

The New Epidemiology of Hepatitis B in the United States

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Although the incidence of hepatitis B virus (HBV) in the United States is decreasing, it remains an important health issue, with nearly 2 million people currently infected and a 7% to 30% lifetime mortality rate. Vaccination has markedly decreased the number of acute HBV cases, especially in children and adolescents; however, there continues to be a substantial incidence of new infections in intravenous drug users and persons with high-risk sexual behavior and of newly recognized disease in immigrants. Perinatal transmission has been significantly reduced with universal infant vaccination, and transfusion/iatrogenic infection has been nearly eradicated by screening blood products and vaccinating at-risk medical professionals. HBV infection rates vary with respect to racial and geographic distribution as well as known risk factors. The Asian/Pacific Islander population continues to have the highest rate (prevalence) of infection in the United States. Further advances in screening and vaccination must be made to further reduce the incidence and prevalence of HBV in the United States.

Introduction

Hepatitis B virus (HBV) infection remains a major public health problem worldwide, with nearly one third of the world's population showing evidence of prior or current infection. In the United States, the prevalence of chronic hepatitis B is much lower, with around 1% of the population chronically infected, which translates to as many as 2 million infected individuals nationwide [1,2]. At least half of these infections likely were preventable through vaccination and/or prevention of high-risk events through "safe" behavioral practices.

In 2006, 4713 acute cases of hepatitis B were reported nationwide [3•]. At a rate of 1.6 cases per 100,000 population, this is the lowest incidence ever reported and represents an 81% decline since 1990. Because hepatitis B is generally asymptomatic at presentation—and because underreporting must be taken into account—it is estimated that there were 46,000 new hepatitis B cases in 2006 [3•]. Much of the decline is attributed to the success of vaccination programs starting in the 1980s with newborn vaccinations and then catch-up vaccination in children and individuals entering secondary school.

Although the incidence of newly acquired HBV infections has continued to decline steadily since the mid-1980s, the prevalence of hepatitis B surface antigen (HBsAg) positivity has remained relatively constant in the US population because of continued immigration from high-prevalence geographic areas [4]. Prevalence rates are extremely variable geographically and racially, ranging from 0.02% among Caucasians in Olmsted County, Minnesota, to 14.9% to 21% in the Asian community in New York City [5–7]. Overall, 86% or more of those with chronic HBV infection were born outside the United States [5,6].

Transmission

The primary modes of HBV transmission are parenteral, sexual, and vertical—from mother to child. HBV requires exposure of blood or mucous membranes to infectious blood or body fluids containing blood. Although HBsAg has been detected in a wide variety of body fluids, only serum, semen, and saliva have been demonstrated to be infectious [8]. HBV may survive drying and is still infectious after 7 days in a desiccated state; therefore, indirect inoculation of HBV also may occur through inanimate objects [4].

In the United States, perinatal transmission has become much less common as the result of universal screening of mothers and vaccination of newborns as well as vaccination and hepatitis B immune globulin (HBIG) administration at birth to infants born to HBsAg-positive mothers. However, perinatal transmission remains an important mode of HBV transmission in immigrants from other countries, especially Asians. Infants infected

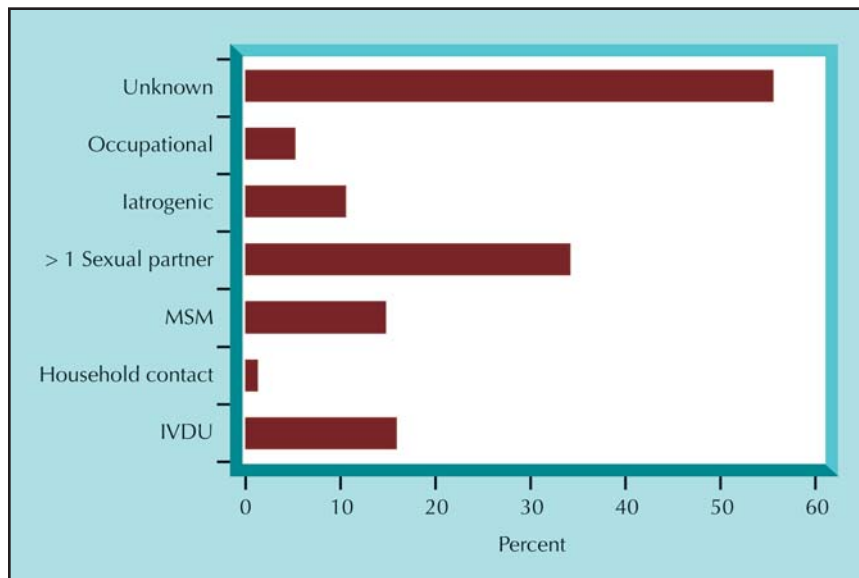


Figure 1. Risk factors for acute hepatitis B virus infection, 2006. Figures do not total 100% because of multiple risk factors in some patients. IVDU—intravenous drug user; MSM—men who have sex with men. (Adapted from Centers for Disease Control and Prevention [3•].)

with HBV are typically asymptomatic and have a 90% likelihood of remaining chronically infected [9]. Up to 25% of chronically infected individuals die prematurely of cirrhosis or primary liver cancer. Two primary modes of HBV transmission are recognized during infancy and early childhood: 1) from an infected mother to her infant during delivery and 2) from infected household contacts to an infant or child; both modes can be prevented by immunizing newborns. The mechanism of perinatal transmission of HBV infection is thought to occur mainly during birth, with only about 5% of infections occurring in utero [10]. Most intrauterine infections occur in the third trimester by the virus's transmission through the placenta. During the third trimester, the layer of trophoblastic cells of the placenta becomes thinner and turns into chorion-vessel membrane, making it easier for HBV to pass the placental barrier [10].

Currently, most acute infections in the United States are acquired in adulthood among high-risk groups such as intravenous drug users (IVDUs; 16%), persons with multiple sexual partners (34%), and men who have sex with men (15%) (Fig. 1). A large proportion of acutely infected individuals have no identifiable risk factors. The risk of HBV infection in IVDUs increases with older age, the number of years of injection drug use, and the frequency of injections and syringe sharing, and is also related to imprisonment history, volume of daily alcohol consumption, and presence of hepatitis C virus (HCV) or HIV coinfection [11]. The risk of sexual infection increases with receptive anal intercourse, an increased number of sexual partners, number of years of sexual activity, and history of other sexually transmitted diseases [8]. Twenty-seven percent of patients with acute hepatitis B have no identifiable risk factor for infection.

The risk of transmission to and from health care workers has diminished since 1991 with the institution

of widespread vaccination and improvement in infection control. There also has been a much lower rate of HBV transmission in renal dialysis patients since the institution of HBV screening, universal infectious precautions, and widespread vaccination, although occasional HBV outbreaks still occur in cases of inadequately sterilized dialysis and other medical equipment, reuse of disposable needles and syringes, and contamination of multidose medication vials. HBV transmission via blood transfusion and plasma-derived products has been nearly eliminated in most countries through donor HBsAg screening and viral inactivation procedures [3•].

Vaccination

As the primary focus of a strategy to eliminate HBV transmission in the United States, in 1991 the Advisory Committee on Immunization Practices (ACIP) recommended that hepatitis B vaccine be administered to all infants. The initial recommendation was for the first dose to be given at birth before discharge or at age 1 to 2 months. In 2002, the ACIP indicated its preference for the first dose to be administered before hospital discharge. In 2005, in an effort to reduce missed vaccinations, the ACIP issued revised recommendations specifying that all medically stable newborns weighing more than 4.4 lb should receive their first dose of hepatitis B vaccine before hospital discharge [9]. These guidelines should result in an infant vaccination rate of greater than 80%.

For infants born to mothers identified as HBsAg positive, hepatitis B vaccination alone is 70% to 95% effective in preventing perinatal HBV transmission when the first dose is given within 24 hours of birth. Thus, perinatal administration of hepatitis B vaccine provides timely postexposure prophylaxis to infants born to HBsAg-positive mothers who were not screened prenatally or were

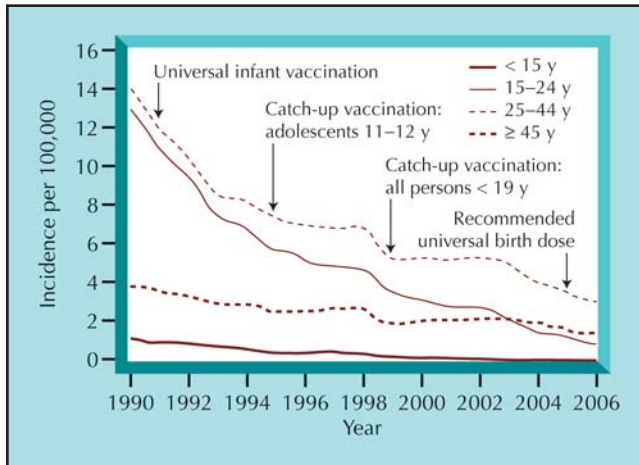


Figure 2. Incidence of acute hepatitis B, by age group and year, in the United States from 1990 to 2006. (Adapted from Centers for Disease Control and Prevention [3•].)

not identified as HBsAg positive because of testing errors or lapses in reporting.

A household survey of newborn infants was conducted in 2006 to identify newborn hepatitis B vaccination rates. Substantial variability was found, with vaccination rates at age 1 day ranging from 8.2% to 77.5%. The median coverage estimate was 50.3% at age 1 day and 58.7% at age 3 days [12••]. Vaccination rates are much better for older children, up to 90% once children are of school age [13].

Despite suboptimal newborn immunization rates, the incidence of acute hepatitis B has declined dramatically, perhaps because of “herd immunity” and changes in risk events and risk behavior (Fig. 2). There has been a 78% decline in acute hepatitis B between 1990 and 2005, with the greatest decline among children and adolescents. The 96% decline of acute hepatitis B in this age group reflects the benefit of vaccination. As early as 1992, many states instituted school-based immunization programs, followed closely by a nationwide program in 1996 to establish a routine health provider visit among adolescents 11 to 12 years old for catch-up immunizations. In 1999, the strategy was expanded to include routine HBV vaccinations for all individuals younger than 18 years. Thirty-two states now require proof of HBV immunization for entry into middle school [3•].

With widespread immunization, the decline in acute hepatitis B infection will continue as the population immunized as children grows to adulthood. Health care providers must continue to screen high-risk populations that do not fall into the previously immunized population and to vaccinate those at risk, as well as to vaccinate anyone who requests protection from HBV infection, even if he or she does not acknowledge a specific risk factor for it. Currently, vaccine coverage is lowest for adults with behavior risks, such as men who have sex with men (16%), IVDUs (6%–22%), and clients of sexually transmitted disease clinics (10%) [4].

Special Populations

Intravenous drug users

With the increased newborn vaccination rate and improved screening of blood banks and infection control practices, today the main sources of newly acquired HBV infection in the United States among persons aged 25 to 45 years are associated with high-risk sexual activity or injection drug use. IVDUs account for 16% of new HBV infections in the United States [4]. As stated earlier, the risk of HBV infection in IVDUs increases with older age, years of injecting, frequency of injections, syringe sharing, imprisonment, daily alcohol consumption, and HCV or HIV coinfection [11]. Younger IVDUs are at higher risk of HBV infection because of riskier behavior, including equipment sharing and unprotected sex [14].

Current data suggest that after 1 year of injection drug use, 9% of users are infected with HBV, and after 10 years of use, 41% of users are infected [9,15]. Infection rates in IVDUs are lower than those reported in the past, which have been as high as 50% [16]. Currently, vaccination coverage is quite low, around 20% in a group with a median age of 22 years [15]. Women and younger persons were more likely to have vaccination coverage. With this information, it is obvious that IVDUs are a group that would benefit from a public health initiative to improve HBV screening and vaccination coverage.

There have been several successful vaccine programs to help identify and immunize young IVDUs, many of which operate using street-based reminders from outreach workers, flexible vaccine schedules, and modest cash incentives [15,17]. Additional components include expanded access to sterile syringes, effective substance abuse treatment, accelerated immunization schedules, and improved condom use.

HIV-coinfected patients

Persons at high risk for HIV infection are also likely to be at risk for other infectious diseases, including hepatitis B. In the era of effective antiretroviral therapy, liver disease has emerged as a leading cause of morbidity and mortality in HIV-infected persons [18]. In patients with HBV, HIV may lead to higher rates of chronicity, decreased rates of hepatitis B e antigen (HBeAg) and HBsAg seroconversion, and increased viral replication, probably through impairment of innate, adaptive cellular, and humoral immune responses. Expert guidelines recommend screening of all HIV-infected persons for infection with HCV and HBV and appropriate management of those found to be chronically infected or nonimmune [4,19,20]. For those who are noninfected and nonimmune, vaccination should be offered, although response to vaccination may be diminished in patients with a CD4 cell count less than 500 cells/mm³.

The most common mode of HBV transmission in persons infected with HIV is through sexual intercourse

(both heterosexual and between men), followed by injection drug use [19,21]. Approximately 90% of HIV-infected persons have evidence of prior HBV infection, with 5% to 15% having active infection, indicated by reactive HBsAg [19,21]. The high rate of coinfection is common not only because of their shared modes of transmission, but also because HBV is transmitted more readily via the percutaneous and sexual routes than is HIV. HBV can be transmitted up to 10 times more efficiently than HIV under similar sexual circumstances [20].

A subset of patients has evidence of HBV DNA in serum in the absence of HBsAg, or “occult HBV infection,” particularly those with antibody to hepatitis B core antigen (anti-HBc) alone. Although the clinical significance of this finding is unknown, it occurs in 0% to 12% of HIV patients [18,22]. Because of these new data, it is now recommended that HBV DNA be checked in patients with HIV who have evidence of anti-HBc alone to rule out occult HBV [19]. It is still unknown whether these patients should be treated for HBV in these circumstances.

Minorities

Latin Americans

It has always been known that Asian/Pacific Islanders (APIs) have a high rate of hepatitis B infection. Latin Americans also are at increased risk for hepatitis B infection, especially coinfection, and this ethnic group has an increased progression of liver disease [23]. The actual prevalence of HBV in Latin America has not been established, but it is estimated that the total number of carriers may exceed 6 million [1]. The Latino population in the United States is expected to more than double in the next 40 years [24].

A study of 679 IVDUs recruited from Los Angeles County found an unexpectedly high rate of hepatitis B, hepatitis C, and HIV coinfection, with the highest proportion of coinfection in the Latino population [25]. Another study looking at National Health and Nutrition Examination Survey data from 1999 to 2004 found that Mexican Americans were more likely than whites to be infected with HBV or HCV (3%), although they did not have as high a prevalence as blacks (6%) [23]. What is more troubling is that 28% of Mexican Americans had elevated levels of serum alanine and aspartate aminotransferases, compared with 14% of their black and 15% of their white counterparts. This is likely attributable to the increased rate of obesity and the metabolic syndrome in this population [23].

African Americans

The African American population is the largest minority in the United States, comprising 14% of the US population [24]. After the Asian population, African Americans account for the highest rate of HBV infection in minority populations in the United States [23]. Some estimates have

shown the rate of HBV prevalence in the African American population to be as high as 12% [4]. In the eastern and southern regions of the United States, African Americans account for 22% and 17% of HBV patients, respectively [26]. The most common genotype in African Americans is genotype A, which correlates with birth in the United States and with parenteral or sexual transmission [26]. Genotype A is predominantly found in central Africa, which may also explain why most African Americans with hepatitis B are infected with genotype A.

Asian/Pacific Islanders

Of the 2 million Americans chronically infected with HBV, more than half are API Americans. Among this population, hepatitis B is transmitted vertically from generation to generation and is generally asymptomatic. Many infected APIs remain undiagnosed. The API population in the United States has increased 73% over the past 10 years, and this rate is projected to triple over the next 40 years so that APIs will constitute 8% of the total US population [24]. Most APIs who are chronically infected with HBV acquire the virus at birth through mother-to-child transmission or during early childhood through horizontal transmission. More than 80% of APIs who are chronically infected with HBV in the United States were born outside the country [5,27]. As of 2004, 2.6% of the US population was made up of foreign-born Asian Americans, who have the highest rate of HBV infection [24]. Most infants born in this country to mothers carrying HBV are protected by HBV screening and subsequent administration of HBIG and/or hepatitis B vaccine [9].

The rate of HBV infection in APIs in the United States is quite variable depending on region. The highest population concentration of APIs is in the West (California and Washington) and in and around New York City, which correlates with a higher HBV infection rate in those areas [24]. In the Midwest, only 2.1% of Asians were infected [5]. Of more than 3000 adults screened in the San Francisco Bay area, 8.9% were chronically infected with HBV. The highest prevalence of infection is in persons of Laotian and Vietnamese descent (~ 14%), followed by those of Chinese descent (~ 9%) [28••]. In the New England area between 1988 and 1990, 8% of Korean men and 4.4% of Korean women were chronically infected with HBV [29]. In New York City, 1836 APIs were screened, and 14.8% were found to be chronically infected with HBV [6]. In another screening study in New York City, the HBsAg positivity rate was as high as 35.1% in persons aged 19 to 25 years [7]. The infection rate was more than two times higher in males (28.8%) than females (12.2%).

Although HBV infection rates are much greater in the API community, access to HBV-related care remains inadequate. Many self-employed API patients lack health insurance, and several studies have reported low levels of knowledge and access to hepatitis B care in the API

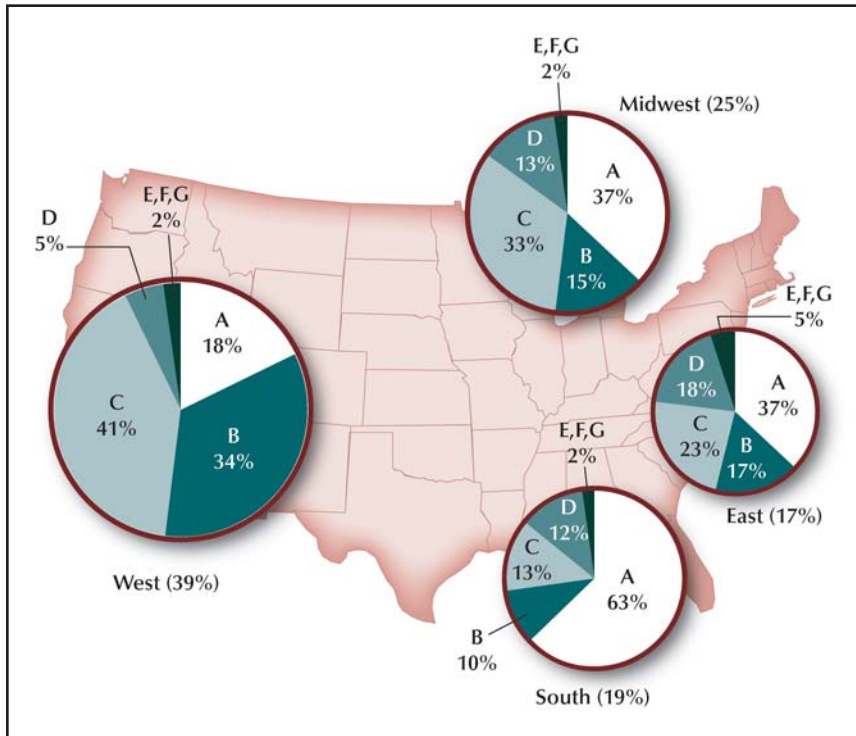


Figure 3. Prevalence of hepatitis B virus genotypes in different regions of the United States. The size of each pie is proportional to the number of patients enrolled in this nationwide study. (Adapted from Chu et al. [26], with permission.)

communities [30]. In screening studies, the majority of patients stated that they did not know they were infected or reported that they had never been tested. More than 40% of patients in each screening study lacked protective antibodies [6,28••,29]. In API patients who reported that they had been vaccinated, 20.3% lacked protective antibodies and 5.2% were chronically infected [28••], which partly may be a result of their not completing the three-dose vaccination series. A 1998 survey of API children found that completion rates for the three-dose series were only 14% to 67% [31].

Genotypes/Mutant Strains

In the United States, genotype distribution varies by geography, but in general genotype A is the most prevalent, followed by genotypes C, B, and D (Fig. 3) [1,26]. Genotypes E, F, G, and H combined are only present in about 2% of the US population. Genotype A is most prevalent in the eastern and southern regions of the United States and is seen most commonly among white and African American patients, whereas genotypes B and C are more common in the northern and western portions of the country and are seen in immigrants from Asia [26]. Genotype D is seen predominantly in Alaska and in immigrants from Greenland. Genotype G has been limited to particular regions of the United States (Georgia and San Francisco, California) [1].

The marked differences in prevalence of HBV genotypes in different regions of the United States may be related to differences in the ethnic composition of patients

in these regions. Non-Hispanic whites constitute more than half the HBV population in the South but only 15% of the HBV population in the West. Genotype A is found in northern Europe (Ae) and central Africa (Af), so it is expected that it would be the most common genotype in the southern United States, where the HBV population is predominantly Caucasian and African American. In contrast, Asians account for more than 75% of the HBV population in the western United States, and the fact that genotype C originated in southeast Asia, China, and Japan may explain why it is the predominant genotype in that part of the country.

HBV genotype may determine the course of the infection. Patients with genotype A have a higher rate of HBsAg and HBeAg seroconversion and spontaneous HBV DNA suppression [32]. Patients with genotype A who do not spontaneously clear the infection have a higher rate of liver disease progression. Infection with genotype C has been associated with the highest risk of developing liver cancer [33,34••]. Genotype also may be used to predict response to therapy. Patients with genotype A respond best to interferon therapy (followed in decreasing order by those with genotypes B, C, and D) but may have the highest risk of developing resistance to lamivudine therapy [35]. Genotype D may be associated with a higher risk of adefovir resistance.

The most common naturally occurring HBV mutant strains are the precore stop codon mutation, which abolishes HBeAg production, and the dual mutation in the core promoter region, which downregulates HBeAg production. These variants frequently are found in HBeAg-negative patients. In the United States, approximately 27%

of patients have precore mutations and 44% have core promoter variants [36]. These mutations are associated with poorer long-term clinical response to therapy and lack of spontaneous remission [37]. A recent large cohort study also showed that the presence of core promoter mutation A1762T/G1764A is an independent risk factor for hepatocellular carcinoma [34••]. The presence of the precore G1896A mutation has been associated with a decreased risk of liver cancer [34••].

Occult HBV

Occult hepatitis B is defined as the presence of HBV DNA in the serum or liver in the absence of HBsAg. The prevalence and clinical correlates of occult HBV remain incompletely defined. Several recent studies found a high rate of occult HBV in special populations. A study in Baltimore of IVDUs with hepatitis C found that 45% also had evidence of circulating HBV on polymerase chain reaction assay, with no evidence of HBsAg [38]. The patients with occult HBV did not have higher liver enzymes or activity grade or stage of liver disease on liver biopsy. Raj et al. [22] looked at 58 patients with HIV and found a 12.2% occult HBV rate in this population. Also of concern is a recent study in a liver transplant population of 56 patients with HCV cirrhosis, 28% of whom had serum levels of HBV DNA and 50% of whom had HBV DNA detected in the explanted liver [39]. The presence of HBV DNA in the explanted liver was more common in patients with explant-proven hepatocellular carcinoma. More information is needed to determine occult HBV's effects on the changing epidemiology of HBV and related patient outcomes.

Conclusions

In considering the changing epidemiology of hepatitis B in the United States, several things are apparent. First, because of universal vaccination programs, the rate of acute hepatitis B has decreased precipitously. We may expect to see this incidence continue to decline as the population of children born during the age of universal vaccination comes of age. Second, high-risk populations such as IVDUs, men who have sex with men, and people with many sexual partners will continue to require aggressive screening and vaccination. Third, many people with chronic hepatitis B infection are immigrants, and more efforts must be made to improve screening, vaccination strategies, and access to treatment to decrease the burden of liver disease in these populations.

Disclosures

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