

Hepatitis B Virus Infection: Epidemiology and Vaccination

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Worldwide, two billion people have been infected with hepatitis B virus (HBV), 360 million have chronic infection, and 600,000 die each year from HBV-related liver disease or hepatocellular carcinoma. This comprehensive review of hepatitis B epidemiology and vaccines focuses on definitive and influential studies and highlights current trends, policies, and directions. HBV can be transmitted vertically, through sexual or household contact, or by unsafe injections, but chronic infections acquired during infancy or childhood account for a disproportionately large share of worldwide morbidity and mortality. Vaccination against HBV infection can be started at birth and provides long-term protection against infection in more than 90% of healthy people. In the 1990s, many industrialized countries and a few less-developed countries implemented universal hepatitis B immunization and experienced measurable reductions in HBV-related disease. For example, in Taiwan, the prevalence of chronic infection in children declined by more than 90%. Many resource-poor nations have recently initiated universal hepatitis B immunization programs with assistance from the Global Alliance for Vaccines and Immunization. Further progress towards the elimination of HBV transmission will require sustainable vaccination programs with improved vaccination coverage, practical methods of measuring the impact of vaccination programs, and targeted vaccination efforts for communities at high risk of infection.

hepatitis B; hepatitis B vaccines; hepatitis B virus; immunization programs

Abbreviations: anti-HBs, antibody to hepatitis B surface antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; MSM, men who have sex with men.

INTRODUCTION

The earliest recognition of the public health importance of hepatitis B virus (HBV) infection is thought to have occurred when it appeared as an adverse event associated with a vaccination campaign. In 1883 in Bremen, Germany, 15 percent of 1,289 shipyard workers inoculated with a smallpox vaccine made from human lymph fell ill with jaundice during the weeks following vaccination (1). The etiology of “serum hepatitis,” as it was known for many years, was not identified until the 1960s (2), and only following the subsequent development of laboratory markers for infection was its significance as a major cause of morbidity and mortality worldwide fully appreciated (3).

According to the most recent World Health Organization estimate, two billion people worldwide have serologic evi-

dence of past or present HBV infection, and 360 million are chronically infected and at risk for HBV-related liver disease. Approximately one third of all cases of cirrhosis and half of all cases of hepatocellular carcinoma can be attributed to chronic HBV infection. HBV is estimated to be responsible for 500,000–700,000 deaths each year (4–6).

Despite the vast population of infected persons, efforts to prevent and control HBV have met with increasing levels of success and hold promise for large reductions in disease burden in the future. A great deal of credit for achievements to date stems from the introduction of hepatitis B vaccines. First licensed in the United States in 1981, hepatitis B vaccine is now one of the most widely used vaccines in the world and is part of the routine vaccination schedule for many of the world's infants and children. It is the world's first cancer prevention vaccine and the first vaccine to

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TABLE 1. Interpretation of serologic test results for hepatitis B virus infection

Hepatitis B surface antigen	Serologic marker			Interpretation
	Total antibodies to hepatitis B core antigen	Immunoglobulin M antibodies to hepatitis B core antigen	Antibodies to hepatitis B surface antigen	
–	–	–	–	Susceptible; never infected
+	–	–	–	Early acute infection; transient (21 days) after vaccination
+	+	+	–	Acute infection
–	+	+	–	Acute resolving infection
–	+	–	+	Past infection; recovered and immune
+	+	–	–	Chronic infection
–	+	–	–	False-positive (i.e., susceptible); past infection; “low-level” chronic infection; passive transfer to an infant born to a mother who is positive for hepatitis B surface antigen
–	–	–	+	Immune if titer is >10 mIU/ml

prevent a sexually transmitted disease. In countries where large-scale vaccination efforts were made in the first decade after introduction of the vaccine, the epidemiology of hepatitis B and HBV infection has been transformed, and there are early signs that the burden of HBV-related sequelae will be significantly reduced as vaccinated populations age.

In this comprehensive review of hepatitis B epidemiology and vaccines, we focus on studies that have been viewed as definitive or influential by most experts, as evidenced by frequent citations by expert panels or published guidelines, to highlight current trends and policies and directions for the future. The brevity of the review precludes an exhaustive review of the literature or a more detailed discussion of most of the cited data.

HEPATITIS B VIRUS

HBV is a DNA virus classified in the virus family Hepadnaviridae. Humans are the only known natural host. HBV enters the liver via the bloodstream, and replication occurs only in liver tissue. The intact, infectious virus is 42–47 nm in diameter and circulates in the blood in concentrations as high as 10^8 virions per ml. The inner core of the virus contains hepatitis B core antigen, hepatitis B e antigen (HBeAg), a partially double-stranded 3,200-nucleotide DNA molecule, and DNA polymerase with reverse transcriptase activity. Hepatitis B surface antigen (HBsAg) is found both on the surface of the virus and as self-assembling, noninfectious spherical or tubular particles.

NATURAL HISTORY AND CLINICAL MANIFESTATIONS OF HBV INFECTION

HBV infection may result in subclinical or asymptomatic infection, acute self-limited hepatitis, or fulminant hepatitis requiring liver transplantation. Persons infected with HBV may also develop chronic HBV infection, which can lead to

cirrhosis or hepatocellular carcinoma. The likelihood that newly infected persons will develop chronic HBV infection is dependent on their age at the time of infection (7). More than 90 percent of infected infants, 25–50 percent of children infected between 1 and 5 years of age, and 6–10 percent of acutely infected older children and adults develop chronic infection (i.e., they are HBsAg-positive but negative for immunoglobulin M antibodies to hepatitis B core antigen; table 1). Immunosuppressed persons (e.g., hemodialysis patients and persons with human immunodeficiency virus infection) are also at higher risk of developing chronic infection (8, 9).

Because of the inverse association between age and risk of chronic infection, persons infected as children assume a disproportionately large burden of morbidity and mortality attributable to HBV. Up to 25 percent of infants and older children who acquire HBV eventually develop HBV-related hepatocellular carcinoma or cirrhosis. Adults who have had chronic HBV infection since childhood develop primary hepatocellular carcinoma at a rate of 5 percent per decade, which is 100–300 times the rate among uninfected persons (3).

Acute hepatitis B

For newly infected persons who develop acute hepatitis, the average incubation period (time from exposure to onset of jaundice) is 90 days (range: 60–150 days) (10, 11). The likelihood of developing symptoms of hepatitis as a result of a new HBV infection is age-dependent. Over 90 percent of perinatal HBV infections are asymptomatic, while the typical manifestations of acute hepatitis are noted in 5–15 percent of newly infected young children (1–5 years of age) and in 33–50 percent of older children, adolescents, and adults (7). Persons with acute hepatitis B can show signs and symptoms that include nausea, abdominal pain, vomiting, fever, jaundice, dark urine, changes in stool color, and hepatomegaly or splenomegaly.

The first serologic markers to become detectable in persons with acute HBV infection are HBsAg and antibodies to hepatitis B core antigen. In the 6–12 months after infection, immunoglobulin M antibodies to hepatitis B core antigen become undetectable. Total antibodies to hepatitis B core antigen persist for life and are found in persons with chronic infection as well as those who recover from infection. In persons who recover from HBV infection, HBsAg is eliminated from the blood, and antibody to hepatitis B surface antigen (anti-HBs) develops during convalescence. The presence of anti-HBs indicates immunity to HBV infection. Most persons who recover from natural infection (resolved infection) will be positive for both anti-HBs and antibodies to hepatitis B core antigen, but anti-HBs becomes undetectable in some over time. Table 1 presents a summary of serologic markers present at various times during HBV infection or after vaccination. Immunosuppressed persons can develop reactivation of previously resolved HBV infection (12, 13). Resolved acute infection is not a risk factor for subsequent cirrhosis or hepatocellular carcinoma (14).

Chronic HBV infection

Chronic HBV infection is defined as either the presence of HBsAg in the serum for at least 6 months or the presence of HBsAg in a person who tests negative for immunoglobulin M antibodies to hepatitis B core antigen. Unlike persons who recover from acute HBV infection, persons with chronic HBV infection do not develop anti-HBs, and HBsAg typically persists for decades. HBeAg, a marker of high viral replication activity which correlates with greater infectivity, is also usually present in the early phases of illness. For many persons with chronic infection, HBeAg becomes undetectable at some point (usually a decade or more) after the acute infection; this change usually indicates a decrease in viral replication. Approximately 0.5 percent of adults, and a lower proportion of children, with chronic HBV infection will clear HBsAg and develop anti-HBs annually (15–18).

Although a substantial proportion of chronically infected persons will remain asymptomatic for decades and die of causes unrelated to HBV, chronic infection is responsible for most of the burden of disease associated with HBV. Based on data from follow-up studies of persons infected with HBV as infants or young children, approximately 15–25 percent of persons with chronic infection die prematurely from cirrhosis or hepatocellular carcinoma (19, 20). Persons developing the HBV-related sequelae of cirrhosis or hepatocellular carcinoma may be asymptomatic until diagnosis, or they may encounter periodic flare-ups of signs and symptoms of acute hepatitis. Extrahepatic complications can also occur, including polyarteritis nodosa, membranous glomerulonephritis, and membranoproliferative glomerulonephritis.

Persons with chronic HBV infection should receive periodic medical evaluation, and some authorities recommend regular screening for hepatocellular carcinoma using α -fetoprotein or ultrasonography (21). Recently approved therapeutic agents for treatment of chronic hepatitis B are now being used to achieve sustained suppression of HBV

replication and remission of liver disease for some patients (21). However, adverse events associated with treatment, expense, development of antiviral resistance, and low rates of HBsAg clearance remain barriers to treatment for many patients with chronic infection.

TRANSMISSION

HBV is transmitted by percutaneous or mucosal exposure to infected blood or other body fluids. HBV transmission has been observed with numerous forms of human contact: perinatal/mother-to-child; household (nonsexual); sexual; needle-sharing; and occupational/health-care-related. The highest concentrations of infectious HBV are found in blood and serum. However, other serum-derived body fluids, such as semen and saliva, are also infectious (22). Persons with chronic HBV infection are the major reservoir for transmission, although any person testing positive for HBsAg is potentially infectious to both household and sexual contacts. Because HBV can remain stable and infectious on environmental surfaces for at least 7 days, transmission may occur indirectly via contaminated surfaces and other objects.

Transmission from a chronically infected woman to her infant during delivery is efficient and is one of the most common routes of HBV infection worldwide. Perinatal transmission of HBV most often occurs during the birth process; in-utero transmission can occur but is rare and accounts for less than 2 percent of perinatal transmissions (23, 24). The risk of perinatal infection is 5–20 percent in infants born to HBsAg-positive mothers and 70–90 percent if the mother is HBeAg-positive (25).

Transmission of HBV can also occur in situations where there is frequent and prolonged close personal contact with an infected person (26). Prior to implementation of universal infant hepatitis B immunization, an estimated 16,000 children under 10 years of age were infected annually in the United States through exposure to HBsAg-positive household members or community contacts (27, 28). Although the exact mode of transmission is unknown, transmission is hypothesized to occur from inapparent blood or body fluid exposures from parents, siblings, or playmates that inoculate HBV into cutaneous scratches, abrasions, or other lesions or onto mucosal surfaces (29–31).

HBV is efficiently transmitted by sexual contact (32). Sexual contacts of chronically infected persons have been shown to have a higher seroprevalence of HBV infection than control populations, including household (nonsexual) contacts of infected persons (33). Persons with acute hepatitis B are more likely to report multiple heterosexual partners than controls, and the seroprevalence of HBV infection correlates with greater numbers of recent and lifetime heterosexual partners (34, 35). Men who have sex with men (MSM) have long been known to have high rates of disease (36), and they have persistently higher HBV seroprevalence rates than the general population (37).

Injection drug users are at high risk for HBV infection because of behaviors such as sharing of needles, syringes, and other drug paraphernalia. On the basis of data collected more than 10 years ago, the majority of injection drug users

in the United States and elsewhere have serologic evidence of past or current HBV infection (38). However, the risk among injection drug users can vary depending on the prevalence of chronic HBV infection in the community, as well as drug-sharing and preparation practices. In the United States in the mid-1990s, approximately 70 percent of injection drug users were infected after 5 years of injecting (39, 40). Outbreaks linked to other percutaneous exposures besides injection drug use, such as tattooing and acupuncture, have been reported (41, 42).

Health-care-related transmission has long been recognized as an important source of new HBV infections worldwide. Provider-to-patient, patient-to-provider, and patient-to-patient transmission have all been observed, although the frequencies with which these types of transmission occur are widely divergent. Patient-to-provider transmission was common before widespread hepatitis B vaccination of health care workers; it is estimated that 12,000 health care workers per year were infected in the United States in the prevaccine era (43). A health care worker's risk of infection has been shown to correlate with his or her level of blood and needle exposure (44). Following needle-stick exposure, the risk of HBV infection varies according to the volume and viral concentration of the infectious fluid. The risk from inoculation after a needle-stick with HBeAg-positive blood is at least 30 percent, but risk is less than 6 percent if blood is HBeAg-negative (45).

Patient-to-patient HBV transmission is a major source of new HBV infections in the developing world. Patient-to-patient HBV transmission can result from percutaneous exposure to contaminated equipment used for injections or other procedures, or from blood or mucosal exposure to contaminated medication. In developing countries, exposures to contaminated therapeutic injection equipment are common in many settings because of lack of awareness of infection control practices, lack of resources for sterilization and the purchase of new disposable equipment, and economic incentives and cultural preferences favoring overuse of injections. Contaminated injections caused an estimated 21 million HBV infections worldwide in 2000, accounting for 32 percent of all new infections (46). In the developed world, outbreaks involving this type of transmission remain a persistent problem as well, and they usually stem from lapses in infection control practice by health care workers. Implicated vehicles for transmission include multidose vials, finger-stick devices, acupuncture needles, and jet injection guns (47–50). Contaminated environmental surfaces in health care settings have also served as a reservoir for HBV transmission, particularly in dialysis units (51).

Provider-to-patient HBV transmission is rarely reported. Most events have been associated with health care workers' performing invasive procedures, and most occurred before the widespread use of hepatitis B vaccine and the implementation of universal precautions in standard infection control practice (52).

Transmission of HBV via transfusion of blood products has been largely eliminated in most parts of the world by screening blood donors and implementing techniques that ensure viral inactivation of products made from blood, such as factor concentrates (53).

GLOBAL PATTERNS OF TRANSMISSION

The global epidemiology of HBV infection has traditionally been described according to three categories of endemicity—high, intermediate, and low—depending on the proportion of the population that is seropositive for HBsAg (figure 1). Countries with high endemicity are those where HBsAg seroprevalence is greater than or equal to 8 percent; countries with intermediate endemicity are those where seroprevalence is 2–7 percent; and those with low endemicity are those where seroprevalence is less than 2 percent. HBsAg seroprevalence has marked geographic variations, and the degree of HBV endemicity often correlates with the predominant mode of transmission. In highly endemic settings, perinatal and horizontal (exposure to chronically infected household members) routes are responsible for most disease transmission, and 70–90 percent of the adult population has serologic evidence of prior infection (54–56). Because hepatocellular carcinoma is a potential sequela of chronic HBV infection, highly endemic countries have markedly higher rates of liver cancer than countries with lower endemicity, and hepatocellular carcinoma is a major cause of mortality in these areas. Countries with intermediate endemicity have a mix of perinatal, horizontal, health-care-related, sexual, and other forms of transmission. In countries with low endemicity, most new infections occur among young adults and are acquired sexually or through injecting drug use. Highly endemic population subgroups may be present within low-endemicity countries, however, depending upon seroprevalence rates of immigrant groups and native/indigenous populations.

Approximately 60 percent of the world's population lives in areas where HBV infection is highly endemic, including China (total population, 1.3 billion), Indonesia (222 million), Nigeria (132 million), and much of the rest of Asia and Africa (57). Some notable examples of high pre-vaccine-era burdens of disease include Taiwan, where 15–20 percent of the general population had chronic HBV infection and 30 percent of those chronically infected were HBeAg-positive (58, 59), and the Gambia, where the prevalence of chronic infection among children was 36 percent (60).

Southern Europe, the Middle East, and South Asia have an intermediate level of HBV endemicity. HBsAg seroprevalence in India is approximately 5 percent, and the major modes of HBV transmission are perinatal, child-related/horizontal, and health-care-related, particularly unsafe injections (61). In Italy, Russia, and Turkey, the prevalence of chronic HBV infection ranges from 3 percent to 10 percent, and unsafe injections have been implicated as a major route of HBV transmission (62–64).

Most of Central and South America is considered a region of low HBV endemicity. However, the western Amazon basin, including Brazil and Peru, is a highly endemic area, with observed HBsAg seroprevalence rates greater than 10 percent (65).

Many developed nations, including the United States, fall into the low endemicity category. Just prior to the era of widespread hepatitis B vaccine use (1988–1994), 0.42 percent of the US population was HBsAg-seropositive, and



FIGURE 1. Geographic distribution of the prevalence of chronic hepatitis B virus infection, 2002. (Source: Mast et al. (28).)

4.9 percent had serologic markers of previous or current HBV infection (66). In the prevaccine era, some indigenous populations and immigrant groups within the United States had seroprevalence rates similar to those of highly endemic countries, and members of these populations comprised a disproportionate share of new HBV infections nationwide (27). Studies conducted in the 1980s among Southeast Asian families recently settled in the United States found that 5–10 percent of children aged 1–10 years and 15 percent of children aged 11–20 years were chronically infected (67, 68). Among Alaska Native children living in Alaska in the 1970s, 15 percent had serologic evidence of infection and 6 percent were chronically infected (7, 69).

PREVENTION

Before the introduction of hepatitis B vaccines, numerous effective hepatitis B prevention measures had been employed to some degree, including screening of blood donors, preparation of plasma-derived products in a way that inactivates HBV virus, implementation of infection control measures, and administration of hepatitis B immune globulin following suspected exposure, especially for infants born to HBsAg-positive women. Although all of these activities can reduce the risk of HBV transmission, none have been as effective as active immunization with hepatitis B vaccine, which remains the single most important hepatitis B prevention measure.

HEPATITIS B VACCINE

The first licensed hepatitis B vaccines were plasma-derived and composed of purified HBsAg; most currently available hepatitis B vaccines are produced by recombinant DNA technology. Hepatitis B vaccines are typically given in a three-dose series, but vaccine formulations employing two- and four-dose schedules have also been licensed in the United States for use in some age groups (70). Only single-antigen hepatitis B vaccine can be given at birth and to infants younger than 6 weeks of age. Single-antigen vaccines can be administered concurrently with other vaccines at any age, and many combination vaccines containing hepatitis B antigens are licensed in the United States and elsewhere. When used in the appropriate age group and given at the manufacturer's recommended dose, hepatitis B vaccines are considered equivalent in their immunogenicity and effectiveness and can be used interchangeably.

Adherence to licensed hepatitis B vaccination schedules results in a protective concentration of anti-HBs (≥ 10 mIU/ml) in 90–100 percent of healthy infants, children, and adults. In vaccine efficacy studies, 90–100 percent of vaccinated persons who developed anti-HBs concentrations greater than or equal to 10 mIU/ml after a primary series were protected from HBV infection (71). Adults over 40 years of age and immunosuppressed persons are less likely to develop protective concentrations (72, 73). Because hepatitis B vaccines are highly immunogenic, postvaccination serologic testing in the United States is not indicated, except under special circumstances—for example, among

infants born to HBsAg-positive women, persons with ongoing occupational exposure to blood, or persons with immunosuppressive conditions.

Hepatitis B vaccines are also highly effective if given as postexposure immunoprophylaxis to prevent perinatal transmission. Hepatitis B vaccine and hepatitis B immune globulin administered within 12–24 hours after birth, followed by completion of a three-dose vaccine series, has been shown to be 89–98 percent effective in preventing acute and chronic HBV infection in infants born to women who are positive for both HBsAg and HBeAg (74). Hepatitis B vaccine without hepatitis B immune globulin is as effective in preventing perinatal infection as vaccine alone in most studies and is used in areas where cost or other considerations make the use of hepatitis B immune globulin impractical (74). The major determinant of the effectiveness of postexposure immunoprophylaxis for infants of HBsAg-positive mothers is on-time administration of the initial doses of vaccine and hepatitis B immune globulin (75).

Vaccine safety

The safety of hepatitis B vaccine has been demonstrated in a large, prospective clinical trial and postlicensure safety analyses (76, 77). The hepatitis B vaccine is now one of the most widely used vaccines in the world. In the United States alone, more than 60 million adults and adolescents and more than 40 million infants and children have been vaccinated.

The most commonly reported adverse events associated with hepatitis B vaccine are pain at the injection site and temperature greater than 37.7°C. Vaccination of newborns does not increase the number of febrile episodes or sepsis evaluations (78). Allergic reactions including anaphylaxis have been reported but are very rare (79). Epidemiologic studies have found no evidence of a causal association between hepatitis B vaccination and sudden infant death syndrome or other causes of death in the first year of life (80, 81). Although concerns have been expressed about suspected associations between hepatitis B vaccine and the development of diabetes mellitus and demyelinating diseases, large, controlled epidemiologic studies have not found evidence of a causal association between hepatitis B vaccination and these conditions (82, 83). After reviewing the available data, an expert panel concluded that hepatitis B vaccine is not associated with multiple sclerosis (84).

Duration of immunity

Anti-HBs, the only easily measurable correlate of vaccine-induced protection, declines in the years following vaccination, making confirmation of vaccine-induced immunity in persons vaccinated years ago impractical, if not impossible. However, despite declines in anti-HBs to levels that are less than protective, results from multiple long-term follow-up studies indicate that immunized persons are still protected against HBV infection. No clinical cases of hepatitis B have been observed in 10- to 22-year follow-up studies among immunocompetent vaccinated populations, and only rare chronic infections have been documented (85–87). Most vaccinees in long-term (10 or more years

after vaccination) follow-up studies will develop a rapid rise in antibody (anamnesic response) if given an additional (booster) dose of hepatitis B vaccine, despite pre-booster anti-HBs concentrations below 10 mIU/ml. This response simulates a response that would occur after exposure to HBV and provides indirect evidence of protective immune memory (86–92).

HBV variants

Vaccine failures due to HBV variants with mutations in the small surface protein (*S*) gene (*S* mutants) have occurred in perinatally exposed infants who received hepatitis B vaccine or hepatitis B immune globulin appropriately and who have concentrations of anti-HBs that are usually protective (93). There has been concern that these HBV variants, which are sometimes resistant to the neutralizing effect of anti-HBs, could threaten the effectiveness of hepatitis B immunization programs and that immunization may accelerate the formation of HBV variants (94). Despite these concerns, there are several reasons to believe that hepatitis B vaccination will continue to reduce disease burden. A study using sensitive detection methods demonstrated that the *S* mutants implicated in perinatally exposed infant vaccine failures were usually of maternal origin and not induced by vaccination (95). In addition, mothers of infants who responded to vaccination were as likely to have these surface antigen variants as mothers of infants who did not respond, suggesting that infections among vaccinated children with *S* mutants represented immunoprophylaxis failures and infection with maternal viral variants rather than breakthrough infections among successfully vaccinated infants (96). Furthermore, vaccinated chimpanzees are protected from challenge with the most common surface antigen variant (97). Most commercially available assays that employ polyclonal anti-HBs detect *S* mutants, making ongoing surveillance for *S* mutants possible (98).

HEPATITIS B VACCINE RECOMMENDATIONS AND PROGRAM IMPLEMENTATION

In 1992, the World Health Organization recommended the integration of hepatitis B vaccine into the national immunization programs of all highly endemic countries by 1995 and all other countries by 1997 (99). As of 2004, more than 150 (78 percent) of 192 World Health Organization member states had adopted universal childhood hepatitis B vaccination policies (100). Notably absent are several highly endemic countries, most of them located in sub-Saharan Africa, including the populous and rapidly growing nation of Nigeria. Several highly developed countries with low endemicity, including the United Kingdom, Japan, and the Scandinavian countries, do not routinely vaccinate children but have instead created policies targeting immigrant groups from highly endemic parts of the world, adolescents, and adults with risk factors for HBV infection (101).

Countries that were early to adopt and implement universal infant hepatitis B immunization include Taiwan (1984), Israel (1989), Malaysia (1990), the Gambia (1990),

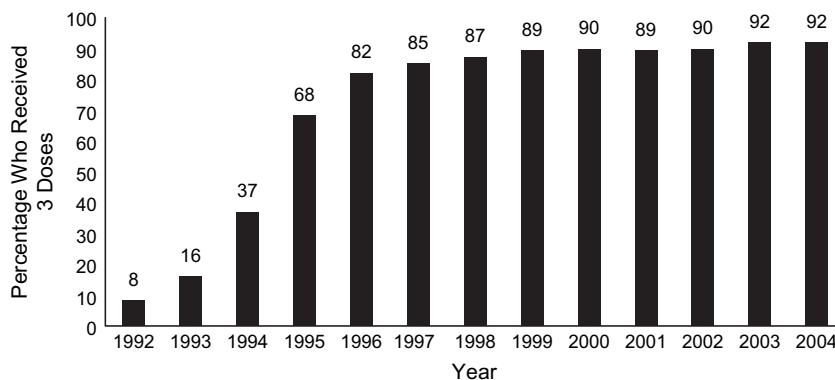


FIGURE 2. Three-dose hepatitis B vaccine coverage among children aged 19–35 months, by year of survey, United States, 1992–2004. (Source: Centers for Disease Control and Prevention, unpublished data.)

Italy, Spain, and the United States (all 1991). In each of these countries, vaccination coverage exceeded 80 percent within a few years of implementation and has been sustained at that level (102). Despite several countries' success in implementing broad vaccination policies, by the end of the 1990s most of the world's population still lived in countries without universal infant vaccination, largely because of the expense of hepatitis B vaccine. In the last 5 years, several resource-poor nations have been able to begin implementing universal infant hepatitis B vaccination programs. Key assistance has been provided by new organizations such as the Global Alliance for Vaccines and Immunization, formed in 2000 (103). Of 70 countries eligible for grants from this initiative based on a per-capita gross national income of less than US\$1,000 per year, seven had hepatitis B immunization programs before 2000; as of December 2004, 50 countries had been approved for funding for hepatitis B vaccine programs. The World Health Organization estimates that global three-dose infant vaccination coverage in 2004 was 48 percent (104).

In the United States, initial recommendations for use of hepatitis B vaccine centered on adults at high risk for HBV infection, such as health care workers, MSM, injection drug users, hemodialysis patients, and persons with multiple sex partners, as well as infants born to HBV-infected women identified through prenatal, risk-factor-based HBsAg screening. However, this strategy did not have a significant impact on hepatitis B incidence. Beginning in the late 1980s, a comprehensive immunization strategy for the United States was developed which incorporated each of the following: 1) prevention of perinatal HBV infection through routine HBsAg screening of all pregnant women and appropriate postexposure immunoprophylaxis of children born to HBsAg-positive women (1988); 2) routine immunization of infants (1992); 3) routine immunization of adolescents not previously immunized (1995); and 4) routine immunization of all previously unvaccinated children under age 19 years (1999). In addition, a consistent focus of the US hepatitis B immunization strategy has been populations with a high prevalence of chronic HBV infection, including Alaska Natives, Pacific Islanders, and

children of immigrant or refugee families from HBV-endemic countries (105–108).

Of the multiple aspects of the US strategy for eliminating HBV infection, infant immunization has had the most successful implementation. Three-dose vaccination coverage for children aged 19–35 months increased from 16 percent in 1991 to 92 percent in 2004 (109–111) (figure 2). There has also been progress towards full implementation of routine immunization of adolescents not previously vaccinated: Vaccination coverage among adolescents aged 13–15 years increased from almost zero in 1993 to 74 percent in 2004 (Centers for Disease Control and Prevention, unpublished data). The introduction of laws requiring immunization prior to school entry has been observed to coincide with a rise in vaccination coverage (112), and school-entry laws are now in effect in most US states (113).

Nearly all pregnant women in the United States receive prenatal HBsAg screening to identify those at risk of perinatal transmission to their infants. A population-based study conducted in 1998 among pregnant women at multiple US sites found that 97 percent received HBsAg testing prior to delivery (114). There is considerable variation, however, in the application of perinatal postexposure prophylaxis. In a large California health maintenance organization, 99.8 percent of perinatally exposed infants received hepatitis B vaccine and hepatitis B immune globulin within 12 hours of birth (115), but in Louisiana only 78–83 percent of exposed infants received appropriate immunoprophylaxis (116).

On the basis of data from the 2004 National Health Interview Survey (117), hepatitis B vaccination coverage among all US adults (with and without indications for vaccination) is estimated to be 35 percent. Results of the survey indicate that coverage is highest among persons aged 18–20 years and declines with age, illustrating the cohort effect of the childhood vaccination program. The highest vaccination coverage rates among adults with an indication for vaccination (table 2) have been observed among persons with potential occupational exposure to HBV. Among health care workers with regular or potential exposure to blood from a representative sample of US hospitals, 75 percent had been vaccinated in 2002–2003, according to medical

TABLE 2. Adults recommended for receipt of hepatitis B vaccine in the United States*

Persons at risk for sexual transmission
Sex partners of persons who are positive for hepatitis B surface antigen (HBsAg)
All sexually active persons who are not in a long-term, mutually monogamous relationship (e.g., persons who had >1 sex partner in the previous 6 months)
Persons evaluated or treated for sexually transmitted diseases, including human immunodeficiency virus infection
Men who have sex with men
Persons at risk for transmission by percutaneous or mucosal exposure to blood
Household contacts of HBsAg-positive persons
Current or recent injection drug users, including needle-sharing contacts of HBsAg-positive persons
Health care and public safety workers with a reasonably anticipated risk of exposure to blood or blood-contaminated body fluids
Persons with end-stage renal disease, including predialysis, hemodialysis, peritoneal dialysis, and home dialysis patients
All persons seeking protection from hepatitis B virus infection
Others
International travelers to areas with high or intermediate levels of endemic hepatitis B virus infection (HBsAg prevalence $\geq 2\%$; figure 1)
Persons with chronic liver disease

* Source: Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention (142).

record data (118). Vaccination coverage among staff members at dialysis centers in the United States was 90 percent in 2002, well above the 56 percent coverage reported among dialysis patients (119).

Data from the National Health Interview Survey showed that vaccination coverage among persons defined as "high-risk" for sexually transmitted and bloodborne diseases was only 30 percent in 2000 and 45 percent in 2004 (117, 120). Findings of other studies are also consistent with low vaccination coverage among adults at risk for disease. Among 1,755 MSM visiting a San Diego, California, sexually transmitted disease clinic in 1998, 16 percent were vaccinated; of 1,106 persons reporting injection drug use at the same clinic, only 6 percent were vaccinated (121). Among 3,432 young MSM in seven US metropolitan areas surveyed between 1994 and 1998, only 9 percent had been immunized against hepatitis B (37). A San Diego study conducted in 1997 to examine adherence to vaccination recommendations among adult household and sexual contacts of persons with chronic hepatitis B found that only 13 percent had received hepatitis B vaccine (122).

IMPACT OF HEPATITIS B VACCINATION

The major objective of hepatitis B immunization is prevention of chronic infection, which prevents sequelae such as cirrhosis and hepatocellular carcinoma. Because

HBV-related cirrhosis and hepatocellular carcinoma usually occur in adults who were infected with HBV as children, decades must pass before the most significant benefits of HBV vaccination are realized. This lengthy interval creates a challenge in monitoring the impact of hepatitis B immunization programs. In the short term, demonstration of a reduction in the HBV-related disease burden relies on indirect measures such as surveillance for acute (symptomatic) hepatitis B, which represents a small but consistent proportion of new infections, and serial cross-sectional seroprevalence studies in populations targeted for vaccination. In the long term, declines in incidence rates and mortality from HBV-related hepatocellular carcinoma can be detected in countries with well-established cancer surveillance systems and registries.

Countries with high endemicity

Taiwan is perhaps the best example of a highly endemic area with a substantial and measurable reduction in disease burden resulting from a long-standing policy of universal childhood hepatitis B vaccination. HBsAg seroprevalence among Taiwanese children decreased from 9.8 percent in 1984, the year when universal infant immunization began, to 0.7 percent in 1999 (123). The average annual incidence of hepatocellular carcinoma among children aged 6–14 years in 1981–1986 (reflecting the prevaccine era) was 0.7 per 100,000, while in 1990–1994 (the postvaccine era) it was 0.36 per 100,000 ($p < 0.01$) (124). Mortality from hepatocellular carcinoma decreased 60–70 percent among children between the period prior to routine vaccination (1974–1983) and the postvaccination era (1984–1999) (125). In addition, fulminant hepatitis mortality among infants decreased significantly (126). In the Gambia, childhood HBsAg seroprevalence has decreased from 10 percent to 0.6 percent since the introduction of routine infant and childhood vaccination in 1986 (127, 128). In highly endemic South Africa, evidence of the impact of routine vaccination has been found through novel means: a statistically significant decrease in the incidence of HBV-associated membranous nephropathy (a complication of acute HBV infection) among children at a single hospital in 2000–2001 as compared with incidence during the prevaccination era (129).

Countries with intermediate endemicity

In Malaysia, which introduced universal infant vaccination in 1990, HBsAg seroprevalence among schoolchildren (ages 7–12 years) decreased from 1.6 percent in 1997 to 0.3 percent in 2003 (130). Population-based surveillance data in Italy have shown a decline in the incidence of acute hepatitis B from 11 per 100,000 population in 1987 to three per 100,000 population in 2000 (131). In addition, the overall prevalence of chronic HBV infection decreased from 13.4 percent in 1978 to 3.7 percent in 1997 (132).

The United States

The most dramatic impact of hepatitis B immunization in the United States can be seen in the Alaska Native

community. In Bristol Bay, Alaska, before routine immunization, 7.6 percent of children had serologic evidence of resolved infection by 9 years of age and 3.2 percent of children were chronically infected. Ten years after the start of routine immunization, no child under 10 years of age was chronically infected and only 1.5 percent had evidence of resolved infection (133). Similar seroprevalence declines have been observed in other US communities with traditionally high rates of disease. Among children of Asian immigrants living in Georgia, seroprevalence of markers of HBV infection decreased from more than 20 percent before 1992 to 1.9 percent in 2001 (134).

National surveillance for acute hepatitis B in the United States is also consistent with an overall decline in new HBV infections. In 2004, the incidence of acute hepatitis B was 2.1 per 100,000 population (6,212 cases), the lowest ever reported in the United States, representing a 75 percent decline since 1990 (135). The most dramatic declines have occurred among children to whom recommendations for routine infant and adolescent catch-up vaccination have applied (136). The incidence of hepatitis B declined 94 percent (from 3.0 per 100,000 to 0.19 per 100,000) in children under 20 years of age from 1990 to 2004 (135).

In recent years, cases of acute hepatitis B have become increasingly concentrated in young adult males. The male:female rate ratio, while traditionally greater than 1.0 and steady at 1.5 through the 1990s, has increased to and remained at 1.7 since 2000. Declines in the incidence of acute hepatitis B among US adults have been slightly less dramatic than the decline among US children: Among persons aged 20–39 years and persons aged ≥ 40 years, acute hepatitis B incidence declined 74 percent and 30 percent, respectively (135).

An increasing proportion of acute hepatitis B cases in the United States occur in persons who report injection drug use and sexual behaviors associated with increased risk of HBV transmission. Between 1990 and 2004, the proportion of persons reporting multiple sex partners (two or more partners in the 6 months prior to diagnosis) increased from 14 percent to 29 percent (135). The proportion of cases identifying themselves as MSM increased from 7 percent to 14 percent over the same time period, with approximately 50 percent of all MSM also reporting multiple sex partners (135). These findings are corroborated by seroprevalence data collected in a cohort of young MSM which suggested that many MSM become infected with HBV during late adolescence and early adulthood. In this cohort, serologic profiles indicating past or present HBV infection were noted among 2 percent of 15-year-olds and 17 percent of 22-year-olds (37).

CHALLENGES TO HEPATITIS B PREVENTION IN THE UNITED STATES

There has been a substantial reduction in the number of new HBV infections each year in the United States as a result of hepatitis B immunization. However, implementation of the comprehensive strategy to eliminate HBV transmission has been uneven, and transmission of HBV

TABLE 3. Settings in which all unvaccinated adults should be assumed to be at risk for hepatitis B virus infection and receive hepatitis B vaccine, per the provisional recommendations of the Advisory Committee on Immunization Practices, October 2005*

Sexually transmitted disease treatment facilities
Human immunodeficiency virus testing facilities
Facilities providing drug abuse treatment and prevention services
Human immunodeficiency virus treatment facilities
Correctional facilities
Health care settings serving men who have sex with men
Chronic hemodialysis facilities and end-stage renal disease programs
Institutions and nonresidential day-care facilities for developmentally disabled persons

* Source: Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention (142).

still occurs among groups for whom vaccine indications have been in place for more than a decade. The primary challenge in the prevention and control of hepatitis B in the United States is full implementation of existing immunization recommendations, particularly those related to the prevention of perinatally acquired infections and infections acquired in adulthood through sexual and needle-sharing exposures.

Perinatal transmission

Despite high rates of prenatal HBsAg screening in the United States, identifying pregnant women who are chronic HBV carriers has proven difficult. On the basis of national seroprevalence data, an estimated 23,000 HBsAg-positive women give birth each year, while only 9,000 HBsAg-positive women are actually identified and reported annually through prenatal screening (137). This disparity suggests that the small proportion of pregnant women without prenatal HBsAg screening have a high prevalence of chronic HBV infection. In addition, HBsAg status often remains unknown, even when unscreened women are hospitalized during labor and delivery (138). Furthermore, the provision of a birth dose of hepatitis B vaccine, which could serve as a safety net for infants whose mothers' HBsAg testing was not done or was incorrectly recorded, is provided to only 33 percent of US newborns, according to data collected in 2000 (139).

Local health departments using enhanced case management systems to improve detection and prevention of perinatal hepatitis B have demonstrated encouraging results in addressing these problems, now identifying a much larger proportion (85 percent) of the expected number of perinatally exposed infants in their areas and far more household and sexual contacts for vaccination per perinatally exposed infant (140, 141). In an effort to improve the proportion of infants receiving their first dose of hepatitis B vaccine at birth, the Centers for Disease Control and Prevention's

Advisory Committee on Immunization Practices in 2005 recommended the institution of specific policies and procedures in delivery hospitals to ensure routine administration of a birth dose to all medically stable infants, unless there is a physician's order to defer administration and a copy of the laboratory report indicating that the mother was HBsAg-negative during this pregnancy in the infant's medical record (70).

Adult vaccination

Because the United States is a low-endemicity country, most HBV transmission in the United States occurs among adolescents and adults, most of whom have known risk factors for hepatitis B. Several studies suggest that most adults with indications for hepatitis B vaccination have not been immunized, despite recommendations that have been in place since 1981 (37, 117, 120–122). There are numerous potential reasons for this low vaccination coverage. "High-risk" adults may have limited or inconsistent access to health care, or their need for vaccination may go unrecognized by health care providers. If the need is identified, there is often limited reimbursement for adult vaccination and minimal public health infrastructure in place for this purpose.

The most promising means of decreasing HBV transmission among US adults is implementation of routine vaccination in institutions or facilities where large numbers of adults at high risk for HBV transmission are routinely seen, such as sexually transmitted disease clinics, correctional facilities, and drug treatment centers (142) (table 3). Multisite US surveillance data have shown that more than half of all persons with cases of acute hepatitis B were seen in at least one of these settings prior to infection (143–145), and several studies suggest that venue-based hepatitis B vaccination would be successful if implemented on a large scale. In multiple surveys, half or more unvaccinated sexually transmitted disease clinic clients were willing to accept a free initial dose of hepatitis B vaccine if offered (146, 147). In three states that have offered hepatitis B vaccine in their correctional facilities, 60–80 percent of inmates have accepted vaccination (148). Venue-based vaccination demonstration programs at a range of facilities, such as county jails, sexually transmitted disease clinics, soup kitchens, and substance abuse treatment centers and syringe exchange programs, have achieved high first-dose coverage rates when hepatitis B vaccine is offered free of charge (121, 149).

CONCLUSIONS

HBV infection is an important cause of morbidity and mortality worldwide, but enormous strides in prevention and control have been made over the last 25 years. As increasing proportions of the worldwide birth cohort are vaccinated each year, the groundwork is laid for major reductions in the burden of hepatocellular carcinoma and cirrhosis in the future.

To eliminate HBV transmission in the United States, not only will the currently high levels of infant vaccination coverage need to be sustained or even increased, but specific

efforts to vaccinate populations at high risk for transmission will have to be made. New HBV infections in the United States are becoming increasingly concentrated among populations such as injection drug users, inmates, and persons at risk for sexually transmitted diseases. These populations often have limited access to settings where routine preventive care and immunization services are provided. Programs such as perinatal case management and venue-based vaccination of high-risk adults will need to be expanded and backed by a consistent commitment of resources.

Also needed to ensure the continued success of hepatitis B immunization is the capacity to measure the impact of vaccination and investigate potential threats to its continued success. Accurate surveillance data are essential to characterize the at-risk population and assess the impact of vaccination—a task that becomes increasingly challenging as morbidity declines. Potential new causes of vaccine failure, such as HBV variants, will need to be assessed, and the need for booster doses to preserve vaccine-induced immunity should be evaluated regularly as vaccinated cohorts age.

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