

# The Evolving Epidemiology of Hepatitis A in the United States

## *Incidence and Molecular Epidemiology From Population-Based Surveillance, 2005-2007*

R. Monina Klevens, DDS; Jeremy T. Miller, MA; Kashif Iqbal, MPH; Ann Thomas, MD; Elena M. Rizzo, MA; Heather Hanson, MS; Kristin Sweet, MPH; Quyen Phan, MPH; Alicia Cronquist, MPH, RN; Yury Khudyakov, PhD; Guo-liang Xia, MD; Philip Spradling, MD

**Background:** The incidence of hepatitis A virus (HAV) disease is the lowest ever in the United States. We describe recent incidence and characteristics of cases of HAV disease from 6 US sites conducting hepatitis surveillance in the Emerging Infections Program.

**Methods:** Health departments conducted enhanced, population-based surveillance for HAV from 2005 through 2007. Demographic and risk factor data were collected on suspected cases (persons with a positive IgM anti-HAV result) using a standard form. Remnant serum specimens from a convenience sample of cases were tested by polymerase chain reaction, followed by sequencing the 315-nucleotide segment of the VP1-P2B junction.

**Results:** There were 1156 HAV cases reported during 2005 through 2007. The combined population under surveillance was 29.8 million in 2007. The overall annual incidence rate was 1.3 per 100 000 population (range by

site, 0.7-2.3). Of reported cases, 53.4% were male, 42.4% were white, 44.7% were aged 15 to 39 years, and 91.4% resided in urban areas. Reported risk factors were international travel (45.8%), contact with a case (14.8%), employee or child in a daycare center (7.6%), exposure during a food or waterborne common-source outbreak (7.2%), illicit drug use (4.3%), and men who had sex with men (3.9%). Genotypes among the 271 case specimens were IA (87.8%), IB (11.4%), and IIIA (0.7%). Of the 271 polymerase chain reaction–positive specimens, 131 (48.3%) were from cases reporting travel or exposure to a traveler; 58 of the 131 cases reported travel to Mexico, and 53 of the 58 were within the US-IA<sub>1</sub> cluster.

**Conclusions:** International travel was the predominant risk factor for HAV transmission. Health care providers should encourage vaccination of at-risk travelers.

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**W**ORLDWIDE, THERE are an estimated 1.4 million cases of hepatitis A virus (HAV) infection each year.<sup>1</sup> Infection patterns vary geographically. In developing countries with poor sanitary infrastructure and high infection rates, exposed children develop immunity without presenting symptoms of

### *See Invited Commentary at end of article*

disease and outbreaks are infrequent. In contrast, residents of areas with low levels of HAV infection have fewer opportunities in childhood for developing passive immunity, leading to populations of susceptible adults who are more likely to develop symptomatic disease if infected. Recent out-

breaks in the European Union illustrate the pattern of developed countries with record low levels of disease incidence. During 2007 through 2008, outbreaks of HAV disease were reported among injection drug users in Czech Republic,<sup>2</sup> among restaurant patrons and others in Latvia,<sup>3</sup> among persons of low socioeconomic status in Slovakia,<sup>4</sup> and among travelers in France,<sup>5</sup> Belgium,<sup>6</sup> and Germany.<sup>7</sup> Understanding HAV transmission patterns is critical for targeting vaccination toward susceptible populations.

In the United States, the National Notifiable Diseases Surveillance System (NNDSS) of the Centers for Disease Control and Prevention (CDC) has received voluntary reports of acute, viral hepatitis from all states and the District of Columbia since 1966,<sup>8</sup> and in 2007, the incidence of HAV disease from NNDSS was

Author Affiliations are listed at the end of this article.

the lowest ever reported. The last large outbreak of HAV in the United States occurred in 2003, associated with uncooked, imported green onions served in restaurants.<sup>9</sup> More than ever, surveillance is needed to identify cases early to limit and prevent disease.

To supplement information from NNDSS and to build a specimen library of hepatitis strains, the CDC recruited states to participate in the Emerging Infections Program (EIP) ([http://www.cdc.gov/ncpdcid/deiss/about\\_eip.html](http://www.cdc.gov/ncpdcid/deiss/about_eip.html)). Funding for molecular testing of HAV specimens in EIP was provided by the Food Safety Initiative of the CDC. The objective of this report was to describe recent incidence and characteristics of cases of HAV disease, including source of infection and molecular characteristics, from the 6 US sites conducting population-based hepatitis surveillance in the EIP.

## METHODS

### SITES AND CASE SELECTION

During 2005 through 2007, the participating EIP sites were Colorado, Connecticut, Minnesota, 34 counties in upstate New York, New York City, and Oregon. The combined population under surveillance in these 6 sites was an estimated 29.8 million in 2007. In all sites, laboratories and health care providers are required to report cases of HAV disease; sites communicate periodically with clinical laboratories to improve compliance. A case of hepatitis A was defined using Council of State and Territorial Epidemiologists criteria as a person with acute illness with discrete onset of symptoms and either jaundice or elevated serum aminotransferase levels and a positive test result for immunoglobulin M to hepatitis A virus (IgM anti-HAV) ([http://www.cdc.gov/ncphi/diss/nndss/casedef/case\\_definitions.htm](http://www.cdc.gov/ncphi/diss/nndss/casedef/case_definitions.htm)). Each site evaluated case reports to determine if they met the definition and then investigated cases to determine the source of infection and prevent secondary transmission to exposed contacts, if needed.<sup>10</sup> Investigations of suspected cases were conducted by health department personnel who collected, either through health care provider or patient interview, basic clinical and demographic characteristics, along with risks for transmission during the 2 to 6 weeks prior to onset of symptoms. Sites submitted these data electronically, without personal identifying information, to the CDC every month. We selected cases reported to the participating sites from January 1, 2005, through December 31, 2007, and submitted to the CDC by December 2008. We defined a travel-related case as a case with a yes response to either of these questions: "In the 2-6 weeks before symptom onset, did the patient travel outside the USA or Canada?" or "In the 3 months prior to symptom onset, did anyone in the patient's household travel outside of the USA or Canada?" Cases with a yes response to either question were also asked to list the country or countries of travel. We categorized reported country of travel by geographic region, consistent with macrogeographic regions used by the United Nations (<http://unstats.un.org/unsd/methods/m49/m49regin.htm>).

### INCIDENCE ESTIMATES

We stratified cases reported from January 2005 through December 2007 by year, site, sex, race, and age as numerators. We obtained corresponding denominators by year, site, sex, race, and age from the US Bureau of the Census. We classified counties into urban and nonurban using criteria for metropolitan

statistical areas and divisions from the Office of Management and Budget (see <http://www.census.gov/population/estimates/metro-city/List4.txt>).

## SPECIMEN COLLECTION AND LABORATORY METHODS

Sites contacted clinical laboratories to collect remnant serum specimens obtained within 6 weeks of the onset of symptoms from confirmed cases, if available. Serum specimens were shipped frozen to the CDC for genetic characterization and storage in a library of viral strains. If the volume of serum was 0.2 mL or greater, the Division of Viral Hepatitis laboratory at the CDC conducted nucleic acid detection and amplification using reverse transcription-polymerase chain reaction (RT-PCR). Specimens that were PCR positive were then sequenced for the 315-nucleotide segment of the VP1-P2B junction using methods described previously.<sup>11</sup> The Accelrys GCG Package (Accelrys Inc, San Diego, California) was used for sequence analyses. Sequences obtained from EIP specimens were compared with a CDC reference library containing more than 3000 HAV isolates and described in more detail elsewhere.<sup>12</sup> Briefly, the CDC reference library of HAV isolates is a convenience sample and includes isolates from multiple sources including a special CDC collaborative project from the interior of Mexico and the US-Mexican border, the CDC Sentinel Counties project, and select sequences from GenBank.<sup>12</sup> The reference library isolates are mostly from North America and have been helpful in understanding transmission networks of HAV in the United States.<sup>13</sup> Within the genotypes and subgenotypes identified, 3 major clusters have been described: US-IA<sub>1</sub>, US-IA<sub>2</sub>, and US-IA<sub>3</sub>. Typically, isolates from Mexico have been closely related to isolates in the US-IA<sub>1</sub> cluster, isolates from injecting drug users (mostly US-IA<sub>2</sub>), and isolates from men who have sex with men (mostly US-IA<sub>3</sub>).<sup>12</sup> Final phylogenetic tree construction was based on an unweighted pair-group method with arithmetic mean algorithms.<sup>12</sup>

## RESULTS

There were 1156 cases of acute HAV disease reported during 2005 through 2007; of these, 566 (49.0%) were reported from New York City. In most sites, at least half of the cases were male (range, 49.1%-54.6%) and white (range, 20.1%-76.7%) (**Table 1**); in New York City, 38.7% of cases were Hispanic. The greatest proportion of cases were aged 15 to 39 years but varied by site, from 36.1% in New York State to 49.2% in Colorado. Most cases were residents of urban areas (range, 77.4%-100%).

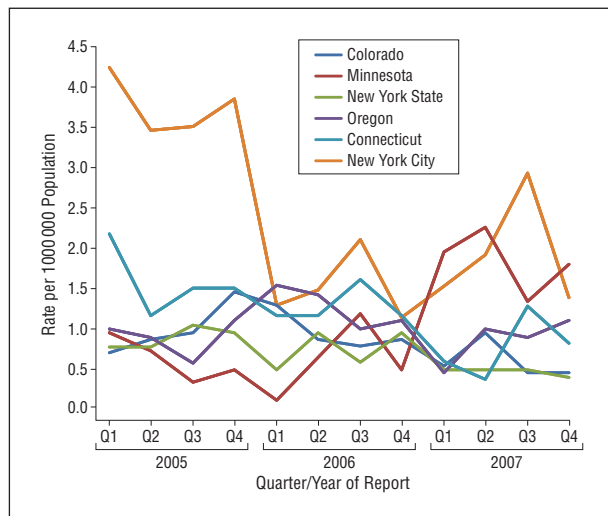
In New York City and Minnesota, there were select peaks in the rate of case reports, consistent with outbreaks (**Figure 1**). In New York City, there were 3 peaks in the rate observed during quarter 3 in 2005, 2006, and 2007. An investigation of 75 confirmed cases during 2006 through 2007 revealed that those cases were mostly Hispanic (43%) and reporting travel (48%) to an endemic region and not part of an outbreak. In Minnesota, the rate peaked during quarters 2 and 3 of 2007, reflecting 2 independent outbreaks. On further investigation, these outbreaks were found to be associated with restaurants; however, no individual contaminated food item or infected food handler was identified. The remaining sites were characterized by relatively constant case reporting over time.

**Table 1. Incidence and Characteristics of Cases of Hepatitis A<sup>a</sup>**

Variable	Colorado	Connecticut	Minnesota	New York State	New York City	Oregon	Row Total
Cases reported, No.	120	121	155	86	566	108	<b>1156</b>
Incidence per 100 000 population	0.8	1.2	1.0	0.7	2.3	1.0	1.3
Sex							
Male	63 (52.5)	64 (52.9)	83 (53.5)	45 (52.3)	309 (54.6)	53 (49.1)	<b>617 (53.4)</b>
Female	57 (47.5)	57 (47.1)	72 (46.5)	41 (47.7)	255 (45.1)	55 (50.9)	<b>537 (46.5)</b>
Missing	0	0	0	0	2 (0.4)	0	2 (0.2)
Race/ethnicity							
American Indian/Alaskan Native	0	2 (1.7)	4 (2.6)	0	0	1 (0.9)	<b>7 (0.6)</b>
Asian/Pacific Islander	5 (4.2)	7 (5.8)	3 (1.9)	7 (8.1)	56 (9.9)	1 (0.9)	<b>79 (6.8)</b>
Black	1 (0.8)	4 (3.3)	7 (4.5)	4 (4.7)	40 (7.1)	0	<b>56 (4.8)</b>
White	76 (63.3)	62 (51.2)	91 (58.7)	66 (76.7)	114 (20.1)	79 (73.2)	<b>488 (42.4)</b>
Hispanic	31 (25.8)	39 (32.2)	28 (18.1)	8 (9.3)	219 (38.7)	20 (18.5)	<b>345 (29.8)</b>
Multiple/other	0	1 (0.8)	0	1 (1.2)	66 (11.7)	0	<b>68 (5.9)</b>
Missing	7 (5.8)	6 (5.0)	22 (14.2)	0	71 (12.5)	7 (6.5)	<b>113 (9.8)</b>
Age, y							
<15	16 (13.3)	22 (18.2)	27 (17.4)	8 (9.3)	149 (26.3)	13 (12.0)	<b>235 (20.3)</b>
15-39	59 (49.2)	49 (40.5)	66 (42.6)	31 (36.1)	267 (47.2)	45 (41.7)	<b>517 (44.7)</b>
≥40	45 (37.5)	50 (41.3)	61 (39.4)	47 (54.7)	147 (26.0)	50 (46.3)	<b>400 (34.6)</b>
Missing	0	0	1 (0.7)	0	3 (0.5)	0	4 (0.4)
Urban residence	101 (84.2)	111 (91.7)	120 (77.4)	69 (80.2)	566 (100)	89 (82.4)	<b>1056 (91.4)</b>
Had specimen <sup>b</sup>	46 (38.3)	42 (34.7)	63 (40.7)	37 (43.0)	94 (16.6)	68 (63.0)	<b>350 (30.3)</b>

<sup>a</sup>Emerging Infections Program Hepatitis Surveillance Sites, 2005-2007. Data are given as number (percentage) of cases unless otherwise specified.

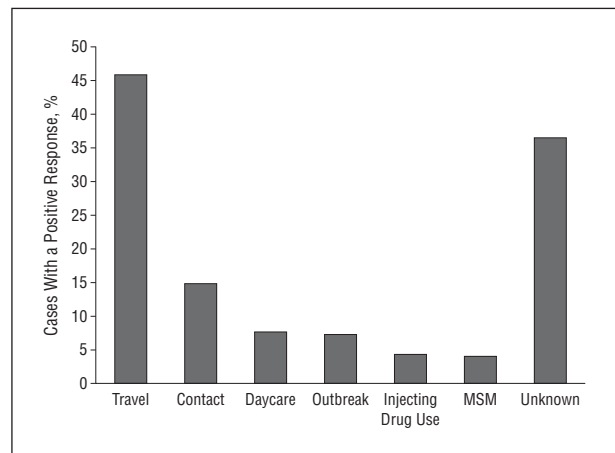
<sup>b</sup>For New York City, prior to Sept 1, 2006, no specimens were sent. Since Sept 1, 2006, specimens were sent for 94 of 210 cases (44.7%).



**Figure 1.** Rate of hepatitis A cases per 100 000 population by date of report and site (Emerging Infections Program, Hepatitis Surveillance, 2005-2007). IDUs indicates injecting drug users; MSM, men who have sex with men.

### INCIDENCE RATES

For all sites combined, the incidence rate of HAV disease was 1.3 per 100 000 population (range by site, 0.7-2.3 per 100 000) during 2005 through 2007 (Table 1). The rate was 1.5 in 2005, 1.1 in 2006, and 1.2 in 2007. Annual incidence was somewhat higher among men (1.4 per 100 000) than women (1.2 per 100 000) and among persons aged 15 to 39 years (1.7 per 100 000), Hispanics (2.7 per 100 000), and persons reporting multiple race/ethnicity (5.6 per 100 000). Within states, county-specific annual incidence per 100 000 population ranged by site as follows: 0.0 to 4.3 in Colorado, 0.4 to 1.1 in Connecticut,

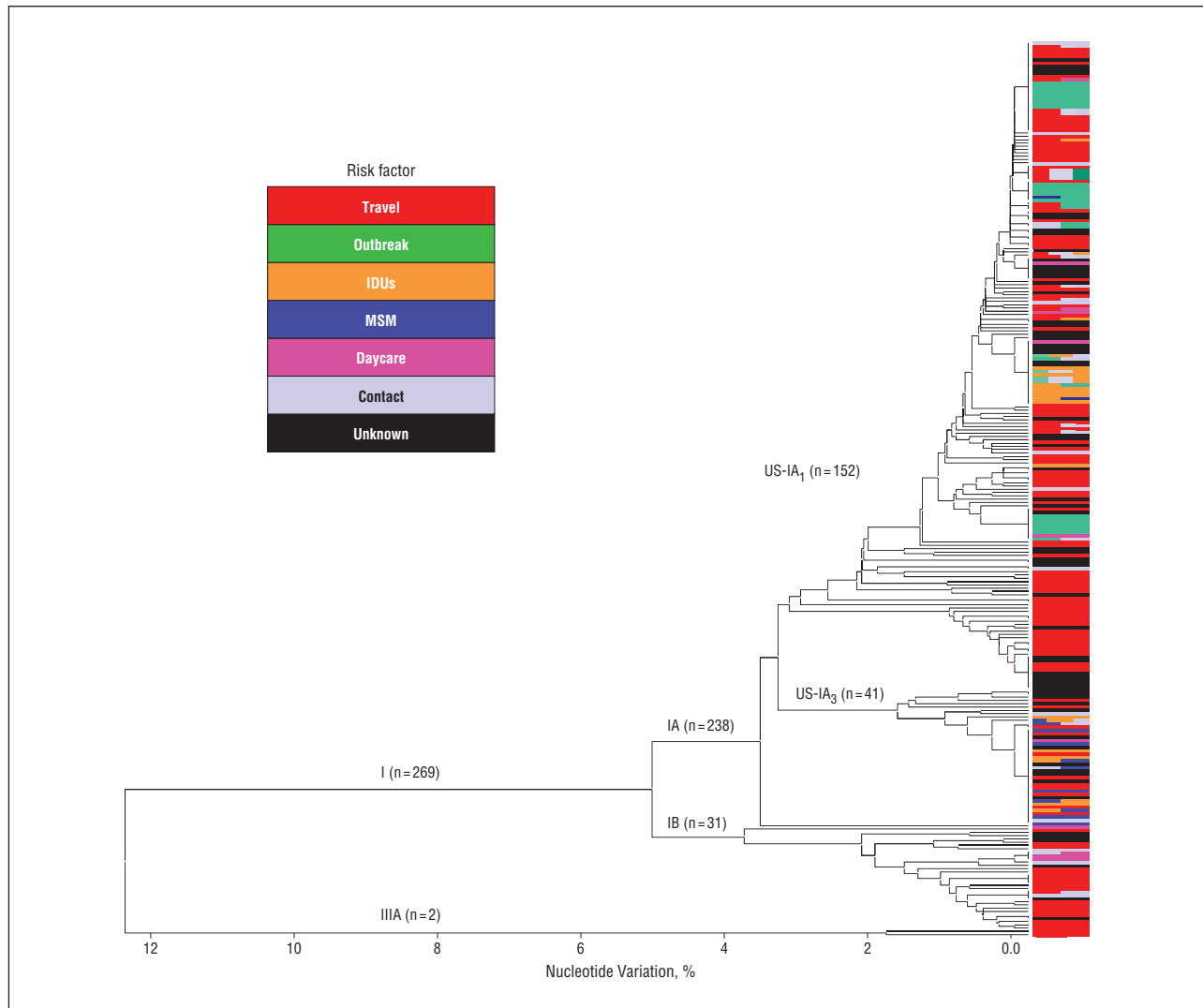


**Figure 2.** Potential source of infection or risk factor for hepatitis A (Emerging Infections Program, Hepatitis Surveillance Sites, 2005-2007). Note: 187 of 1156 cases had more than 1 source or factor with a positive response. MSM indicates men who have sex with men.

0.0 to 26.5 in Minnesota, 0.0 to 2.0 in participating counties in New York State, 0.5 to 2.7 in New York City, and 0.0 to 5.3 in Oregon.

### POTENTIAL SOURCES OF INFECTION

Cases could report more than 1 behavior or exposure during the 2- to 6-week period before onset of symptoms as potential risk factors for infection (**Figure 2**). Overall, 529 (45.8%; range by site, 32.2%-50.8%) of the 1156 cases reported travel as a risk factor, including 476 (41.2%) cases reporting personal international travel and 217 (18.4%) cases reporting exposure to an international traveler. Of the 529 travel-related cases, 164 (14.2%) both traveled *and* were exposed to a traveler, and 52 (4.5%) reported being exposed to a traveler without having trav-



**Figure 3.** Hepatitis A virus sequence analysis (Emerging Infections Program, Hepatitis Surveillance Sites, 2005-2007). IDUs indicates injecting drug users; MSM, men who have sex with men.

eled personally. In 395 cases (34.2%), traveling or being exposed to a traveler was reported as their only risk factor. The destination most frequently reported among travelers (30.3%) and household contacts (26.3%) was Mexico. However, the frequency of travel destinations reported varied widely by site: 69.8% of cases from Oregon reported travel to Mexico, in contrast to only 6.9% of cases from New York State.

Other risk factors reported among cases, during the 2- to 6-week period before onset of symptoms, included contact with a case (14.8%), being an employee or child in a daycare center (7.6%), exposure during a common-source outbreak (7.2%), using illicit drugs (4.3%), or men who have sex with men (3.9%). In 421 cases (36.4%), the case denied all the above risk factors.

### LABORATORY RESULTS

Overall, specimens were available for 350 of the 1156 cases (30.3%), but availability varied by site (range, 16.6%-63.0%; Table 1). Of the 350 specimens, 271 (77.4%) were PCR positive and could be sequenced. There were dif-

ferences in PCR positivity by age and risk factor but not by site, sex, or race. Genotypes among the 271 case specimens were IA (87.8%), IB (11.4%), and IIIA (0.7%) (**Figure 3**).

Travel-related cases were largely similar to strains from other countries or cases traveling to other countries in the historic reference library. A total of 131 PCR-positive specimens were observed among travel-related cases (ie, cases reported travel or were exposed to a traveler); 58 of these cases involved travel to Mexico (**Table 2** and Figure 3, shown in red). Of the 58, 53 (91.4%) were within the US-IA<sub>1</sub> cluster. Similarly, 9 of 10 specimens (90%) from cases involving travel to Central America were within the US-IA<sub>1</sub> cluster. In contrast, 19 of 22 specimens (86.4%) from travel-related cases to South America were genotype IA but not IA<sub>1-3</sub> clusters. A total of 17 (13.0%) of all PCR-positive specimens from travel-related cases were genotype IB, 2 (1.5%) were genotype IIIA, and 30 (22.9%) were IA but were not within the IA<sub>1-3</sub> cluster.

Of 68 PCR-positive specimens with no known epidemiologic risk factor, 37 (54.4%) were similar to historical reference outbreak strains of genotype IA, cluster US-

**Table 2. Polymerase Chain Reaction (PCR)-Positive Specimens Among Cases of Hepatitis A Reporting Travel or Exposure to Someone Who Traveled Outside the United States and Canada by Destination<sup>a</sup>**

Destination <sup>b</sup>	Case Traveled or Exposed to Traveler and PCR Positive	Cases, No. (%)					Genotype IB	Genotype IIIA
		Genotype IA						
		US-IA <sub>1</sub>	US-IA <sub>2</sub>	US-IA <sub>3</sub>	Other IA Clusters			
Mexico	58	53 (91.4)		1 (1.7)	4 (6.9)			
Central America	10	9 (90.0)			1 (10.0)			
South America	22			3 (13.6)	19 (86.4)			
Caribbean	18	4 (22.2)		4 (22.2)	2 (11.1)	8 (44.4)		
Africa or Middle East	9					9 (100)		
Asia or Pacific Islands	7	1 (14.3)			4 (57.1)		2 (28.6)	
Other areas	7	3 (42.9)	1 (14.3)	3 (42.9)				
<b>Total</b>	<b>131</b>	<b>70 (53.4)</b>	<b>1 (0.8)</b>	<b>11 (8.4)</b>	<b>30 (22.9)</b>	<b>17 (13.0)</b>	<b>2 (1.5)</b>	

<sup>a</sup>Emerging Infections Program Hepatitis Surveillance Sites, 2005-2007.

<sup>b</sup>Destination was categorized by using the United Nations geographic region and composition (<http://unstats.un.org/unsd/methods/m49/m49regin.htm>) with the exception of countries listed as Western Asia and Mexico. Most Western Asian countries were grouped with Africa and the Middle East with the exception of Turkey and Georgia, which were included in the "Other areas" category. Mexico was categorized separately from Central America owing to the high proportion of cases. Countries listed in Asia or Pacific Islands combined countries listed in Central Asia, Eastern Asia, Southern Asia, and Southeastern Asia. Europe and Oceania are listed in the "Other areas" category.

IA<sub>1</sub>. All HAV strains from men who have sex with men were IA, almost exclusively found in the US-IA<sub>3</sub> cluster (Figure 3, shown in blue); in addition, 11 of 68 specimens with no reported risk factors matched these strains. There were 37 specimens from cases with more than 1 risk. These are illustrated in Figure 3 by a partitioned strip with more than 1 color.

#### COMMENT

The overall incidence of HAV disease during 2005 through 2007 in these sites was low (1.3 per 100 000 population), consistent with the rate in NNDSS for the same period (1.0-1.5 per 100 000).<sup>8</sup> Rates varied moderately by site, from 0.7 to 2.3 per 100 000 population. In contrast, geographic variability was more extreme in the United States before the availability of the vaccine. For example, in 1995, the incidence of HAV disease ranged from 1.1 per 100 000 in Kentucky and New Hampshire to 86.7 per 100 000 in Oregon.<sup>8</sup> One extreme observed in our data was the rate of 26.5 per 100 000 observed in a small county in Minnesota (population, approximately 9000 residents), where a foodborne outbreak of HAV was investigated. This illustrates how the epidemiologic pattern of HAV is in transition from outbreak-driven cases to only sporadic outbreaks in the United States. Continued disease surveillance is essential to controlling outbreaks and represents an important system needed to inform vaccination programs and target groups at highest risk of infection.<sup>13</sup>

The HAV vaccination strategy in the United States was initiated in 1996 with the Advisory Committee on Immunization Practices (ACIP) recommendation to vaccinate travelers among other groups at increased risk of disease.<sup>14</sup> By 1999, there was epidemiologic evidence that the impact on national disease incidence was limited; thus, the vaccination strategy was expanded to include routine vaccination of children 2 years or older residing in areas where incidence was at least twice the US aver-

age.<sup>15</sup> The impact of this expansion was dramatic; by 2003, the incidence rate of HAV disease had declined by 76% overall and by 87% among children aged 2 to 18 years.<sup>16</sup> In 2006, the ACIP recommended routine, universal vaccination of children 12 months or older in the United States.<sup>10</sup>

Before routine vaccination, the epidemiologic patterns of HAV disease were well documented in 4 US counties participating in the Sentinel Counties Study of Acute Viral Hepatitis of the CDC. This study conducted enhanced case surveillance including patient interview and serologic testing using a rigorous standardized protocol from 1982 through 2006.<sup>17</sup> Analyses of data from 1983 through 1995 demonstrated that HAV disease was transmitted largely by local, sustained outbreaks.<sup>17</sup> Disease occurred primarily among persons aged 15 to 29 years. The most frequently reported risk factors were history of injecting drug use (14%) and sexual or household contact with an individual with HAV (12%). Risk factor information remained unknown in 52% of cases, and travel was identified as a risk factor in only 4% of cases.<sup>17</sup>

We document major, but not unexpected, differences in the epidemiologic pattern of HAV disease during 2005 through 2007 in participating sites. The most frequent potential source of infection among persons reported with HAV disease was travel. Our epidemiologic findings used patient self-report but were confirmed by genetic patterns indicating similarities to HAV strains available in the reference library from international travelers. While a departure from the 4% of travel-associated cases in the prevaccination era, our finding of 45.8% of travel-related HAV disease is consistent with surveillance in Switzerland, where between 2000 and 2004, 41.2% of cases reported a history of travel.<sup>18</sup>

This finding points to a prevention opportunity in the hands of health care providers to recommend pre-exposure vaccination to their patients planning travel to HAV endemic areas.

In the prevaccination era (before 1995), asymptomatic children were thought to be the source of infection among cases with unknown risk factors. For example, in the Sentinel Counties study, 33% of cases with unknown risk were exposed to children younger than 5 years.<sup>17</sup> In NNDSS, risk factor information was not available for 50% of reported cases of HAV disease during 2007.<sup>8</sup> In EIP sites, 36% of cases had no risk factor identified. Future studies should evaluate how to improve descriptions of risk patterns among HAV cases.

Molecular epidemiologic methods have been useful in understanding HAV transmission within networks of persons with similar risk factors.<sup>11</sup> When applied in combination with conventional epidemiologic methods, HAV sequencing has also been useful in the investigation and control of outbreaks, where it clearly augments and complements the epidemiologic information.<sup>19</sup> However, for routine surveillance purposes, collecting specimens and conducting molecular characterization of HAV strains does not provide actionable information. The sequencing of specimens from EIP HAV cases during 2005 through 2007 confirmed existing data on risk factors but did not provide insight into transmission routes among cases with unknown risk factors. The intent of molecular characterization of specimens collected during routine surveillance may provide useful background data to be used in the event of an outbreak to discriminate outbreak-related strains from sporadic strains.<sup>9</sup>

Specimens from case patients in a variety of countries have revealed some consistency in the worldwide distribution of HAV genotypes. Among the specimens sequenced from the EIP sites, almost 90% were genotype IA, the most common genotype in the United States and worldwide; the remainder were largely genotype IB (less than 1% were genotype IIIB). Whereas the distribution of genotype IA includes Mexico and many Central and South American countries, the distribution of genotype IB has been limited to Brazil.<sup>12</sup> Consistent with our findings for travelers to Mexico, viral sequences from patients with a history of travel are closely related to the sequence patterns of isolates from countries where the travel occurred.<sup>12</sup>

In the United States, pre-exposure vaccination is recommended for travelers to areas of high or intermediate HAV endemicity. The risk of hepatitis A among susceptible travelers to developing countries has been estimated to range from 3 to 20 per 1000 travelers<sup>20</sup> depending on length of stay and region visited. Unfortunately, awareness of the risk among travelers appears to be low: in an airport survey, only 17% of US travelers to mostly developing countries identified hepatitis A as a risk at their destination.<sup>21</sup> Furthermore, travelers' risk behaviors may vary by whether they are familiar with the area vs not. In an effort to measure the frequency of travel "home" (as opposed to tourism), we found that 86 of 108 cases reporting direct travel and known to have been born outside the United States had traveled to their country of birth. Overall, based on our finding that 45.8% of HAV cases may be travel related, enhanced implementation of existing recommendations for the prevention of HAV among travelers pre-exposure and postexposure could further

reduce HAV disease in the United States.<sup>22</sup> Identifying reasons for travel (eg, business, visiting family and relatives, tourism) among persons with HAV may be helpful in directing future vaccination initiatives.

We also found that 24% of cases reporting exposure to a traveler did not travel themselves. Investigations of HAV disease among contacts of international adoptees<sup>23</sup> prompted the ACIP to expand the recommendation for use of hepatitis A vaccine in February 2009 to include household members and other close personal contacts (eg, regular babysitters) of internationally adopted children from countries of high or intermediate HAV endemicity (<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5901a5.htm>). We did not ascertain the number of cases from EIP sites that were contacts of adoptees; however, implementation of this expanded recommendation should further reduce the incidence of HAV disease in the United States.

This report is subject to several limitations. Incidence values represent a minimum estimate because the current surveillance case definition captures only persons with symptomatic illness and even symptomatic cases are underreported to local and state public health authorities.<sup>24</sup> We may have overestimated travel as a risk factor because it is easier for investigators to elicit travel history during interviews in contrast to, for example, drug use history. Furthermore, while cases may have reported travel, it is impossible to know whether they acquired their infection during travel. We do know that, compared with prevaccination dates, our finding of frequent reported travel among HAV cases does not reflect an underlying increase in travel in the population. In 1990, an estimated 19.7 per 100 000 US residents traveled internationally, whereas in 2007, 21.2 per 100 000 did so.<sup>25</sup> Specifically, the proportion of US residents traveling to Mexico decreased, from 36.6% of international travelers in 1990 to 30.4% in 2007.<sup>25</sup>

Other limitations include a lack of complete geographic diversity and an overrepresentation of urban areas among the EIP sites. Also, the New York City data for the first 6 months of this report may have included cases that did not meet the CDC case definition; this is because, prior to July 2005, New York City classified all hepatitis A IgM reports as confirmed cases. Finally, specimens were a convenience sample of remnant serum specimens and collection rates varied by site, thus molecular data are not representative of the US population. However, even with these limitations, findings from hepatitis surveillance in the EIP are valuable to describe the epidemiologic pattern of viral hepatitis in the United States. For example, the frequency of unknown risk factors for HAV disease was lower in EIP cases (34%) than in NNDSS (50%) cases. In addition, EIP sites are representative of a larger US population (29.8 million) compared with the Sentinel Counties project (estimated 2008 population, 2.9 million).

Vaccination of children and high-risk groups in the US has reduced the incidence of HAV disease to record lows. Further reductions will depend on the continuation of routine, universal vaccination as well as health care providers encouraging vaccination of susceptible travelers.

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**Author Affiliations:** Division of Viral Hepatitis, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia (Drs Klevens, Khudyakov, Xia, and Spradling and Messrs Miller and Iqbal); Oregon Public Health Division, Portland (Dr Thomas); New York State Department of Health, Albany (Ms Rizzo); New York City Department of Health and Mental Hygiene, New York (Ms Hanson); Vaccine Preventable Disease Surveillance, Minnesota Department of Health, St Paul (Ms Sweet); Epidemiology and Emerging Infections Program, Connecticut Department of Public Health, Hartford (Mr Phan); and Colorado Department of Public Health and Environment, Denver (Ms Cronquist).

**Correspondence:** R. Monina Klevens, DDS, Division of Viral Hepatitis, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, 1600 Clifton Rd, MS G-37, Atlanta GA 30333 (rmk2@cdc.gov).

**Author Contributions:** Dr Klevens and Messrs Miller and Iqbal had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Klevens and Khudyakov. *Acquisition of data:* Klevens, Iqbal, Thomas, Rizzo, Hanson, Sweet, Phan, Cronquist, Khudyakov, and Xia. *Analysis and interpretation of data:* Klevens, Miller, Iqbal, Thomas, Hanson, Cronquist, Khudyakov, Xia, and Spradling. *Drafting of the manuscript:* Klevens, Iqbal, Thomas, Xia, and Spradling. *Critical revision of the manuscript for important intellectual content:* Klevens, Miller, Thomas, Rizzo, Hanson, Sweet, Phan, Cronquist, Khudyakov, and Spradling. *Statistical analysis:* Miller and Xia. *Obtained funding:* Klevens and Xia. *Administrative, technical, and material support:* Klevens, Iqbal, and Phan. *Study supervision:* Klevens, Thomas, Hanson, Khudyakov, and Spradling.

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## INVITED COMMENTARY

# Hepatitis A

## A Traveling Target

Approximately 26 000 cases of acute HAV infection were reported annually in the United States prior to the advent of the HAV vaccine.<sup>1</sup> The actual rate of infection was likely 10 times higher because most infections occur in young children, in whom the disease generally causes few or no symptoms.<sup>2</sup> The virus is spread through fecal-oral transmission, and there is no evidence of a chronic carrier state or long-term sequelae. Historically, adult infections in the United States originated from contact with a child who had unrecognized infection or through epidemics attributable to contaminated food or water.<sup>3</sup> In developing countries, where childhood infection is prevalent, most of the population develops immunity, and adult infection is rare. In countries with a low incidence of infection, such as the United States, immunity to HAV is less common, and the disease is more likely to affect adults, in whom symptoms are common and include fever, malaise, jaundice, and abdominal discomfort, with rare cases of acute liver failure (for which chronic liver disease is considered a risk factor).<sup>4</sup> The case-fatality rate for HAV infection is 0.3% to 0.6% overall but may be as high as 1.8% among persons older than 50 years.<sup>5</sup>

When the HAV vaccine was first licensed in 1995, the challenge was to develop a strategy to eliminate the hundreds of preventable deaths from HAV infection occurring each year in the United States. In 1996, the ACIP<sup>5</sup> recommended vaccination of persons in specific high-risk target groups, including international travelers, men who have sex with men, and injection drug users, as well as children living in communities with high rates of HAV infection.<sup>5</sup> This practice resulted in only a limited reduction in the number of new hepatitis A cases. In 1999, the ACIP expanded the recommendations to include vaccination of all children living in communities with rates of infection at least twice the national average. The incidence of infection declined markedly in these communities but not in communities in which vaccination of children was not universal. In 2005, the vaccine was approved for use in children aged 12 to 23 months, thereby allowing the vaccine to be incorporated into the schedule of routine childhood immunizations. The following year, the ACIP recommended universal childhood vaccination for HAV throughout the United States.<sup>5</sup> In this issue of *Archives*,

Klevens and colleagues present surveillance data for HAV from 2005 to 2007 that demonstrate the lowest incidence of HAV infection in US history.

Prior studies, as cited by Klevens et al, have reported HAV incidence rates derived from the National Notifiable Diseases Surveillance System of the CDC, which receives voluntary reports of acute viral hepatitis from all states. In the study by Klevens et al, the CDC's Emerging Infections Program required mandatory reporting of all cases of HAV infection in participating regions: Colorado, Connecticut, Minnesota, Oregon, 34 counties in upstate New York, and New York City, encompassing a total population of 29.8 million persons. The investigators defined cases of acute HAV infection by the presence of an acute illness with jaundice, elevated serum aminotransferase levels, and a positive test for IgM to HAV. Health department personnel obtained additional information regarding potential causes of infection from confirmed cases and collected serum specimens within 6 weeks of the onset of symptoms when possible. Reverse-transcriptase polymerase chain reaction genetic sequencing was performed on these samples to identify HAV genotypes that have been linked to transmission networks in other studies.

The reduction in incidence of HAV infection from 14 per 100 000 population before vaccination to 1.3 per 100 000 during this surveillance period is dramatic.<sup>3</sup> The more striking finding is that universal childhood vaccination appears to have changed the entire epidemiology of HAV infection from an outbreak-associated disease to sporadic cases associated largely with international travel. In the study by Klevens et al, 41% of cases reported personal international travel as a risk factor for infection, and 18% reported exposure to an international traveler, with or without actual travel. These figures compare with just 4% of infected persons reporting travel as a risk factor in the decade before vaccination.<sup>3</sup> In addition, several peaks in the rate of infection during the surveillance period suggested the occurrence of outbreaks. Interestingly, however, further investigation demonstrated that even these cases stemmed from travel to an endemic region. In fact, the last major outbreak of HAV disease in the United States occurred in 2003 as a result of contaminated green onions.