.0)	134 (6.5)	11 (6.3)	22 (6.5)
Homosexual activity	296 (6.7)	201 (10.9)	49 (2.4)	17 (9.8)	29 (8.6)
International travel	195 (4.4)	93 (5.1)	49 (2.4)	21 (12.1)	32 (9.4)
Injection drug use	618 (13.9)	155 (8.4)	447 (21.5)	8 (4.6)	8 (2.4)
Unknown	2296 (51.8)	936 (50.8)	1077 (51.8)	77 (44.3)	206 (60.8)

[a] In decreasing order of exclusion.

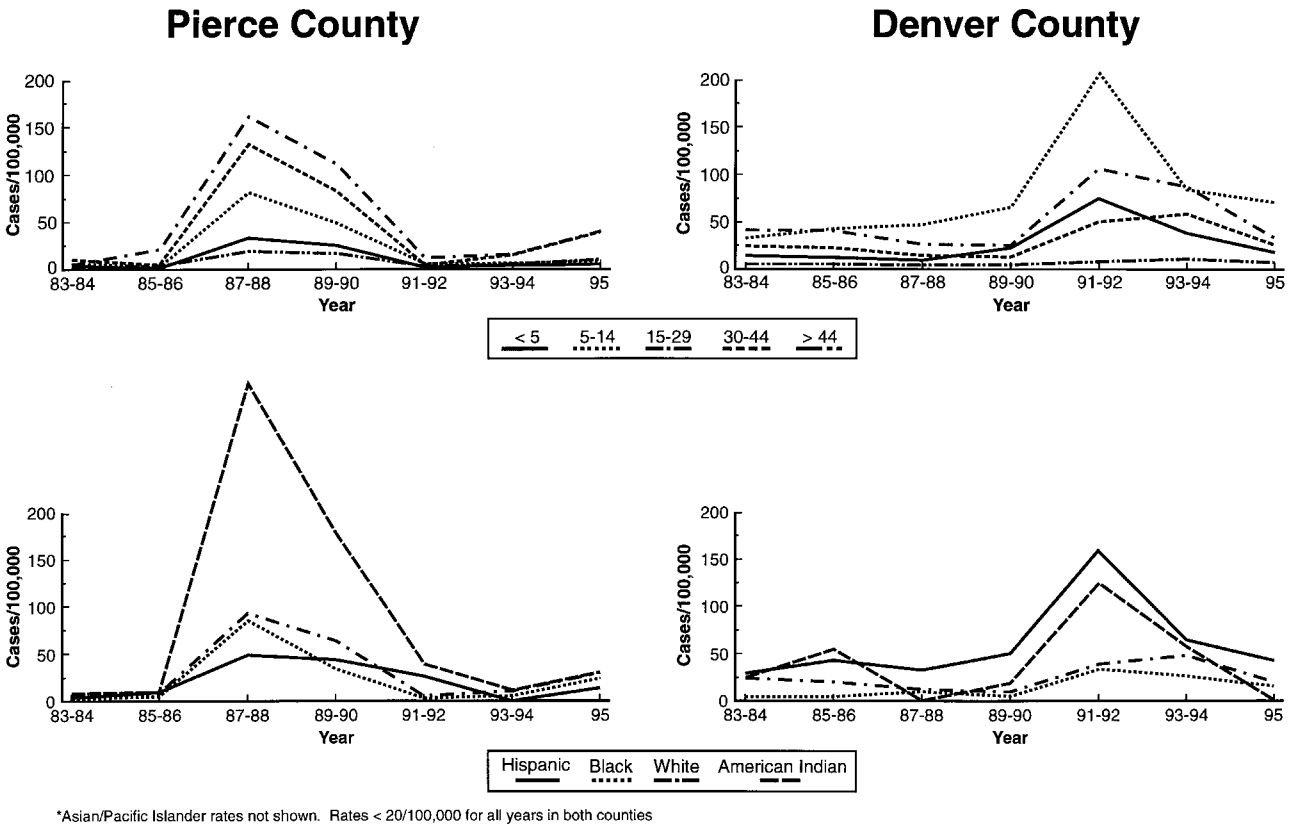

Figure 2. Hepatitis A rates, by age (top row) and race/ethnicity (bottom row), Denver and Pierce Counties, 1983–1995.

porting each of the major potential sources of infection during the epidemics in Denver and Pierce Counties (figure 3). In Denver County, the largest increase occurred in the number of patients reporting male homosexual activity in the 6 months prior to illness onset (12 [5%] patients during the 3 years before the epidemic compared with 122 patients [13%] during the 3-year epidemic [$P < .01$]). During 1991, this behavior accounted for 36% of cases among persons aged 15–29 years. In Pierce County, particularly large increases were observed among persons reporting injecting drugs, 341 (24%) during epidemic years compared with 22 (9%) during the 3 subsequent nonepidemic years ($P < .001$) (figure 3). The highest proportion of patients (33%) reported this source of infection during the first year of the epidemic, and the proportion decreased to 17% in 1989. The reverse was true for the proportion of patients with no identified source of infection, which increased from 40% in 1987 to 60% in 1989.

Discussion

On the basis of data reported nationally, the epidemiology of hepatitis A in the United States can be described as strikingly heterogeneous, with considerable geographic and year-to-year variability [5]. National data are limited, however, because of a presumed high degree of underreporting, lack of risk factor information on cases, and in the past, a relatively high proportion of cases not confirmed serologically.

The ongoing Sentinel Counties Study was established in 1981 to overcome these problems. In these counties, CDC supports staff to conduct enhanced surveillance, intensive case investigation, and serologic follow-up. This analysis of data from the Sentinel Counties confirms the overall features of hepatitis A epidemiology and provides a detailed representation of the heterogeneity suggested by national data, such as regional and year-to-year variability. The overall average incidence in the Sentinel Counties during the 13-year study period, 15 cases/100,000 population, was similar to the national average rate during this time of 11 cases/100,000 population. However, rates varied depending on the county and year, consistent with patterns seen in national data [5]. Pinellas and Jefferson Counties had consistently low rates, while overall rates in Denver and Pierce Counties were relatively high. In Denver and Pierce Counties, yearly incidence varied considerably because of epidemics. The majority of cases reported during the 13-year study period occurred during these epidemics, each lasting ~3 years. During epidemics, rates increased among all age and racial/ethnic groups, and disease was not limited to specific risk groups, indicating that the epidemic spread widely throughout

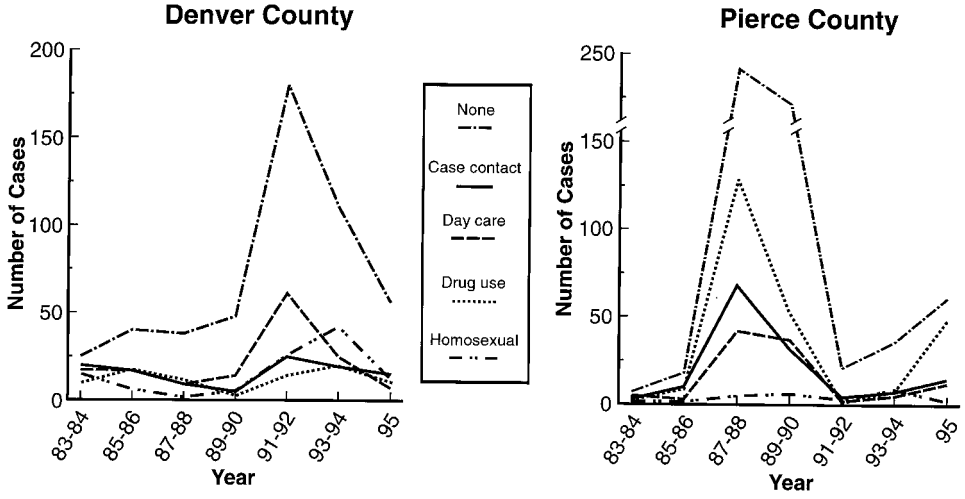

Figure 3. Risk factors reported by patients with hepatitis A, by mutually exclusive groups, Denver and Pierce Counties, 1983–1995.

the community. During epidemics, disproportionate increases did occur among persons reporting certain potential sources of infection, but the particular source varied between counties. In Denver County, the proportion of patients who reported recent male homosexual activity more than doubled during the 1991–1993 epidemic. Similar outbreaks among homosexual men in New York City, San Francisco, Toronto, and other areas were reported during this period [6]. In Pierce County, an analogous increase occurred in the proportion of cases among injecting drug users during the large epidemic in 1987–1989, during which time similar epidemics were seen in other parts of the United States [7, 8].

Outbreaks among children and staff of day care centers have been recognized since the 1970s, and communitywide reductions in the number of reported hepatitis A cases were observed in Phoenix when day care center–related outbreaks were controlled with immune globulin [9, 10]. Because outbreaks in day care centers occur, household contact with a child or employee of a day care center has been considered a risk factor for hepatitis A. However, when patients identified through routine surveillance report this exposure, hepatitis serologic testing of the day care contact is not routinely done to determine if he or she actually had recent HAV infection. Furthermore, serologic surveys have not shown a substantially increased prevalence of HAV infection among day care center staff compared with that of control populations [11–13]. That day care center–related contact accounted for a larger proportion of cases in Denver County compared with Pierce County suggests that persons reporting this exposure may be at increased risk of hepatitis A in some communities but not in others, a situation analogous to that demonstrated for other groups, such as homosexual men and drug users. Alternatively, it is possible that the larger proportion of day care center–associated hepatitis A cases in Denver County reflects more use of day care centers in the community rather than more disease in the centers. The extent to which day care center–related contact may be associated with an increased risk of hepatitis A cannot be addressed by this analysis, and ultimately, the importance of day care centers in HAV transmission needs to be addressed by epidemiologic studies that include a control group.

Previous studies suggest that some persons who cannot identify a source acquire hepatitis A from an asymptomatic or unrecognized case. For example, during an investigation of a communitywide hepatitis A epidemic, 30% of persons with hepatitis A who could not identify a source of infection had, it was found on further testing, an asymptomatic child <6 years old in their household who was IgM anti-HAV–positive (CDC, unpublished data). Our analysis showed that 33% of patients who could not identify a source of infection had a child <5 years old in their household, but this result is difficult to interpret without a control group. A considerable proportion of these patients also reported exposures (e.g., ever injecting drugs, using street drugs but not injecting) that suggest that they lived in the same social or geographic environment as cases with identifiable sources, where close contact with unrecognized or asymptomatic cases might be expected to occur.

The data from the Sentinel Counties Study as well as national surveillance reflect the epidemiology of symptomatic hepatitis A. Because young children who develop infection with HAV are usually asymptomatic, hepatitis A incidence may underestimate the incidence of HAV infection in this age group [2]. Lower hepatitis A incidence among older persons may be explained in part by the higher prevalence of immunity in this age group from prior infection [2]. However, some of the highest incidence rates occurred among population groups in which the prevalence of immunity is higher than the national average, such as American Indians and Hispanics (CDC, unpublished data).

In 1996, the Advisory Committee on Immunization Practices (ACIP) published recommendations for the use of hepatitis A vaccine, primarily focused on persons at increased risk (e.g., sexually active homosexual and bisexual men and users of injecting and noninjecting street drugs) and persons living in communities with high rates, which include many American Indian reservations and Alaska Native villages [2]. The majority of hepatitis A, however, occurs in communities characterized as having an intermediate rate of hepatitis A. In these communities, most disease occurs among children, adolescents, and young adults, and epidemics may occur, with rates during epidemic periods usually ranging from 50 to 200/100,000 population per year.

The ACIP suggests that communities with intermediate rates of hepatitis A, such as Denver and Pierce Counties, consider targeted use of hepatitis A vaccine to control epidemics and prevent their recurrence [2]. Although the effectiveness of such strategies is still unclear [13, 14], it has been hypothesized that vaccination of such a target group early in the course of an epidemic might prevent extension to the entire community. Our findings in Pierce County that one-third of patients early in the epidemic reported injecting drugs and that, over the 3 years of the epidemic, the proportion of cases among persons reporting this behavior decreased while the proportion of cases with no identified source of infection increased suggest that disease may have been more concentrated among persons in a particular risk group early in the epidemic and subsequently spread throughout the community.

This analysis of data from the Sentinel Counties Study provides more complete and detailed information to support evidence from national surveillance data that most cases of hepatitis A in the United States do not occur among persons in identified risk groups. Rather, most disease occurs in the context of communitywide epidemics that display differing epidemiologic patterns and move from community to community over time. Therefore, it is unlikely that sustained nationwide reductions in hepatitis A incidence will occur through vaccination of selected high-risk groups or short-term programs to control individual communitywide epidemics. Our analysis suggests that achieving a rapid reduction in hepatitis A incidence will require widespread vaccination of children and adults. Because HAV does not produce chronic infection and humans are the only natural reservoir of the virus, it is likely that this reduction in incidence will be sustained by maintaining a high level of population immunity through ongoing routine vaccination of infants or young children.

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