

Epidemiology of Acute Hepatitis B in the United States From Population-Based Surveillance, 2006–2011

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Background. An estimated 20 000 new hepatitis B virus (HBV) infections occur each year in the United States. We describe the results of enhanced surveillance for acute hepatitis B at 7 federally funded sites over a 6-year period.

Methods. Health departments in Colorado, Connecticut, Minnesota, Oregon, Tennessee, 34 counties in New York state, and New York City were supported to conduct enhanced, population-based surveillance for acute HBV from 2006 through 2011. Demographic and risk factor data were collected on symptomatic cases using a standardized form. Serum samples from a subset of cases were also obtained for molecular analysis.

Results. In the 6-year period, 2220 acute hepatitis B cases were reported from the 7 sites. For all sites combined, the incidence rate of HBV infection declined by 19%, but in Tennessee incidence increased by 90%, mainly among persons of white race/ethnicity and those aged 40–49 years. Of all reported cases, 66.1% were male, 57.1% were white, 58.4% were aged 30–49 years, and 60.1% were born in the United States. The most common risk factor identified was any drug use, notably in Tennessee; healthcare exposure was also frequently reported. The most common genotype for all reported cases was HBV genotype A (82%).

Conclusions. Despite an overall decline in HBV infection, attributable to successful vaccination programs, a rise in incident HBV infection related to drug use is an increasing concern in some localities.

Keywords. hepatitis B; drug use; incidence; surveillance; genotype.

Hepatitis B virus (HBV) infection is a major public health problem, with an estimated 0.7–1.4 million persons living with chronic HBV infection in the United States [1]. There are approximately 1800 deaths annually due to hepatitis B–related liver disease [2]. Although chronic infection represents the larger burden of disease, an estimated 18 800 (10 800–46 100) new HBV infections

occurred in 2011 [3]. The major modes of transmission were sexual contact, sharing of needles for drug injection, household contact with an HBV-infected person, exposure to HBV-infected blood in healthcare settings, and perinatally from infected mother to child [4, 5].

HBV is vaccine preventable, and the United States has conducted childhood immunization for hepatitis B since 1991 and adolescent immunization since 1995 [6, 7]. Vaccine coverage data indicate that since 1993, when vaccine coverage was very low (approximately 37%), the percentage of children 19–35 months of age and adolescents aged 13–17 years who received hepatitis B vaccine has increased and reached >90% in 2011 for both age categories [8, 9]. The impact of vaccination on the disease incidence and risk factors for acute HBV from 1982 to 1998 were described

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previously by Goldstein and colleagues [10]. This article provides an update of the epidemiology of acute hepatitis B, including trends in incidence, and molecular characterization of HBV recovered from acute cases from 2006 through 2011 from US sites conducting enhanced population-based viral hepatitis surveillance.

METHODS

The US Centers for Disease Control and Prevention (CDC) funded 7 sites to conduct enhanced surveillance for viral hepatitis, which included Colorado, Connecticut, Minnesota, Oregon, Tennessee, 34 counties in New York state, and New York City [11]. In all sites, laboratories and providers were required to report cases of viral hepatitis, including hepatitis B, to the CDC on a weekly basis. Each site evaluated the reports to determine if they were previously reported. All new reports were investigated to collect supplemental epidemiologic information, basic clinical information, and information about behaviors/exposures that increased the risk of acquiring the infection. To obtain this additional information, health department personnel contacted the healthcare provider and/or the case patient. Case reports were submitted electronically to the CDC on a monthly basis. The 2000 CDC/Council of State and Territorial Epidemiologists case definition was used to identify cases of acute hepatitis B. A case of acute hepatitis B was defined 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 B core antigen or hepatitis B surface antigen (<http://wwwn.cdc.gov/NNDSS/script/casedef.aspx?CondYrID=709&DatePub=2000-01-01>). This study included cases reported by the participating sites from 1 January 2006 through 31 December 2011 and submitted to the CDC by December 2011. Descriptive analyses were conducted using SAS software version 9.3 (SAS Institute, Cary, North Carolina).

Incidence Estimates

We stratified cases by year, site, sex, race, and age categories as numerators. We obtained corresponding population denominators using intercensal estimates from the US Census Bureau (<http://www.census.gov/popest>) [12]. Temporal trends in annual incidence by year, site, sex, race, and age categories were assessed using the Spearman correlation trend test, and changes in incidence over time were considered statistically significant at $P < .05$. The incidence data were analyzed in aggregate for all sites; however, because 1 site displayed a pattern different from other sites, the data for that site were analyzed separately.

Risk Hierarchy (Mutually Exclusive)

For cases reported with >1 risk, we applied a reported hierarchy similar to that described by Goldstein and colleagues to create

categories that were mutually exclusive for risk that was collected 6 weeks to 6 months of the onset of symptoms from cases as follows [10]: (1) patient received a blood transfusion; (2) drug use including illegal injection drug use (IDU) and non-injection drug use; (3) men who have sex with men (MSM); (4) occupational exposure to blood, including employment in a medical or dental field and public safety worker who had frequent contact with blood; (5) hemodialysis; (6) heterosexual contact with a person known or suspected to have acute or chronic HBV infection; (7) household contact with a person known or suspected to have acute or chronic HBV infection; (8) institutionalization in a long-term-care facility or incarcerated; (9) having >1 heterosexual partner; (10) receipt of healthcare, including having an accidental stick or puncture with a needle or other object contaminated with blood, receipt of intravenous infusions and/or injections in an outpatient setting, dental work, or surgery; and (11) other potential exposures that did not fit in any category (tattoo, piercing, and other contacts). More detailed information for the risk variables can be found on the case report form in the patient history acute hepatitis B section at <http://www.cdc.gov/hepatitis/PDFs/HepatitisCRF-20130508.pdf>.

Individual Risk (Non-Mutually Exclusive)

To determine the most common risk of all risks reported for a single case, we also assessed risk among cases by looking at non-mutually exclusive risk categories as defined in the risk hierarchy. All cases with a “yes” response to any of the risk variables were included in these analyses.

Laboratory Methods

Sites contacted clinical laboratories to collect remnant serum specimens that were obtained within the 6 weeks to 6 months of the onset of symptoms from cases. Serum specimens were shipped frozen to the CDC laboratory for viral characterization. HBV genotyping was performed by nucleotide sequencing of a 435-bp DNA segment amplified from the HBV S gene as previously described [13]. HBV genotypes were classified based on the S-gene sequence by comparing each sequence with published reference sequences from GenBank. Phylogenetic trees were constructed using the maximum likelihood algorithm implemented in Dnaml (PHYLP package, version 3.6).

Ethical Conduct

These activities were part of public health surveillance and thus exempt from institutional review board review.

RESULTS

A total of 2220 cases of acute hepatitis B cases were reported from the 7 sites during 2006–2011. Of the total, 56% of cases were reported from New York City and Tennessee combined

Table 1. Percentage of Acute Hepatitis B Cases by Site and Characteristics

Characteristic	CO (n = 186)	MN (n = 157)	NYS (n = 163)	OR (n = 290)	TN (n = 677)	CT (n = 179)	NYC (n = 568)	Total (N = 2220)	
	Col. %	Col. %	Col. %	Col. %	Col. %	Col. %	Col. %	No.	Col. %
Age									
10–19	2.2	3.8	1.8	0.3	0.9	0.6	0.9	26	1.2
20–29	11.8	19.1	8.0	10.7	21.0	11.7	13.7	337	15.2
30–39	23.1	20.4	25.2	24.5	33.7	24.6	28.9	623	28.1
40–49	33.3	26.1	39.3	22.2	28.8	35.2	28.0	673	30.3
50–59	17.2	16.6	14.7	20.0	10.6	18.4	16.0	336	15.1
60–69	8.1	10.2	8.0	11.7	3.7	5.6	7.0	153	6.9
≥70	4.3	3.8	3.1	2.1	1.2	3.9	5.5	71	3.2
Missing	0.0	0.0	0.0	0.0	0.1	0.0	0.0	1	0.0
Sex									
Female	31.2	31.2	28.2	31.0	38.7	32.4	32.9	750	33.8
Male	68.8	68.8	71.8	69.0	61.3	67.6	66.7	1468	66.1
Missing	0.0	0.0	0.0	0.0	0.0	0.0	0.4	2	0.1
Race									
AI/AN	1.6	3.2	1.2	0.7	0.1	0.6	0.0	14	0.6
API	4.8	5.7	3.1	1.7	0.0	1.7	11.1	94	4.2
Black	6.5	18.5	17.8	3.8	10.5	24.0	33.1	383	17.3
White	50.5	46.5	68.7	78.3	75.9	51.4	27.5	1268	57.1
Hispanic	17.2	2.5	8.0	7.2	1.5	15.6	25.0	250	11.3
Other	0.0	1.9	0.6	0.3	0.0	1.1	0.5	10	0.5
Missing	19.4	21.7	0.6	7.9	12.0	5.6	2.8	201	9.1
Birth country									
United States	73.7	17.8	85.9	62.8	83.3	26.3	41.7	1335	60.1
Foreign born	17.2	14.0	14.1	6.6	16.7	14.0	43.3	480	21.6
Unknown	9.1	68.2	0.0	30.7	0.0	59.8	15.0	405	18.2

Abbreviations: AI/AN, American Indian/Alaska Native; API, Asian or Pacific Islander; CO, Colorado; CT, Connecticut; MN, Minnesota; NYC, New York City; NYS, New York state; OR, Oregon; TN, Tennessee.

(Table 1). A majority of the cases were male (60%), aged 30–49 years (58%) with a mean age of 42 years, white non-Hispanic (57%), and born in the United States (60%).

Trend Analyses

Overall, the average annual incidence rate of acute HBV was 0.86 per 100 000 persons, with the average annual incidence significantly decreasing for all sites combined during 2006 through 2011 (Figure 1). Minnesota, New York state, Oregon, Connecticut, and New York City each showed significant declines in incidence ($P_{\text{trend}} < .05$) from 2006 to 2011. In contrast, the incidence increased in Tennessee from 2006 to 2011, peaking at 2.65 cases per 100 000 in 2011, representing the highest incidence reported from any site during any year. Because the trends in Tennessee differed substantially from those seen in the other 6 sites, we analyzed the data for Tennessee separately (Figure 1).

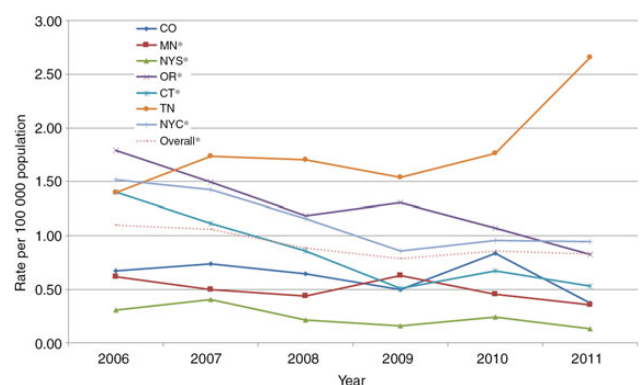


Figure 1. Rate of acute hepatitis B cases per 100 000 population by year of report and site (Emerging Infections Program, Hepatitis Surveillance, 2006–2011). *Trend was considered statistically significant at $P < .05$. Abbreviations: CO, Colorado; CT, Connecticut; MN, Minnesota; NYC, New York City; NYS, New York state; OR, Oregon; TN, Tennessee.

Trend and Risk Analyses

For the 6 sites combined, excluding Tennessee, there was a significant decrease in the incidence of HBV infection from 2006 to 2011 ($\rho = -0.94$, $P = .0048$; Figure 2), the largest of which was observed in Connecticut with a rate that ranged from 1.4 cases per 100 000 in 2006 to 0.5 cases per 100 000 in 2011 ($\rho = -1.0$, $P_{\text{trend}} < .0001$). All age groups across the 6 sites showed a decline from 2006 to 2011; however, these declines were significant only among cases aged 20–29 ($\rho = -1.0$, $P < .0001$), 30–39 ($\rho = -0.94$, $P < .0048$), and 40–49 ($\rho = -0.83$, $P = .0416$) years. For both females and males, the incidence of acute hepatitis B declined, but the decline was significant only for males ($\rho = -0.94$, $P = .0058$) from 2006 to 2011. A significant decline in incidence also was found for all racial/ethnic groups, with the

exception of American Indians/Alaska Natives, for which no cases were reported in 2009 and 2011. Across racial/ethnic groups, the most striking decline over time occurred among Hispanics ($\rho = -0.94$, $P = .005$), followed by Asians/Pacific Islanders and blacks (both with $\rho = -0.89$ and $P = .02$).

Most cases (75.8%) reported at least 1 risk factor, and 31% of cases reported ≥ 2 risk factors. The mutually exclusive risk hierarchy showed that the predominant risk factors were drug use (29.7%), healthcare exposure (20.1%), and multiple heterosexual partners (14.5%). Combined, they accounted for 64.3% of cases for which a risk factor could be identified (Figure 3). When we analyzed the data by non-mutually exclusive risk factor categories, healthcare exposure (25.2%), occupational exposure (23.1%), and drug use (18.3%) were the most commonly

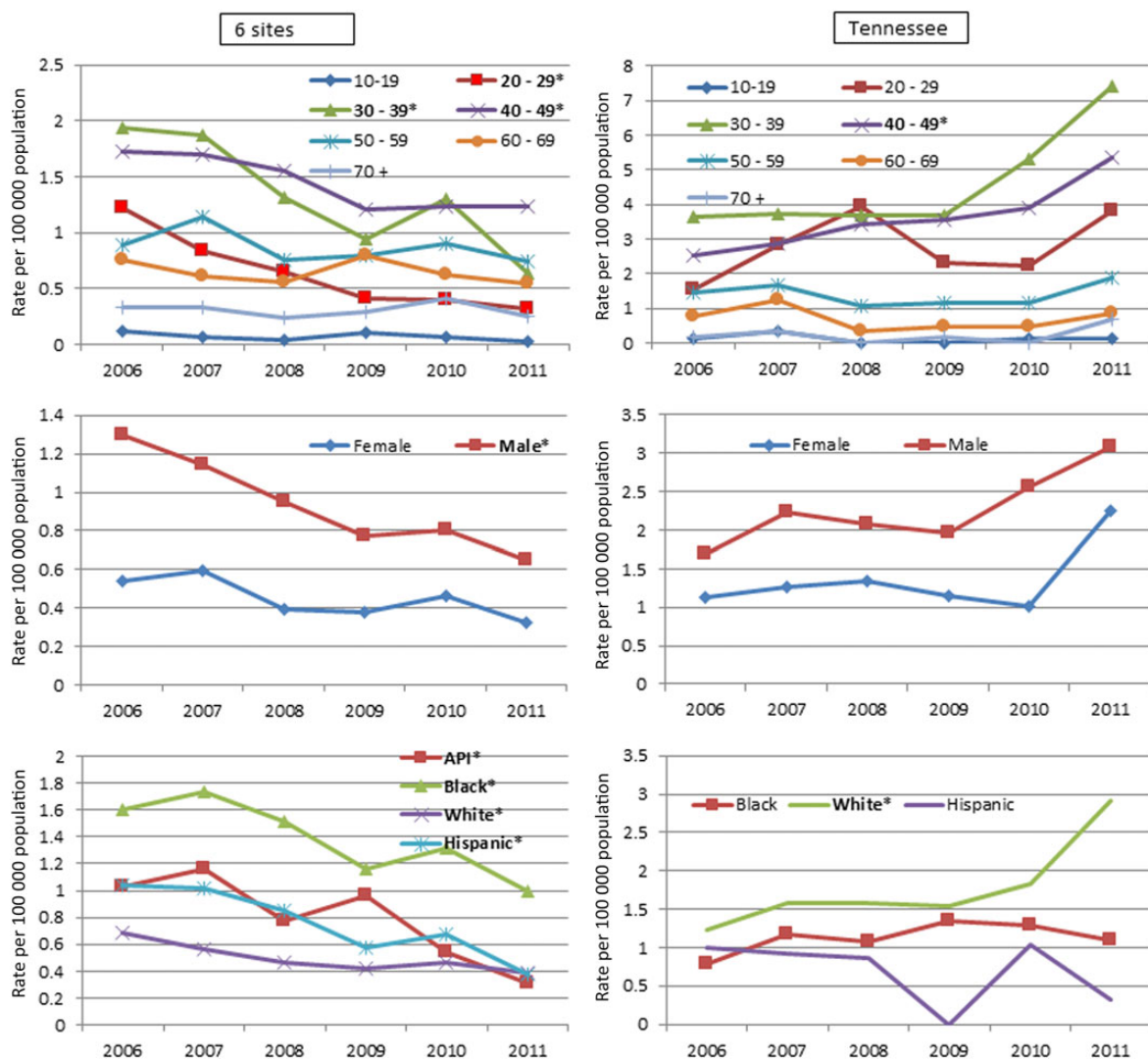


Figure 2. Rate of acute hepatitis B cases per 100 000 population by year of report and age, sex, and race/ethnicity (Emerging Infections Program, Hepatitis Surveillance, 2006–2011). *Spearman test for trend was done to test changes in incidence over time by age, sex, and race/ethnicity; statistical significance was set at $P < .05$. Abbreviation: API, Asian or Pacific Islander.

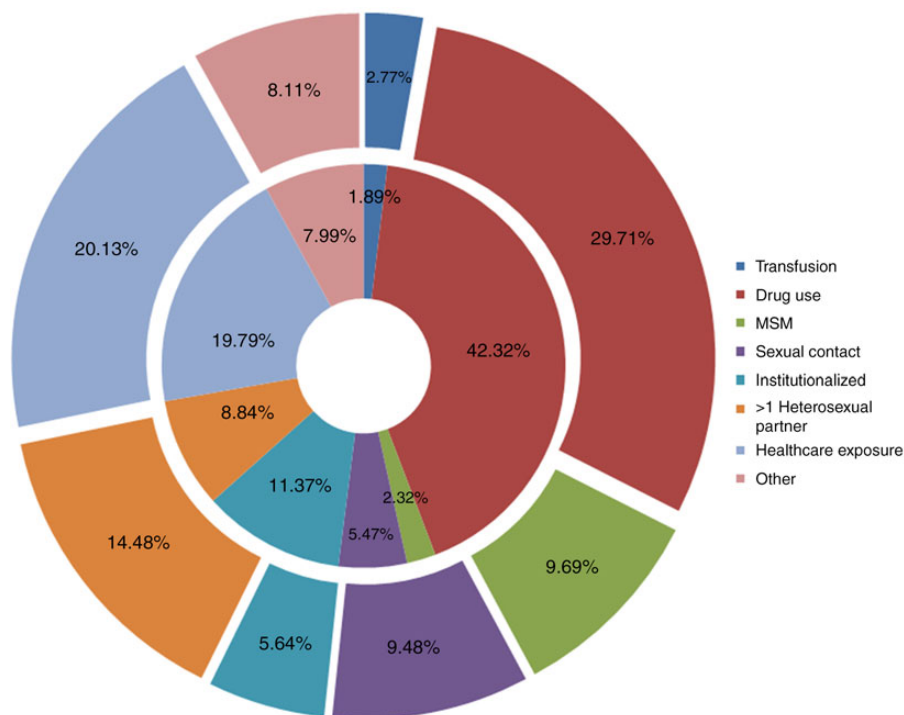


Figure 3. Risk hierarchy of potential sources of acute hepatitis B virus infection (mutually exclusive categories). Tennessee is represented by the inner circle and the other 6 sites are represented by the outer circle. Abbreviation: MSM, men who have sex with men.

reported risks (Figure 4), accounting for 66.6% of risk factors combined.

Among cases where country of birth was reported (1138/1542 [74%]; “yes” or “no” response), 771 (68%) of the cases were born in the United States; a majority of whom were male (68%), aged 30–49 years (59%) with a mean age of 44 years, and white (69%). Further, among US-born cases that reported risk, drug use (31%) was the most frequently reported risk behavior. Among the 367 (32%) foreign-born cases, the majority were male (72%), aged 30–49 years (54%) with a mean age of 43 years, and Hispanic (32%). Also among foreign-born cases, healthcare exposure (32%) was the primary risk reported compared with other risk categories.

In Tennessee, there was a 90% increase in the incidence of acute hepatitis B infection, from 1.4 cases per 100 000 in 2006 to 2.7 cases per 100 000 population in 2011, although this trend was not significant ($p = 0.77$, $P = .07$; Figure 2). All age categories showed an increase in incidence, but only among cases aged 40–49 years was there a significant increase from 2006 to 2011 ($p = 1.0$, $P < .0001$). No significant change in the incidence of acute hepatitis B was observed over time by sex or by race/ethnicity, except among whites ($p = 0.83$, $P = .04$) where a significant increase was found.

The majority of cases (82%) in Tennessee reported at least 1 risk factor, and 38% reported ≥ 2 risk factors. When looking at

the mutually exclusive risk hierarchy, drug use (42.3%), healthcare exposure (19.8%), and being institutionalized (11.4%) were the predominant risk factors reported, accounting for 73.5% of cases for which a risk factor could be identified (Figure 3). Among the non-mutually exclusive risk factor categories, healthcare exposure (35.5%) and drug use (30.3%) predominated (Figure 4). Tennessee reported fewer cases of occupational, MSM, and sexual contact than the other 6 sites.

All cases from Tennessee had a known country of birth, of which 83% were born in the United States. Most US-born cases for which race was reported were white (91%), male (62%), and 30–49 years of age (63%), with a mean age of 40 years. The most frequently reported mutually exclusive risk was drug use (43%) among cases where a risk was identified. Among the 113 foreign-born cases (17%), the largest proportions were white (63%), male (58%), and aged 20–39 years (65%), with a mean age of 36 years. Drug use was the risk behavior reported by the largest proportion (40%) of foreign-born cases for which risk was reported.

Laboratory Results

Overall, specimens for phylogenetic study were available from 393 of the 2220 cases (18%) from the 7 sites, and availability varied by site (range, 4.3%–34.6%). Of the 393 specimens, 300 (76.3%) were positive by polymerase chain reaction (PCR) and

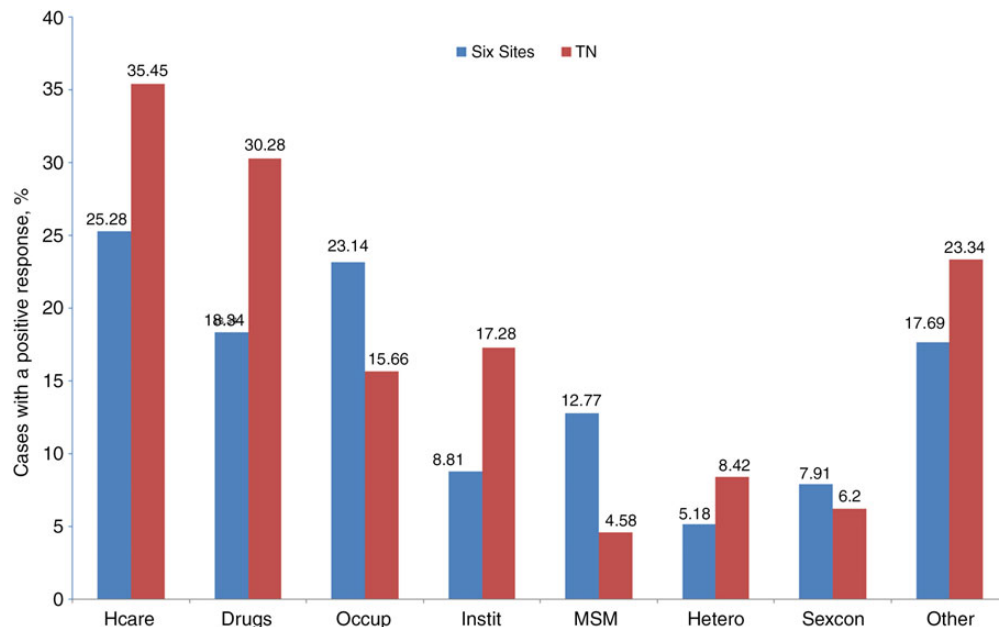


Figure 4. Individual risk factors that are potential sources of acute hepatitis B virus infection (not mutually exclusive categories). Abbreviations: Drugs, illegal injecting and noninjecting drug use; Hcare, healthcare exposure; Hetero, having >1 heterosexual partner; Instit, institutionalization in long-term-care facility or incarcerated; MSM, men who have sex with men; Occup, occupational exposure to blood; Other, other potential exposures that did not fit any category, such as tattoo, piercing, and other contacts including potential exposures with $\leq 2\%$ responses such as receiving a blood transfusion, hemodialysis, or a household contact with a person known or suspected to have acute or chronic hepatitis B virus infection; SexCon, heterosexual contact with a person known or suspected to have acute or chronic hepatitis B virus infection; TN, Tennessee.

could be sequenced. The remaining samples were either negative (14.3%) or did not have sufficient quantity of specimen to be tested (9.4%). There were differences in PCR positivity by site and country of birth but not by age, sex, race/ethnicity, or risk

factor. HBV genotypes among the 300 case specimens were A (82.0%), B (1.3%), C (3.3%), D (11.7%), E (0.3%), F (0.3%), and H (1.0%) (Figure 5). Phylogenetic analyses showed no specific clusters or patterns by site, time, or risk factor (Figure 5).

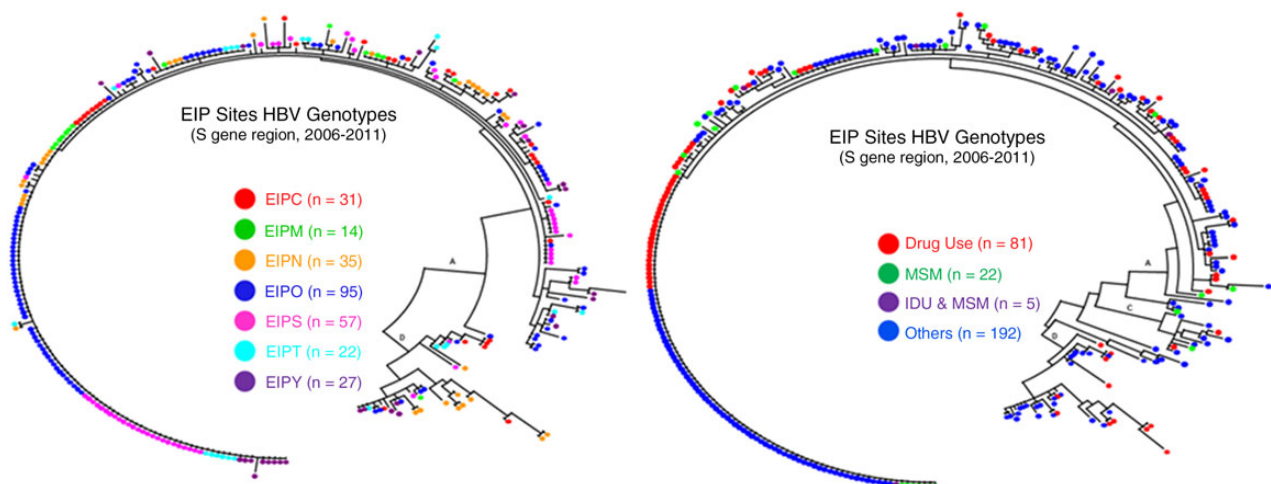


Figure 5. Phylogenetic analyses of hepatitis B virus (HBV) specimens from a convenience sample in 7 US sites, 2006–2011. Abbreviations: EIP, Emerging Infections Program; EIPC, Colorado; EIPM, Minnesota; EIPN, New York State; EIPO, Oregon; EIPS, Tennessee; EIPT, Connecticut; EIPY, New York City; IDU, injection drug use; MSM, men who have sex with men.

DISCUSSION

Overall, the incidence of acute hepatitis B declined from 2006 to 2011; however, in Tennessee the incidence increased by 90% over the 6-year period. These results are consistent with the rates found in the National Notifiable Disease Surveillance System where the overall incidence rate in the United States has declined from 2006 (1.6/100 000 population) to 2011 (0.9/100 000 population) but showed a few localities (eg, Kentucky and West Virginia), including Tennessee, where the incidence has been increasing [3]. Even with high vaccine coverage and the overall decrease in incidence of HBV infection, a segment of the population is unvaccinated and at potential risk of being infected. The data from Tennessee highlight the need for strong state-based surveillance systems to ensure that individual state differences are not masked by aggregating state data to produce national estimates. Some states will need to carefully examine their data, which may reveal an increase HBV infection that needs to be addressed.

Among the cases in Tennessee, drug use was considerably more common than in the other 6 sites. Recent reports from the Appalachian region of the United States, including Tennessee, show a marked increase in the incidence of hepatitis C virus (HCV) infection linked to IDU and abuse of prescription opioids among younger (aged ≤ 30 years) white males [14–19]. In Tennessee, the data showed a significant increase in incidence of acute hepatitis B among persons who were white and those aged 40–49 years, an age group not included in the routine or catch-up hepatitis B vaccination recommendations. This increase could be a reflection of the trend among susceptible older populations that were not vaccinated but are engaging in risky behaviors, similar to reported cases of HCV infection.

During 1982–1998, the most common reported risk factor for acute HBV was high-risk heterosexual activity, followed by MSM and IDU [10]. This is in sharp contrast to our findings from analyses of risk behaviors, where the predominant risk factor was drug use, including both injection and noninjection drugs. The main mode of transmission of HBV thus appears to have changed since the 1990s [1, 20]. Continued monitoring of transmission routes by surveillance is critical for developing prevention strategies. More specific studies examining trends in modes of transmission are needed to confirm our findings and identify possible future epidemiologic shifts.

Our data also indicate that healthcare exposure was the most commonly reported (non-mutually exclusive) risk factor for all sites, which is different than the mutually exclusive hierarchical risk, which shows that drug use is most commonly reported. This could be attributed to a higher frequency of healthcare utilization due to aging of the population [21]. In addition, over the last few years there has been an increase in outbreaks and clusters of HBV infections reported from US healthcare facilities

[22–25]. Improper infection control practices among healthcare workers have been implicated as the cause of many of the outbreaks [26–28]. Better training, policies, and regulation are needed to prevent transmission and outbreaks in healthcare facilities.

The molecular characterization of the surveillance specimens indicated that HBV genotype A was identified for 82% of the samples. Furthermore, almost all sequences belonged to HBV subgenotype A2. These results are similar to what was found during 1999–2005 where 72% of specimens were HBV genotype A [29]. The higher proportion of genotype A among our sites compared to previous results found during 1999–2005 might reflect a shift toward a more homogenous HBV genotype A2 infection in the United States, which has also been observed in Asia [30]. More extensive specimen collection and analyses are needed to better understand any changes in acute HBV genotypic characteristics over time in the United States. A shift to a predominance of genotype A has clinical and public health implications with regard to emergence of mutant strains and response to treatment [31, 32]. Specifically, acute infection with genotype A has been observed to lead more frequently to both chronicity and emergence of mutations associated with resistance to HBV drug treatment with lamivudine [33, 34]. The phylogenetic analysis did not find clustering by site or other demographic factors to suggest the occurrence of outbreaks. This is likely because the sample of specimens tested was not representative of reported cases. Molecular epidemiologic surveillance of all or a representative sample of specimens will allow monitoring of HBV genotypes to identify shifts in strains and modes of transmission in the United States over time.

This report is subject to multiple limitations. Incidence rates of reported hepatitis B represent a minimum estimate, as cases may be underreported to local and state public health authorities [35, 36]. Moreover, comparisons of risk using the hierarchy described by Goldstein and colleagues [10] are limited. For example, the risk of blood transfusion is the first risk in the hierarchy but, currently, the risk of transmission from blood transfusion is smaller compared with other risk factors farther down the hierarchical list. In addition, specimens were collected for descriptive purposes using a convenience sample of remnant serum. Specimen collection rates varied by site, and thus are not representative of the population in those sites. Moreover, increases in cases in Tennessee coincided with new funding for surveillance, so results could be a surveillance artifact, especially as there was a dramatic increase in reported cases in the last few years. Tennessee, however, validated all cases, but increases could have occurred earlier and gone undetected, resulting in underreporting of cases in the past. Finally, due to limited information on hepatitis B vaccination status, it was difficult to assess if any of the cases were vaccinated, especially infected persons born after 1992 when routine vaccination recommendations

would have been implemented in some locales. However, even with these limitations, findings from enhanced hepatitis surveillance are valuable to supplement passive surveillance for acute hepatitis B in the United States [35].

In conclusion, despite an overall decline in HBV infection that is attributable to the success of vaccination programs, a rise in incidence of HBV infection is a potential concern in some states. Health departments should examine their data on new cases of acute hepatitis B as well as vaccination coverage and prevalence of risk behaviors. Additionally, with an increase in reports of HCV infection in many of the same locations seeing a rise in reports of HBV infection, it would be beneficial to integrate services and target resources to control and prevent hepatitis B by vaccinating susceptible individuals with known risk factors—especially IDU—for infection.

Notes

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