ABSTRACT

Despite widespread availability of a safe and efficacious vaccine, chronic hepatitis B infection remains prevalent in historically endemic areas, such as Asia and the Pacific Basin, where it is the leading cause of cirrhosis and hepatocellular carcinoma. In these areas, hepatitis B virus (HBV) is mostly transmitted perinatally or in early childhood (<5 years) and, therefore, follows a pattern that is somewhat distinct from adulthood-acquired infections that commonly occur in the United States and Europe. As a result of a general increase in US immigration from areas of high HBV prevalence, the burden of HBV, in regard to transmission and sequelae, continues to have substantial public health implications. This article offers an extensive discussion of HBV disease distribution, burden, transmission, and natural history, with a focus on the Asian/Pacific Islander population. Also discussed are diagnostic techniques and vaccination efforts, including recommendations for a comprehensive immunization strategy.

ease (4.9-fold) and HCC, in-hospital deaths, and HBV-related hospital charges (doubled over a 10-year period). A decision analysis performed by the National Immunization Program estimates that achievement of routine HBV vaccination with 3-dose coverage in 90% of infants could prevent 68% of HBV-related deaths.

**Distribution of Hepatitis B**

The regional prevalence of hepatitis B surface antigen (HBsAg) positivity varies widely between 8% in highly endemic areas (sub-Saharan Africa, Asia excluding Japan, the Pacific Basin, parts of the Middle East, and the Amazon Basin) to less than 2% in North America and Western Europe. In areas of high endemicity, 70% to 90% of the general population has serologic evidence of current or resolved HBV infection, which was mostly transmitted perinatally or in early childhood (<5 years). In intermediate and low endemicity areas, transmission is more likely to occur in later childhood or in adulthood. Race and ethnicity contribute to local variability in prevalence, especially in areas housing immigrants from highly endemic areas. To this point, a recent study found a 15% prevalence rate of HBV among Chinese Americans residing in New York City. A recent analysis of a community-based registry of 145 patients with HBV living in Minnesota found a large majority of these patients to be immigrants from endemic areas. A race-specific HBV prevalence of 1.3% to 3.6% was noted among Asians and Africans, as compared to 0.02% in Caucasians.

**Transmission**

Hepatitis B virus is present in body fluids, including blood, saliva, sweat, breast milk, tears, urine, vaginal secretions, semen, and menstrual blood. Viral transmission can occur via mother-to-child (vertical or perinatal transmission) or percutaneous or mucosal exposure to infectious bodily fluids (horizontal transmission). The incubation period following infection ranges from 45 to 160 days with the mean time period being 120 days. In areas with a low prevalence of HBV, horizontal transmission is more common (eg, sexual contact, injection drug use, or occupational exposure to blood or blood products). Percutaneous routes of exposure include direct contact with infected blood/blood products and contaminated health-related paraphernalia/needle sticks, as well as injection drug use. Rarely, tattooing and acupuncture have also been implicated in HBV transmission. Although screening of blood products and sterile techniques have virtually eliminated percutaneous HBV transmission in US healthcare facilities, this mode of transmission remains a threat in developing countries, where reuse of medical instruments/disposable needles and contaminated multiple-dose vials still occurs. Contamination of dialysis equipment is also a source of transmission, particularly if infected patient isolation and strict adherence to infection control practices are not employed. Clusters of acute HBV have been reported in hemodialysis units.

Percutaneous transmission can also occur with mucosal exposure during high-risk sexual behaviors, with men who have unprotected sex with men remaining at highest risk. Although uncommon, person-to-person spread of HBV between household contacts can occur, because HBV can survive in the environment for 7 days or more. Contamination of surfaces with blood or other secretions is the most common source of this type of transmission. Reports among Southeast Asian and among refugee children showed that 6% to 11% of children born to HBsAg (-) mothers were HBsAg (+), indicating probable child-to-child or household transmission.

In regions of high endemicity, perinatal transmission remains the predominant mode of HBV acquisition. If a pregnant woman contracts acute HBV infection during the first or second trimester, HBV rarely infects the infant. But if infection occurs in the third trimester or in the postpartum period, it will more likely lead to infection in the infant. This observation suggests that infection of infants born to HBV (+) mothers is more likely to occur in the perinatal period as opposed to in utero, and the risk is associated with maternal replicative status. Wang et al reported that 70% of infants born to 33 hepatitis B e antigen (HBeAg) (+) mothers had HBeAg positivity at the time of delivery, suggesting transplacental HBeAg acquisition. Infants born to mothers who are both HBsAg (+) and HBeAg (+) have up to a 95% risk of HBV acquisition, with a 90% chance of chronicity.

Children born to HBeAg (-) mothers have a somewhat lower risk of infection (10%–40%), although the majority will develop chronic infection as well. Immediate postnatal vaccination with both passive
and active immunoprophylaxis of at-risk infants born to HBsAg (+) mothers significantly reduces the risk of transmission. However, 5% to 10% of vaccinated infants born to HBeAg (+) mothers subsequently become HBsAg positive, which may be related to high levels of maternal viremia, intrauterine infection, or HBV mutation in the surface protein.29-32 Mothers with high levels of viremia, especially those with HBeAg, should be considered for antiviral treatment during the third trimester of pregnancy. It has been shown that antiviral treatment (see drugs approved for this purpose in article by Ke-Qin Hu, MD) could be safely given in the third trimester of pregnancy.

NATURAL HISTORY

Age and immune competence at the time of infection are the major determinants of outcomes from acute HBV, whereas duration of infection is associated more with development of HBV-related sequelae. In infants and children, initial HBV infection is typically subclinical and a large percentage of acute cases proceed to chronic infection. If HBV is acquired in adulthood, as is often the case in areas of lower endemicity, chronicity is uncommon and symptomatic acute HBV is more common.

PERINATAL OR CHILDHOOD-ACQUIRED INFECTION

Broadly, 4 sequential phases of infection can be defined as: (1) immune tolerance; (2) immune activity/clearance; (3) nonreplicative; and (4) reactivation.

- In the immune tolerance phase, there is minimal immune activity against the virus, viral replication is high (ie, high serum HBV DNA levels), serum aminotransferase levels are normal, and patients are generally asymptomatic. Histology in this phase shows minimal inflammatory activity. In perinatally infected persons, this phase may last for the first 2 to 3 decades of life, with a low rate of spontaneous HBsAg clearance.33

- In the immune activity/clearance phase, previously inactive HBV carriers have recurrent episodes of clinical reactivation as immune-mediated destruction of infected hepatocytes occurs, leading to elevated liver enzymes and decreased HBV DNA levels. In this phase, perinatally infected patients often become symptomatic for the first time, presenting with elevated liver enzymes. They may also seroconvert soon-er, becoming positive for antibody to HBeAg (anti-HBe). The duration of this phase is variable (months to years), and reactivation can be clinically severe enough to mimic fulminant acute infection.

- In the nonreplicative phase, HBV DNA levels have fallen, seroconversion from HBeAg (+) to HBeAg (-)/anti-HBe (+) status occurs, aminotransferase levels normalize, and histologic activity is reduced.

- Although commonly referred to as the “inactive carrier” state, reactivation (phase 4) can occur spontaneously or under circumstances of immunosuppression and is usually associated with elevated alanine aminotransferase (ALT) and HBV DNA levels. More rapid progression from active hepatitis (phase 2) to seroconversion of HBeAg (phase 3) is seen as favorable, because it is associated with cessation of viral replication and reduced necroinflammatory activity, with diminished risk of disease progression.34,35 Regression of fibrosis also may occur months to years after seroconversion.36 The Figure depicts the 4 phases of HBV infection.37

![Figure. The 4 Phases of HBV Infection](https://example.com/figure.png)

- anti-HBe = antibody to HBeAg; anti-HBs = antibody to HBsAg; ALT = alanine aminotransferase; CH = chronic hepatitis; HAI = histologic activity index; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus. Reprinted with permission from Fattovich. Semin Liver Dis. 2003;23:47-58.37

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**Figure. The 4 Phases of HBV Infection**

- Immune Tolerance
- Immune Clearance
- Low or Nonreplicative Phase
- Reactivation Phase

- HBsAg (+)
- HBeAg (-) / anti-HBe (+)
- HBV-DNA
- ALT
- mild CH moderate/severe CH HAI < 4 moderate/severe CH cirrhosis
- HBeAg (+) CH inactive-carrier state resolved hepatitis B (HBsAg [-] / anti-HBs [+] ) HBeAg (-) CH

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Johns Hopkins Advanced Studies in Medicine
**Precore/Core Promoter Mutation**

Precore mutants of HBV appear during HBeAg seroconversion and carry mutations in the precore region, preventing HBeAg synthesis despite continuing production of infectious virions. G1896A is the most common of these mutations and is restricted to specific viral genotypes (B, C, D, and E).38 The mutation is more prevalent in geographic regions where genotypes B, C, and D are predominant (eg, Asia and Mediterranean area), and its presence should be considered in individuals who are HBsAg (+) and HBeAg (-) in the presence of detectable HBV DNA. Additionally, they may be anti-HBc (+) or (-) and serum aminotransferases may be normal or elevated.38 The core promoter mutant is characterized by point mutations in the promoter for both HBeAg mRNA and core protein mRNA. The most frequent core promoter mutation is the double A1762T and G1764A nucleotide exchange, which results in a substantial decrease in HBeAg expression but enhanced viral genome replication. As opposed to precore variants, which may be present in HBeAg (-) patients, core promoter variants can be detected in patients who are either HBeAg (+) or HBeAg (-) and the mutation is evenly distributed among the major HBV genotypes. During chronic infection, core promoter mutants have been linked to fulminant forms of HBV and liver cancer, but more studies are needed to clarify the relationship.38 Treatment of these variants can be challenging because the response rate for precore mutants to interferon α is low.

**Adult-Acquired Infection**

In contrast to childhood-acquired infection, only 1% to 5% of immune competent adults become chronically infected after acute HBV infection, and a much higher percentage (30%–50%) present with icteric illness at the time of infection.39 Fulminant hepatitis occurs in 0.1% to 0.5% of acute HBV cases.40

**HBV in the Asian Patient**

Chronic HBV (CHB) infection remains highly endemic in most Asian countries, where it affects up to 16% of the population and is a major cause of morbidity and mortality due to cirrhosis and HCC.41 According to the 2000 US census data, Asians comprise 3.6% of the US population (ie, 10 million people) and are expected to reach 37.6 million by 2050. Asian immigrants from endemic areas have an HBV prevalence that is comparable to that of their native country, whereas those born in the United States have a significantly lower prevalence (1.6%).42 Most Asians acquire HBV via perinatal transmission and studies have shown HBsAg positivity in 8.3% of 38 000 tested pregnant Asian women.43 The highest and lowest rates of HBsAg positivity were found in women of Chinese origin (11.4%) and in those born in Japan (2%), respectively. Although perinatal transmission accounts for more than 50% of HBV cases in endemic Asian countries, horizontal transmission in early childhood is also an important mode of transmission. A proportion of children become HBV (+) from HBsAg (+) siblings, and this risk of infection increases with increasing age and the presence of an HBsAg (+) household relative.38

The National Cancer Institute reported that, compared to Caucasian Americans, Asian Americans have a 6 to 13 times higher risk of developing HCC as a result of HBV.44 Although uncommon, cirrhosis and HCC have been reported in children, but can be prevented with vaccination. In regard to treatment, several factors may hinder outcomes in Asian patients (see article by Dr Hu for more detailed information). Although Asians with HBeAg (+) CHB and elevated ALT levels have been shown to have similar response rates as non-Asians to interferon and oral nucleos(t)ides, the response may be less durable and ultimate loss of HBsAg may be less frequent.45 Also, most Asians have normal or near normal ALT levels and high HBV DNA, which are predictive of lower therapeutic response rates.46 Because many Asian patients have HBeAg (-) CHB, relapse rates are high once interferon or nucleos(t)ide therapy is discontinued. Therefore, long-term therapy is usually required but is accompanied by risks of antiviral resistance. In regard to liver transplants due to HBV infection, recent data related to Asian patients appear positive. In one analysis of the United Network for Organ Sharing database of US patients transplanted for HBV, Kim et al found excellent outcomes with the use of immunoprophylaxis with hepatitis B immune globulin and lamivudine.47 No difference in survival was seen between Asians and non-Asians, despite earlier concerns of poorer outcomes among Asians.47-51 In another observation, the proportion of Asian patients transplanted for HBV increased from 14% to 21%, reflecting US immigration trends.
During the second phase of HBV infection, mutations in the core promoter and precore region may occur, which decrease or prevent the synthesis of HBeAg but do not impair viral replication. The host immune pressure may select for these so-called precore and core promoter variants, the most common of which is a G-to-A change at nucleotide 1896. Patients who are HBsAg (+) (age >6 months), anti-HBe (+) or (-), and HBeAg (-) but with high (possibly >20 000 IU/mL, but the cut-off is somewhat controversial) serum HBV DNA levels and evidence of disease activity (elevated aminotransferases or histologic inflammation) are considered to have HBeAg (-) CHB. A recent literature review by Funk et al suggests that HBeAg (-) CHB is more common worldwide than previously reported, with a prevalence rate of 33% in the Mediterranean, 15% in the Asian Pacific, and 14% in the United States and Europe.52 Chu et al described the presence of the precore and core promoter variant in 27% and 44% of 694 US patients, respectively.53 Several reports also suggest an increasing prevalence of HBeAg (-) CHB, but further studies are warranted to determine true prevalence rates.54,55 The reason for this changing epidemiology is still not clear, but it may be related to several factors. HBeAg (-) CHB is increasingly being recognized and is more difficult to treat because there is a higher rate of relapse after cessation of treatment.56-59

**Table. Individuals Who Should Be Screened for Hepatitis B**

<table>
<thead>
<tr>
<th>Pregnant women</th>
<th>Healthcare workers</th>
<th>Hemodialysis patients</th>
<th>Recipients of clotting factor concentrates</th>
<th>Individuals from areas of high prevalence</th>
<th>Active or previous injection drug usage history</th>
<th>Individuals with multiple sexual partners</th>
<th>Men who have sex with men</th>
<th>Household and sexual contacts of chronically infected persons</th>
<th>Inmates of correctional facilities</th>
<th>Evidence of liver disease</th>
<th>Coinfection with HCV or HIV</th>
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| HCV = hepatitis C virus.
rates have decreased by 90%, prevalence of CHB infection in children younger than 15 years was reduced from 10% to 0.7%, and rates of HCC among children also declined by 50%. In the United States, universal infant vaccination was introduced in 1991, and recent data show that more than 90% of children younger than age 3 are vaccinated for HBV. The comprehensive strategy for elimination of HBV transmission includes universal vaccination of all infants at birth; prevention of perinatal transmission through screening of all pregnant women for HBsAg, prophylactic treatment of pregnant women with high viremia in the third trimester, and postexposure immunoprophylaxis of infants born to HBsAg (+) women or women of unknown status; and vaccination of adolescents not previously vaccinated in early childhood, adults at risk for infection, and sexual partners and household contacts of chronically infected individuals.

CONCLUSIONS

Chronic HBV and its sequelae remain a major global health concern. Despite recommendations and implementation of vaccination programs, the health and economic burdens are still significant. Individuals living in endemic areas and immigrants from these areas need to be adequately screened and treated. More priority should be given to primary prophylaxis programs, in which high-risk adult and adolescent groups receive vaccination.

REFERENCES