

EPIDEMIOLOGY OF HEPATITIS B IN EUROPE AND WORLDWIDE

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Introduction

Hepatitis B virus (HBV) infection is a major public health problem and cause of infectious disease mortality worldwide. Approximately 2 billion people - one third of the world's population - have serologic evidence of past or present HBV infection, and 350 million people are chronically infected. Each year over 1 million people die from HBV-related chronic liver disease, including cirrhosis and hepatocellular carcinoma (HCC) (1). HCC is one of the most common cancers worldwide, and HBV is responsible for at least 75% of these cancers (2).

Geographic Patterns of Transmission

The endemicity of HBV infection varies greatly worldwide (3,4) and is influenced primarily by the predominant age at which infection occurs (Table 1). Endemicity of infection is considered high in those parts of the world where at least 8% of the population is HBsAg-positive. In these areas, 70% to 90% of the population generally have serological evidence of previous HBV infection. Almost all infections occur during either the perinatal period or early in childhood which accounts for the high rates of chronic HBV infection in these populations. Risk of HBV infection continues after the first five years of life, but its eventual contribution to the high rate of chronic infection is less significant. Chronic infection with HBV is strongly associated with HCC, and areas with a high endemicity of chronic HBV infection have the highest death rates from this neoplasm.

In areas of the world with an intermediate pattern of HBV infection, the prevalence of HBsAg positivity ranges from 1% to 7% and serological evidence of past infection is found in 10% to 60% of the population. In these areas there are mixed patterns of infant, early childhood and adult transmission.

In most developed parts of the world, the prevalence of chronic HBV infection is <1%, and the overall infection rate is 5% to 7%. Within these areas most infections occur among high risk adult populations that include injection drug users, persons with multiple heterosexual partners, men who have sex with men (MSM), and health care workers. Although the proportion of infant and early childhood infections is low, they can account for a disproportionately high number of chronic HBV infections.

Modes of Transmission

The incubation period of hepatitis B is long, ranging from 45-160 days (average 120). HBV is transmitted by percutaneous and mucous membrane exposures to infectious blood and body fluids that contain blood. Although HBsAg has been detected in a wide variety of body fluids, only serum, semen, and saliva have been demonstrated to be infectious (5,6). The presence of HBeAg in serum correlates with higher titers of HBV (up to 10^9 particles/mL) and greater infectivity (7-9). However, HBV strains that have mutations in the precore region of the viral genome that prevents expression of HBeAg also have been associated with transmission (10).

Percutaneous exposures that have resulted in HBV transmission include transfusion of blood or blood products (11,12), contaminated equipment used for therapeutic injections and other health-care related procedures (13-17), illegal injection drug use (18), and needle sticks or other injuries from sharp instruments sustained by hospital personnel (7,19). In addition, occasional outbreaks of hepatitis B have been associated

with tattooing and acupuncture (20,21). Because HBV is stable on environmental surfaces for ≥ 7 days (22), indirect inoculation of HBV can also occur via inanimate objects.

Perinatal and sexual transmission of HBV usually results from mucous membrane exposures to infectious blood or serum-derived body fluids (23,24). No infections have been demonstrated in susceptible persons orally exposed to HBsAg-positive saliva, although transmission has been demonstrated to animals by subcutaneous inoculation of saliva (5,6,25,26).

The risk of perinatal HBV transmission has been well described. This risk is greatest for infants born to women who are HBeAg-positive and ranges from 70%-90% at 6 months of age; about 90% of these children remain chronically infected (24). The risk of perinatal infection among infants born to HBeAg-negative mothers ranges from 10%-40%, with 40%-70% of these infected infants remaining chronically infected (24,27). Children born to HBsAg-positive mothers who do not become infected during the perinatal period remain at high risk of infection during early childhood (28-30); in one study, 40% of infants born to HBeAg-negative mothers became infected by 5 years of age (27).

Person-to-person spread of HBV can occur in settings involving nonsexual interpersonal contact over a long period of time, such as among household contacts of a chronically infected person (31-34). The precise mechanisms of transmission are unknown; however, frequent interpersonal contact of nonintact skin or mucous membranes with blood containing secretions or perhaps saliva are the most likely modes of transmission (35). Because of the extremely high concentration of virus in the blood, the number of virions in even very small amounts of blood or body fluids can be quite high. In addition, HBsAg contamination of surfaces is widespread in homes of chronically infected persons (35), and HBV remains infectious for long periods of time under ambient conditions.

Among adults, high-risk sexual activity is one of the most frequent routes of transmission for HBV. Historically, MSM were one of the groups at highest risk for HBV infection. Infection in this risk group has been associated with receptive anal intercourse, increased numbers of sexual partners, and number of years of sexual activity (70% of homosexual men were infected after 5 years of sexual activity) (23). Similar factors have been associated with an increased risk of HBV infection among heterosexual men and women, including number of sexual partners, number of years of sexual activity, and history of other sexually transmitted diseases (STDs) (23).

Transmission of HBV from persons with acute or chronic hepatitis B to their sexual partners is also an important source of infection (23). However, most persons with chronic HBV infection are not aware that they are infected. These silent carriers are the most likely source of infection for persons with multiple sexual partners.

Current Epidemiology

In most developed countries, including those in northern and western Europe, the highest incidence of acute hepatitis B is among young adults, and high-risk sexual activity and injecting drug use account for most cases of newly acquired hepatitis B (36-39). However, even in these low HBV endemic countries, a substantial number of children become infected with HBV, many of whom belong to families that have immigrated from high HBV endemic countries (3,40,41). Since over 90% of childhood HBV infections are asymptomatic, the true incidence of childhood disease is not accurately represented by most surveillance data, which reflect reported cases of clinically apparent disease.

Although HBV infection was recognized as a frequent occupational hazard among persons working in laboratories or exposed to blood while caring for patients (42,43), hepatitis B vaccination of health care workers (and implementation of universal precautions) has made this infection a rare event in this population (44). HBV transmission from infected healthcare personnel to patients is relatively uncommon, but has occurred during invasive surgical, obstetrical, or dental procedures. Most of the reported cases occurred prior to 1991, before hepatitis B vaccination was widely used and before standard (universal) infection

control precautions were implemented. These mostly involved infected surgeons or dentists who transmitted during the performance of invasive procedures (45-67). However, other healthcare providers also have been implicated in HBV transmission to patients (61,62,68-70). Most of these involved skin conditions in these healthcare providers (e.g., exudative dermatitis, bleeding lesions or cuts) that contributed to transmission. Substantially fewer episodes of HBV transmission to patients from infected surgeons have been reported worldwide since 1991, most of which were from the United Kingdom (10,71,72). All but one of the cases in the United Kingdom involved healthcare providers who were infected with precore mutations and were negative for HBeAg (10).

Transmission of HBV via transfusion of blood and plasma-derived products has been eliminated in most countries through donor screening for HBsAg and viral inactivation procedures. However, transmission also occurs with inadequately sterilized needles and medical instruments, the reuse of disposable needles and syringes, and contamination of multiple dose medication vials. Contaminated environmental surfaces have been a major source for HBV transmission among chronic hemodialysis patients (73). HBV transmission among hemodialysis patients is consistently associated with the presence of a chronically infected patient, failure to dialyze that patient in a separate room using dedicated equipment and staff, and failure to vaccinate patients against hepatitis B.

In developing countries, transmission through contaminated injection equipment remains a significant problem because of the difficulty in obtaining disposable needles and syringes and the lack of means to adequately sterilize reusable equipment (13). In developed countries, episodes of HBV transmission from one patient to another in healthcare settings also have been reported (14-17,74-77). In most cases, these transmissions resulted from noncompliance with recommended infection control practices that were designed to prevent cross-contamination of medical equipment and devices.

Prevention

The primary goal of hepatitis B prevention programs is reduction of HBV-related chronic liver disease and chronic HBV infection. A secondary goal is the prevention of acute hepatitis B. HBV infection can be prevented by screening blood, plasma, organ, tissue, and semen donors, virus inactivation of plasma-derived products, risk-reduction counseling and services, and implementation and maintenance of infection control practices. Although such activities can reduce or eliminate the potential risk for HBV transmission, by far the single most effective prevention measure is immunization.

In 1992, the World Health Organization recommended that all countries include hepatitis B vaccine in their routine infant immunization programs. In 2000, only 116 of 215 countries have such a policy, representing 31% of the global birth cohort. Thus, despite the availability of an effective vaccine for more than 15 years, most of the world's children remain at risk for HBV infection.

Immunization strategies in developed countries vary widely. In the United States, the immunization strategy has evolved over time and now includes 1) prevention of perinatal HBV infection through routine screening of all pregnant women and appropriate postexposure immunoprophylaxis of infants born to HBsAg positive women; 2) routine vaccination of infants; 3) routine vaccination of adolescents who have not previously been vaccinated; and 4) vaccination of adults at increased risk of infection (78,79). Most countries in western Europe have focused efforts on prevention of perinatal infection and routine vaccination of adolescents; rarely, routine immunization of infants also has been included (80-84). In eastern European countries, routine immunization of infants has been the primary strategy (84,85).

The success of routine immunization of children and adolescents in interrupting HBV transmission already has been demonstrated in both high and low HBV endemic areas. During the 15 years after routine childhood hepatitis B immunization was implemented in Taiwan, the prevalence of chronic HBV infection among children <15 years old declined from 10% to 0.7%, a decrease of 93%, and rates of HCC among children 6-14 years old declined by 50% (86,87). Similarly, almost a 90% decline was observed in the overall prevalence of infection (as measured by antibody to hepatitis B core antigen), while prevalence of protective

antibody (antibody to hepatitis B surface antigen) remained high. In countries such as Italy and the United States, the incidence of acute hepatitis B has declined dramatically during the past decade, particularly among persons in younger age groups (39,83,88).

The integration of vaccine into existing childhood vaccination schedules has the greatest likelihood of successfully lowering the disease incidence. There is already an established infrastructure for vaccine delivery to children which can ensure high coverage levels, and the hepatitis B vaccine has been shown to provide long-term protection against chronic HBV infection. In addition, routine infant immunization ensures the prevention of HBV infections in subpopulations that have high rates of early childhood infection (e.g., infants and children of immigrant women from high endemicity areas). The addition of routine adolescent vaccination achieves a more rapid reduction in HBV transmission.

However, until the cohorts of vaccinated children reach adolescence and adulthood, efforts must be strengthened to vaccinate older adolescents and adults with high-risk behaviors or occupations. Most HBV transmission and the morbidity associated with acute hepatitis B occurs among older adolescents and young adults, and most of these infections result from sexual transmission. Adults at highest risk for infection are the most difficult to reach with vaccine and a substantial proportion do not self-identify as belonging to a risk group. There are long-standing recommendations to vaccinate persons who report a history of multiple sex partners, treatment for a sexually transmitted disease, men who have sex with men and injecting drug users. However, vaccine is rarely offered in settings that provide health-care to adults. Although continued immunization of successive birth cohorts should achieve the eventual elimination of HBV transmission, this will not occur for decades without successful vaccination adults at increased risk for infection.

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Table 1. Characteristics of endemic patterns of hepatitis B virus infection

Characteristic	Endemicity of infection		
	Low	Intermediate	High
Chronic infection prevalence	0.1-1%	2-7%	8-15%
Past infection prevalence	4-15%	16-55%	40-90%

Perinatal infection	Rare ($<10\%$) [*]	Uncommon ($10-60\%$) [*]	Common ($>20\%$) [*]
Early childhood infection	Rare ($<10\%$) ^H	Common ($10-60\%$) ^H	Very common ($> 60\%$) ^H
Adolescent/adult infection	Very common ($70-90\%$)	Common ($20-50\%$)	Uncommon ($10-20\%$)

Source: adapted from reference 4

^{*} Estimated percent of total infections among children up to 1 year of age.

^H Estimated percent of total infections among children 1-5 years of age.