

Epidemiology of Hepatitis B in the United States

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Hepatitis B virus (HBV) remains an important cause of acute and chronic liver disease globally and in the United States. An encouraging trend is that the incidence of acute hepatitis B in the United States declined as much as 80% between 1987 and 2004, attributable to effective vaccination programs as well as universal precautions in needle use and in healthcare in general. Although encouraging, these decreases in acute infections have not translated into diminished prevalence or burden of chronic HBV infection. The prevalence for HBV in the United States has been estimated to be approximately 0.4%. However, these estimates have been based on surveys conducted in samples in which population groups with high prevalence of HBV infection, namely foreign-born minorities, were underrepresented. Voluntary screening data indicate prevalence in excess of 15% in some of these groups. Recent immigration trends suggest a substantial increase in the number of Americans with chronic HBV infection. This trend is reflected in the health and economic burden associated with HBV infection. The number of outpatient visits and hospitalizations for a HBV-related diagnosis increased several-fold during the 1990s. Similarly, the total charges for hospitalizations have been estimated to have increased from \$357 million in 1990 to \$1.5 billion in 2003. Most recent data indicate that death and liver transplant waitlist registration for HBV-related liver disease, which had been increasing, have now reached a plateau or started to decline. This encouraging trend might be attributable to recent advances in treatment for HBV infection; however, to the extent that the number of Americans living with chronic HBV is growing, careful clinical monitoring and continued epidemiologic surveillance remain important. (HEPATOLOGY 2009;49:S28-S34.)

Introduction

Hepatitis B virus (HBV) infection is an important cause of acute and chronic liver disease in the United States and globally.¹ The term, “disease burden” encompasses several aspects of the impact of a disease on the health of a population, including: (1) the frequency of the disease, as measured by incidence and prevalence; (2) its effect on longevity, such as mortality rate and years of life lost because of premature death; (3) morbidity, including

impairment in health status and quality of life as well as the need for healthcare; and (4) finance, including direct healthcare expenditures and indirect costs related to lost income from premature death or disability.^{2,3} Although accurate data are sparse to address all of these parameters for HBV-related disease, available information about its epidemiology and burden is summarized in the following sections.

Transmission of Hepatitis B Virus

HBV is transmitted by percutaneous and mucous membrane exposures to infectious body fluids, such as serum, semen, and saliva.⁴ Perinatal transmission is thought to be the major route by which HBV infection is perpetuated in endemic populations. Children born to mothers who are positive for hepatitis B surface antigen (HBsAg) who do not become “vertically” infected during the perinatal period remain at risk of infection during early childhood.⁵ Although the exact mechanism by which this “horizontal” transmission of HBV occurs in children is not completely understood, contacts involving contaminated environmental objects may play an important role.

Abbreviations: CDC, Centers for Disease Control and Prevention; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IgM anti-HBc, IgM antibody to hepatitis B core antigen; NHANES, National Health and Nutrition Examination Survey.

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Among adults, high-risk sexual activity is one of the most frequent routes of transmission for HBV.⁶ Historically, male homosexual contacts have been associated with a high risk for HBV infection. More recently, heterosexual transmission is the most common cause of acute HBV infection in adults.⁷ Transmission of HBV via transfusion of blood and plasma-derived products has been essentially eliminated through donor screening and viral inactivation procedures. However, transmission of HBV may continue to occur in other healthcare settings.⁸ For example, nonadherence to isolation guidelines in a hemodialysis unit or direct person-to-person exposure (e.g., surgeon-to-patient or dentist-to-patient) may transmit HBV.

The distinction between HBV infection acquired in early childhood and that in adulthood is important, because the subsequent course of HBV infection differs substantially.⁹ Infection acquired in children usually leads to chronic lifelong infection without a clinically apparent acute hepatitis. This pattern occurs most commonly in areas of the world in which HBV is endemic. Infection acquired in adulthood, in contrast, frequently results in symptomatic acute hepatitis followed by clearance of HBsAg in the majority of patients. In a low prevalence setting, such as the general population of the United States, most persons with acute HBV infection are adults and chronic infection develops in only 1%-5% of the newly infected.¹⁰

These two patterns of HBV infection have important implications in measuring the burden of HBV-related disease in the population. If HBV transmission occurs early in life (<5 years of age), most infections will be chronic and the disease burden is primarily that of long-term consequences of the infection. When HBV transmission mostly occurs during adulthood, the majority of the burden is related to the harms of symptomatic acute hepatitis, including fulminant hepatitis which occurs in 0.1%-0.5% of those with acute HBV infection.

Incidence and Prevalence of HBV Infection in the United States

Disease frequency may be measured either by the pool of existing cases and/or by the occurrence of new cases. The former (prevalence) describes what proportion of the population has the disease in question at a specific point in time, whereas the latter (incidence) is measured by the frequency of new cases developing during a defined time period. From the standpoint of HBV infection, prevalence is a more relevant measure in endemic populations in which babies and children acquire HBV and are left with chronic lifelong infection, whereas in other settings, incidence is a more appropriate measure of disease bur-

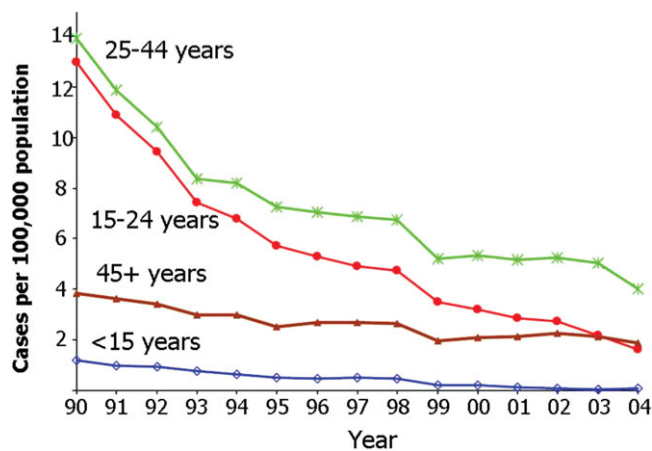


Fig. 1. Incidence of acute hepatitis B per 100,000 population in the United States by year (1990-2004) and age group. (Reproduced from Centers for Disease Control and Prevention⁷, permission waived by CDC.)

den, because most of the impact of HBV infection is a result of acute hepatitis.

HBV is a reportable infectious disease in the United States and the Centers for Disease Control and Prevention (CDC) has been monitoring its incidence for several decades.⁷ National surveillance is conducted for acute viral hepatitis B, defined by immunoglobulin M (IgM) antibody to hepatitis B core antigen (IgM anti-HBc) or newly found HBsAg. In addition, nationwide reporting of perinatal HBV infection was implemented in 2001. In January 2003, chronic HBV infection was added to the list of nationally notifiable conditions.

Incidence of HBV Infection in the United States

Based on data from CDC, the incidence of acute hepatitis B in the United States has declined steadily since the late 1980s.⁶ Between 1987 and 2004, the incidence of acute hepatitis B declined 80%, from 10.7 per 100,000 (25,916 cases reported) to 2.1 per 100,000 (6212 cases reported).⁷ Figure 1 summarizes acute hepatitis B incidence by age group. The highest incidence of acute hepatitis B has been seen among persons 25-44 years of age (4.0 per 100,000 persons in 2004) and the lowest among children less than 15 years of age (0.1 per 100,000 in 2004). Over time, the incidence decreased in all age groups with the greatest proportional decline occurring among age groups <15 years (95% decline) and 15-24 years (87% decline). Although less dramatic, substantial decreases were also seen among older persons with a 71% and 51% decrease in rates observed for the groups of 25-44 years of age and 45+ years of age, respectively. In general, the incidence of acute hepatitis B is higher in men than in women (2.7 per 100,000 versus 1.6 per 100,000, respectively, in 2004).

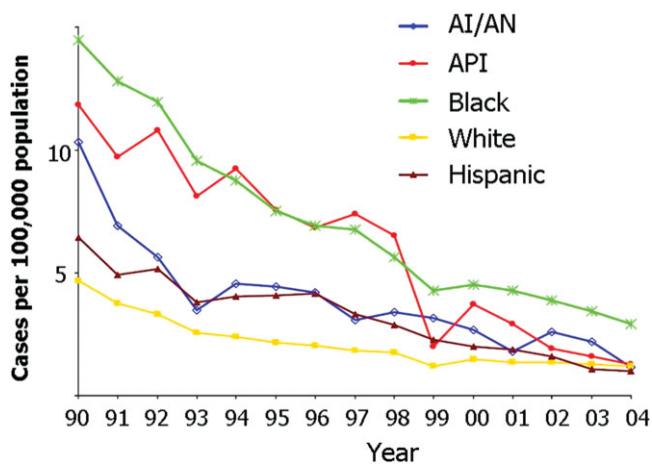


Fig. 2. Incidence of acute hepatitis B per 100,000 population (sex-adjusted) in the United States by year (1990-2004) and racial group. (Reproduced from Centers for Disease Control and Prevention⁷, permission waived by CDC). Abbreviations: AI/AN, American Indian and Alaskan Native; API, Asian or Pacific Islander.

Figure 2 illustrates the incidence of acute hepatitis B by race. Although HBV infection is commonly associated with Asian/Pacific Islander races, the incidence of acute hepatitis B in the United States has historically been the highest among non-Hispanic blacks. The decline in HBV incidence over time affected all racial and ethnic groups. By 2004, racial disparity in the incidence of HBV infection was essentially eliminated. While numerically the incidence in non-Hispanic blacks remained nearly three times higher than that in other groups, nevertheless, the occurrence of acute hepatitis B among non-Hispanic blacks was reduced to a historic low (2.9 per 100,000 in 2004).

The reduction in HBV incidence in the United States may be attributed to several measures implemented since 1991.⁴ Elements of this strategy included (1) universal vaccination of infants beginning at birth, (2) prevention of perinatal HBV infection through routine screening of all pregnant women for HBsAg and the provision of immunoprophylaxis to infants born to HBsAg-positive women, (3) routine vaccination of previously unvaccinated children and adolescents, and (4) vaccination of previously unvaccinated adults at increased risk for infection. The last includes healthcare workers, dialysis patients, household contacts and sex partners of persons with chronic HBV infection, recipients of certain blood products, persons with a recent history of multiple sex partners or a sexually transmitted disease, men who have sex with men, and injection drug users.

Prevalence of HBV

The prevalence of viral hepatitis infection in the U.S. population at large has been estimated using the National

Health and Nutrition Examination Surveys (NHANES), a series of cross-sectional national surveys designed to provide representative health measures and conditions among civilian noninstitutionalized individuals in the United States.^{11,12} HBV data in the NHANES surveys indicate the prevalence of HBsAg-positive individuals is low (0.33% in 1976-1980 and 0.42% in 1988-1994).^{11,13} More recent unpublished data from 2005-2006 are similar (0.30%).¹⁴ These estimates project to approximately 800,000 Americans with ongoing infection with HBV. Because the NHANES data are designed to be representative of the U.S. general population, the survey data have important limitations for estimating HBV prevalence. The NHANES samples did not include statistically valid samples from populations in which HBV is most common, such as Asians, Pacific Islanders, and Alaskan Natives.^{6,15} In addition, the surveys by design excluded institutionalized, homeless, or incarcerated individuals, all of whom are expected to have increased prevalence of HBV infection. Thus, it is widely held that NHANES data underestimate the true prevalence of HBV in the United States.

The importance of taking into account individuals not represented in the NHANES surveys has been underlined by several studies. In a report of a community cohort with HBV, out of 191 residents of Olmsted County, Minnesota, diagnosed with HBV infection between 1994 and 2000, more than half (53%) were Asians whereas whites accounted for only 13%.¹⁶ Most of the nonwhite individuals had been born outside the United States, including nearly all Asian (99%) and African (91%) patients. These data were further corroborated by a recent study that measured HBV prevalence among refugees arriving in Minnesota and enrolled in a health assessment program.¹⁷ Between 1998 and 2001, 12,389 refugees were evaluated. The highest HBV prevalence was seen among African refugees (8.4%), followed by Asian (5.1%) and European (3.1%) counterparts. The peak prevalence in excess of 10% was seen in adults between 20 and 40 years of age (Fig. 3).

Another survey assessed the prevalence of chronic HBV infection among Asian/Pacific Islander populations living in New York City.¹⁸ Of 925 survey participants who reported not having been tested previously for HBV infection, 137 (14.8%) were HBsAg-positive, whereas another 496 (53.6%) had evidence of resolved HBV infection. Chronic HBV infection was more common among males (19.7%) than females (8.7%). Prevalence of chronic HBV infection varied by country of birth, from 21.4% among those born in China to 4.6% among those born in South Korea and 4.3% among those born in other Asian countries.

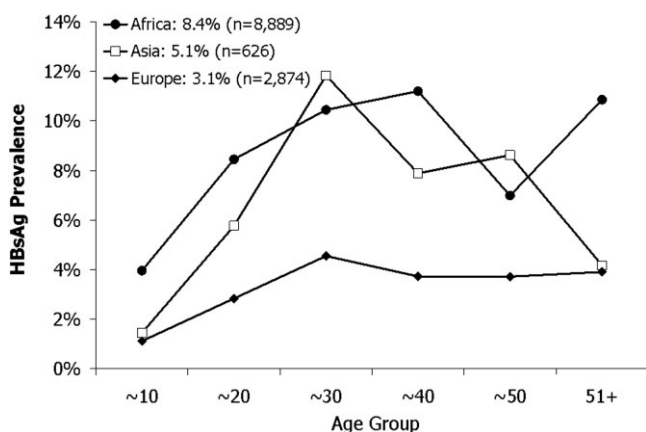


Fig. 3. Prevalence of HBsAg among 12,389 refugees arriving in Minnesota between 1998 and 2001 by continent of origin and age group (decade). Overall percentage and numbers tested given in the legend. Data from Ugwu et al.¹⁷

One of the most striking elements of the survey results was the prevalence of HBV by age group. Consistent with the Minnesota refugee data, the highest prevalence was seen in young adults. In Fig. 4, among respondents aged between 20 and 29, HBV prevalence was 25.2%, followed by 21.5% among those 30-39 years of age. The prevalence progressively decreased according to age. The majority of the respondents in the survey were immigrants with 46% having lived in the United States for less than 10 years. To the extent that this survey was voluntary and not based on population-based sampling, a certain degree of self-selection is undoubtedly present. Incidentally, the prevalence of HBV infection was higher among respondents who reported to be uninsured (17% versus 10% among those with insurance). Of all the respondents, 77% reported having no health insurance.

Results of these and other screening programs in Atlanta, Chicago, New York City, Philadelphia, and California indicate that the prevalence of HBV infection is disproportionately high (10%-15%) among Asians, Pacific Islanders, and other immigrant populations.^{19,20} These statistics are not surprising given the geographic distribution of HBV in the world and the recent pattern of immigration. In order to accurately gauge the disease prevalence in immigrant groups, systematic screening would be necessary. However, screening for HBV is not universally required for immigrants, as it is for human immunodeficiency virus infection or tuberculosis. Given the lack of data, estimates have been made based on number of immigrants and the prevalence of HBV in their originating countries. A recent study estimated the number of immigrants living in the United States in 2008 based on the U.S. Census data and computed the number of prevalent cases with HBV. Of the estimated 41 million

Americans born elsewhere, 1.5 million (range: 0.9 million to 2.2 million) were estimated to have HBV infection, including 863,000 from Asia, 291,000 from Central America and the Caribbean, 196,000 from Africa, and 173,000 from Eastern Europe and elsewhere.²¹ When these estimates are compared with the NHANES data, the true prevalence of HBV infection in the United States might be several times higher than what was projected in the U.S. general population.

Burden of Liver Disease from HBV Infection in the United States

HBV infection incurs significant health burden in a number of disease states: (1) acute hepatitis which may range from symptomatic cases requiring inpatient and outpatient care to fulminant cases leading to liver failure and death unless liver transplantation is performed; (2) chronic hepatitis and cirrhosis which are largely asymptomatic, yet require monitoring and treatment as indicated, as well as screening for hepatocellular carcinoma (HCC); (3) decompensated cirrhosis which is usually associated with significant reduction in quality of life, substantial risk of mortality, and increased resource utilization from frequent inpatient and outpatient care; and (4) HCC, which has extremely high risk of mortality and incurs significant healthcare utilization for curative or palliative treatment. When all of these are taken into account, the total burden of HBV-related liver disease is likely substantial; however, to date, there are only limited data about the burden of liver disease associated with HBV infection in the United States.

A recent report on the burden of digestive diseases used the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey esti-

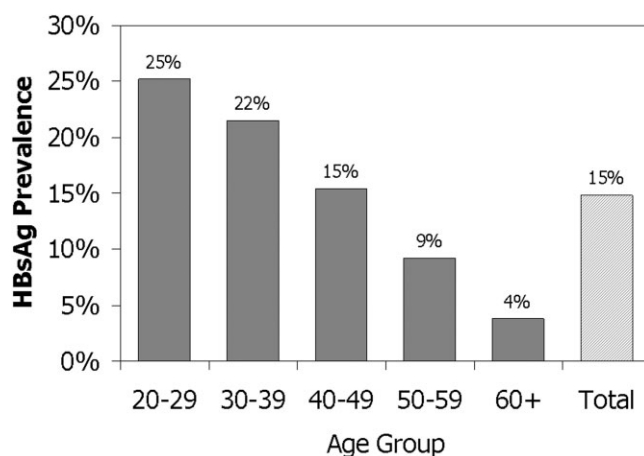


Fig. 4. Prevalence of HBsAg among Asian or Pacific Islander populations in New York City by age group. Data from Morbidity and Mortality Weekly Report.¹⁸

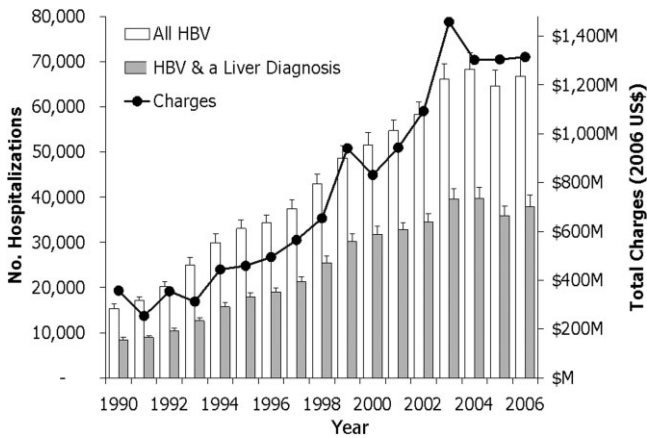


Fig. 5. Number of hospital discharges and total charges (in 2006 adjusted U.S. dollars) with a hepatitis B-related illness in the United States by year (1990-2006). Agency for Healthcare Research and Quality, unpublished data. Error bars indicate the upper half of 95% confidence interval.

mated that outpatient visits for a HBV-related diagnosis in the United States occurred at a rate less than 100 visits per 100,000 in 1996, which increased by at least four-fold to greater than 400 visits per 100,000 by 2004.²² The National Hospital Discharge Survey data indicate a similar increase in discharges with a HBV diagnosis: in 1992, the rate of hospitalization for a HBV-related illness was 5 per 100,000, which increased to more than 20 per 100,000 in 2002.²² These data strongly suggest that the number of patients with HBV requiring inpatient and outpatient care increased substantially during the late 1990s and early 2000s.

Figure 5 summarizes results of an analysis of hospital discharges with an HBV diagnosis based on another data set, the Nationwide Inpatient Sample of the Healthcare Utilization Project database (Agency for Healthcare Research and Quality, Rockville, MD). In the figure, the taller bars represent all hospitalizations with any HBV diagnosis, whereas the shorter ones indicate hospitalizations in which HBV infection was the principal diagnosis or was associated with a diagnosis indicative of liver complication (e.g., ascites, HCC). There was a similar magnitude of increase (approximately four-fold) in either type of HBV hospitalizations between 1990 and 2006. The increase was linear up to 2003 or 2004, when a plateau seems to have reached. Again, these increases in hospital resource utilization for liver disease related to HBV suggest increased prevalence of illnesses related to chronic HBV infection in the United States during the 1990s and early 2000s.

As expected, these increases in hospital resource utilization were accompanied by substantial health economic expenditures. The line in Fig. 5 estimates the total charges

by hospitalizations (exclusive of physician charges) for HBV in the United States. The total charges, inflation-adjusted to 2006 U.S. dollars, increased from \$357 million in 1990 to \$1.5 billion in 2003 and then formed a plateau at \$1.3 billion. These estimates appear much higher than what was reported in the recently published "Burden of Digestive Diseases in the United States", which estimated the direct cost of hepatitis B in 2004 at \$205 million and indirect cost at \$253 million.²³ The discrepancy likely arises from different methods of allocating costs. For example, in the data presented in Fig. 5, the total charges of a hospitalization classified to be liver-related were attributed to hepatitis B, whereas only 20% of charges were thought to be for hepatitis B in Burden of Digestive Diseases report, if HBV was a secondary diagnosis. Another potentially large health expenditure related to hepatitis B is anti-HBV drugs. According to market research data, the anti-HBV prescription market (exclusive of interferon products) grew in a linear fashion from \$38 million in the first quarter of 2006 to \$82 million in the second quarter of 2008. This represents an approximately 13% increase per quarter and more than 50% increase annually (IMS Health, personal communication, 2008).

Figure 6 summarizes the longitudinal trend in the number of waitlist registrants for liver transplantation for HBV-related indications.²⁴ Waitlist registration for acute liver failure, end-stage liver disease, and HCC increased steeply in the mid-1990s, coinciding with widespread adoption of hepatitis B immune globulin for prevention of recurrent hepatitis B of the transplanted liver.²⁵ Since then, waitlist registration for end-stage liver disease reached a peak in 2000, followed by a sharp decrease.

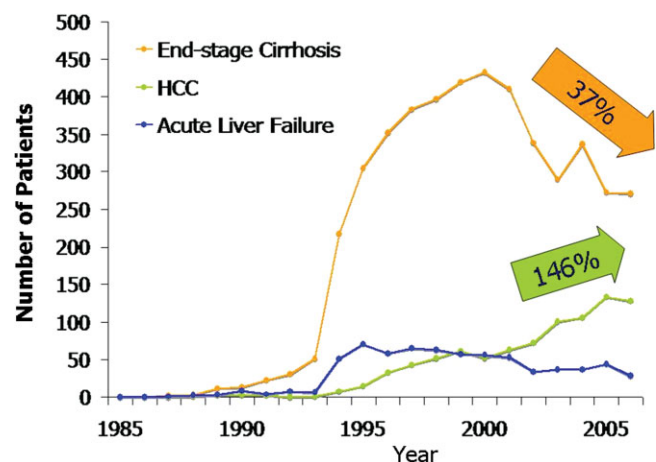


Fig. 6. Number of patients placed on the liver transplantation waitlist by year for hepatitis B-related indications in the United States. Registrants for end-stage cirrhosis have been declining (-37%) while those for hepatocellular carcinoma (HCC) have been rising (+146%). Data from Kim et al.²⁴

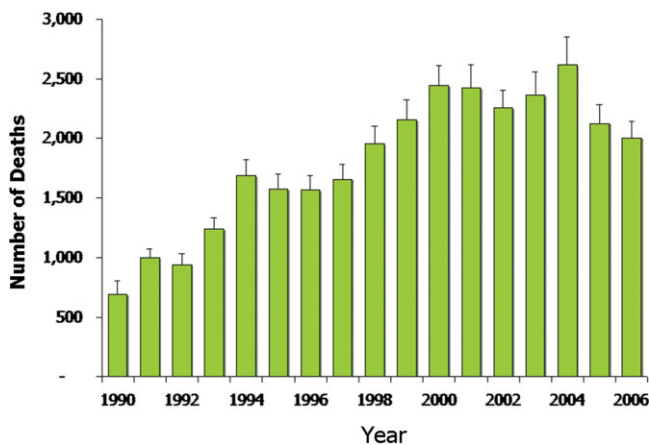


Fig. 7. Number of in-hospital deaths due to hepatitis B-related causes in the United States by year (1990-2006). Nationwide Inpatient Sample, Agency for Healthcare Research and Quality, unpublished data. Error bars indicate the upper half of 95% confidence interval.

There was a 37% reduction in waitlist registration between 2000 and 2006. In contrast, waitlist registration for HCC remained on an incline throughout. Finally, waitlist registration from fulminant liver failure from HBV infection peaked in 1995 and then decreased, mirroring the trend in the incidence of acute hepatitis B. The reason for the recent decline in the waitlist registration for end-stage liver disease may be multifactorial, including implementation of a new liver allocation system based on the Model for End-Stage Liver Disease (MELD) score. The new allocation system assigned a high level of priority to patients with a high risk of death from liver failure and other reasons such as HCC and its implementation in 2002 led to an overall reduction in waitlist registration.²⁶ It is also feasible that antiviral agents introduced in the mid to late 1990s may have decreased the number of patients developing complications of end-stage liver disease due to HBV.

According to an analysis of the national death registry, the age-adjusted mortality rate for HBV-related illness increased throughout the 1980s and early 1990s from 0.2 per 100,000 to 0.8 per 100,000.²⁷ This increase was followed by a relative plateau and then a decline starting in 1999. As of 2004, the mortality rate was approximately 0.6 per 100,000.²² These figures are again corroborated by the Nationwide Inpatient Sample data; there was a rise in the number of in-hospital deaths from less than 700 in 1990 to almost 2500 in 2000 (Fig. 7). Since then, the trend was reversed and the number of deaths decreased to 2003 in 2006. These data about liver transplant waitlist registration and death indicate that there has been a recent decrease in the number of patients who experience liver failure and die or require liver transplantation. While this obviously is an encouraging trend, extrapolation of these

declines into the future is not necessarily warranted. To the degree that there are many indications that the number of Americans with chronic HBV infection has been increasing, as these (recent immigrant) individuals age and their disease progresses, these downward trends may reverse. Regardless of whether antiviral drugs have had a role in the decline in liver failure and mortality, there is little doubt that an increasing number of Americans are taking anti-HBV agents and the eventual fate of these individuals remains to be seen.

Needs for Future Research

From the standpoint of epidemiology, the greatest need for research is in accurate measurement of prevalence of HBV infection in the United States. The current estimates are primarily based on the NHANES survey, which does not address the population groups in which HBV is prevalent. Data from other ad-hoc screening surveys are limited, because they were derived from individuals who participated in the surveys voluntarily, and it is difficult to gauge whether the data are generalizable. NHANES-type surveys that employ probabilistic sampling of the target population (e.g., Asian immigrants) that will produce data that are generalizable to the population will be very helpful not only to assess the current burden of HBV infection in the population but also to monitor the impact of public health interventions.

With regard to the impact of HBV infection on health, mortality, and health service utilization, statistics based on public source data will remain important. However, those data sets, including death registries and hospital discharge summaries, lack the clinical details that are necessary for complete understanding of what is going on with HBV infection in the population, such as impact of widespread application of antiviral therapy. Large cohort studies that include representative samples of the population and incorporate detailed clinical information may complement the information from public health sources. In that regard, studies such as the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-sponsored hepatitis B clinical research network may represent an important step in the right direction.

Conclusions

HBV remains an important cause of acute and chronic liver disease in the United States. The incidence of new infections with HBV has decreased dramatically in the past two decades, largely due to widespread vaccination programs in children as well as safer needle-using practices and universal precaution in healthcare as well as exclusion of blood donors with infection. These decreases in

acute infections have not translated into diminished prevalence or burden of chronic HBV infection in the United States. The prevalence estimates (approximately 0.4%) for the general population have underestimated the true burden of chronic HBV infection, and recent data indicate that migration of people with existing HBV infection has had an important impact on the prevalence of HBV infection. The burden of HBV infection, as measured by inpatient and outpatient healthcare utilization, waitlist registration for liver transplantation, and mortality related to HBV infection, increased substantially throughout the 1990s and leveled off or declined more recently. These data suggest that a growing number of Americans are living with chronic HBV and that careful clinical monitoring and continued epidemiologic surveillance are warranted.

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