

Hepatitis B

Viral hepatitis is a term commonly used for several clinically similar yet etiologically and epidemiologically distinct diseases. Hepatitis A (formerly called infectious hepatitis) and hepatitis B (formerly called serum hepatitis) have been recognized as separate entities since the early 1940s and can be diagnosed with specific serologic tests. Delta hepatitis is an infection dependent on the hepatitis B virus (HBV). It may occur as a coinfection with acute HBV infection or as superinfection of an HBV carrier.

Epidemic jaundice was described by Hippocrates in the 5th century BCE. The first recorded cases of “serum hepatitis,” or hepatitis B, are thought to be those that followed the administration of smallpox vaccine containing human lymph to shipyard workers in Germany in 1883. In the early and middle parts of the 20th century, serum hepatitis was repeatedly observed following the use of contaminated needles and syringes. The role of blood as a vehicle for virus transmission was further emphasized in 1943, when Beeson described jaundice that had occurred in seven recipients of blood transfusions. Australia antigen, later called hepatitis B surface antigen (HBsAg), was first described in 1965, and the Dane particle (complete hepatitis B virion) was identified in 1970. Identification of serologic markers for HBV infection followed, which helped clarify the natural history of the disease. Ultimately, HBsAg was prepared in quantity and now comprises the immunogen in highly effective vaccines for prevention of HBV infection.

Hepatitis B Virus

HBV is a small, double-shelled virus in the family Hepadnaviridae. Other Hepadnaviridae include duck hepatitis virus, ground squirrel hepatitis virus, and woodchuck hepatitis virus. The virus has a small circular DNA genome that is partially double-stranded. HBV contains numerous antigenic components, including HBsAg, hepatitis B core antigen (HBcAg), and hepatitis B e antigen (HBeAg). Humans are the only known host for HBV, although some nonhuman primates have been infected in laboratory conditions. HBV is relatively resilient and, in some instances, has been shown to remain infectious on environmental surfaces for more than 7 days at room temperature.

An estimated 2 billion persons worldwide have been infected with HBV, and more than 350 million persons have chronic, lifelong infections. HBV infection is an established cause of acute and chronic hepatitis and cirrhosis. It is the cause of up to 80% of hepatocellular carcinomas. The World Health Organization estimated that more than 600,000 persons died worldwide in 2002 of hepatitis B-associated acute and chronic liver disease.

Hepatitis B

- Epidemic jaundice described by Hippocrates in 5th century BCE
- Jaundice reported among recipients of human serum and yellow fever vaccines in 1930s and 1940s
- Australia antigen described in 1965
- Serologic tests developed in 1970s

Hepatitis B Virus

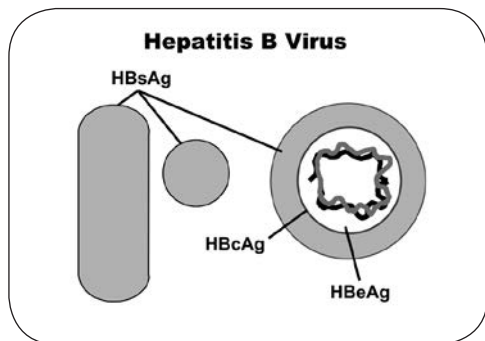
- Hepadnaviridae family (DNA)
- Numerous antigenic components
- Humans are only known host
- May retain infectivity for more than 7 days at room temperature

Hepatitis B Virus Infection

- More than 350 million chronically infected worldwide
- Established cause of chronic hepatitis and cirrhosis
- Human carcinogen—cause of up to 80% of hepatocellular carcinomas

Hepatitis B

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Hepatitis B Clinical Features

- Incubation period 45-160 days (average 120 days)
- Nonspecific prodrome of malaise, fever, headache, myalgia
- Illness not specific for hepatitis B
- At least 50% of infections asymptomatic

Several well-defined antigen–antibody systems are associated with HBV infection. HBsAg, formerly called Australia antigen or hepatitis-associated antigen, is an antigenic determinant found on the surface of the virus. It also makes up subviral 22-nm spherical and tubular particles. HBsAg can be identified in serum 30 to 60 days after exposure to HBV and persists for variable periods. HBsAg is not infectious. Only the complete virus (Dane particle) is infectious. However, when HBsAg is present in the blood, complete virus is also present, and the person may transmit the virus. During replication, HBV produces HBsAg in excess of that needed for production of Dane particles.

HBcAg is the nucleocapsid protein core of HBV. HBcAg is not detectable in serum by conventional techniques, but it can be detected in liver tissue of persons with acute or chronic HBV infection. HBeAg, a soluble protein, is also contained in the core of HBV. HBeAg is detected in the serum of persons with high virus titers and indicates high infectivity. Antibody to HBsAg (anti-HBs) develops during convalescence after acute HBV infection or following hepatitis B vaccination. The presence of anti-HBs indicates immunity to HBV. (Anti-HBs is sometimes referred to as HBsAb, but use of this term is discouraged because of potential confusion with HBsAg.) Antibody to HBcAg (anti-HBc) indicates infection with HBV at an undefined time in the past. IgM class antibody to HBcAg (IgM anti-HBc) indicates recent infection with HBV. Antibody to HBeAg (anti-HBe) becomes detectable when HBeAg is lost and is associated with low infectivity of serum.

Clinical Features

The clinical course of acute hepatitis B is indistinguishable from that of other types of acute viral hepatitis. The incubation period ranges from 45 to 160 days (average, 120 days). Clinical signs and symptoms occur more often in adults than in infants or children, who usually have an asymptomatic acute course. However, approximately 50% of adults who have acute infections are asymptomatic.

The preicteric, or prodromal phase from initial symptoms to onset of jaundice usually lasts from 3 to 10 days. It is nonspecific and is characterized by insidious onset of malaise, anorexia, nausea, vomiting, right upper quadrant abdominal pain, fever, headache, myalgia, skin rashes, arthralgia and arthritis, and dark urine, beginning 1 to 2 days before the onset of jaundice. The icteric phase is variable but usually lasts from 1 to 3 weeks and is characterized by jaundice, light or gray stools, hepatic tenderness and hepatomegaly (splenomegaly is less common). During convalescence, malaise and fatigue may persist for weeks or months, while jaundice, anorexia, and other symptoms disappear.

Most acute HBV infections in adults result in complete recovery with elimination of HBsAg from the blood and the production of anti-HBs, creating immunity to future infection.

Complications

While most acute HBV infections in adults result in complete recovery, fulminant hepatitis occurs in about 1% to 2% of acutely infected persons. About 200 to 300 Americans die of fulminant disease each year (case-fatality rate 63% to 93%). Although the consequences of acute HBV infection can be severe, most of the serious complications associated with HBV infection are due to chronic infection.

Chronic HBV Infection

Approximately 5% of all acute HBV infections progress to chronic infection, with the risk of chronic HBV infection decreasing with age. As many as 90% of infants who acquire HBV infection from their mothers at birth become chronically infected. Of children who become infected with HBV between 1 year and 5 years of age, 30% to 50% become chronically infected. By adulthood, the risk of acquiring chronic HBV infection is approximately 5%.

Persons with chronic infection are often asymptomatic and may not be aware that they are infected; however, they are capable of infecting others and have been referred to as carriers. Chronic infection is responsible for most HBV-related morbidity and mortality, including chronic hepatitis, cirrhosis, liver failure, and hepatocellular carcinoma. Approximately 25% of persons with chronic HBV infection die prematurely from cirrhosis or liver cancer. Chronic active hepatitis develops in more than 25% of carriers and often results in cirrhosis. An estimated 3,000 to 4,000 persons die of hepatitis B-related cirrhosis each year in the United States. Persons with chronic HBV infection are at 12 to 300 times higher risk of hepatocellular carcinoma than noncarriers. An estimated 1,000 to 1,500 persons die each year in the United States of hepatitis B-related liver cancer.

Laboratory Diagnosis

Diagnosis is based on clinical, laboratory, and epidemiologic findings. HBV infection cannot be differentiated on the basis of clinical symptoms alone, and definitive diagnosis depends on the results of serologic testing. Serologic markers of HBV infection vary depending on whether the infection is acute or chronic.

HBsAg is the most commonly used test for diagnosing acute HBV infections or detecting carriers. HBsAg can be detected as early as 1 or 2 weeks and as late as 11 or 12

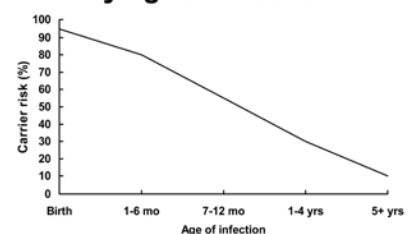
Hepatitis B Complications

- Fulminant hepatitis
- Hospitalization
- Cirrhosis
- Hepatocellular carcinoma
- Death

Chronic Hepatitis B Virus Infection

- Chronic viremia
- Responsible for most mortality
- Overall risk 5%
- Higher risk with early infection

Risk of Chronic HBV Carriage by Age of Infection



weeks after exposure to HBV when sensitive assays are used. The presence of HBsAg indicates that a person is infectious, regardless of whether the infection is acute or chronic.

Anti-HBc (core antibody) develops in all HBV infections, appears shortly after HBsAg in acute disease, and indicates HBV infection at some undefined time in the past. Anti-HBc only occurs after HBV infection and does not develop in persons whose immunity to HBV is from vaccine. Anti-HBc generally persists for life and is not a serologic marker for acute infection.

IgM anti-HBc appears in persons with acute disease about the time of illness onset and indicates recent infection with HBV. IgM anti-HBc is generally detectable 4 to 6 months after onset of illness and is the best serologic marker of acute HBV infection. A negative test for IgM-anti-HBc together with a positive test for HBsAg in a single blood sample identifies a chronic HBV infection.

Interpretation of Hepatitis B Serologic Tests

| Tests | Results | Interpretation |
|------------------------|--|--|
| HBsAg | Negative | Susceptible |
| anti-HBc | Negative | |
| anti-HBs | Negative | |
| HBsAg | Negative | Immune due to vaccination |
| anti-HBc | Negative | |
| anti-HBs | Positive with $\geq 10\text{mIU/mL}^*$ | |
| HBsAg | Negative | Immune due to natural infection |
| anti-HBc | Positive | |
| anti-HBs | Positive | |
| HBsAg | Positive | Acutely infected |
| anti-HBc | Positive | |
| IgM anti-HBc | Positive | |
| anti-HBs | Negative | |
| HBsAg | Positive | Chronically infected |
| anti-HBc | Positive | |
| IgM anti-HBc | Negative | |
| anti-HBs | Negative | |
| HBsAg | Negative | Four interpretations possible [†] |
| anti-HBc | Positive | |
| anti-HBs | Negative | |

*Postvaccination testing, when it is recommended, should be performed 1-2 months following dose #3.

- †
1. May be recovering from acute HBV infection.
 2. May be distantly immune and the test is not sensitive enough to detect a very low level of anti-HBs in serum.
 3. May be susceptible with a false positive anti-HBc.
 4. May be chronically infected and have an undetectable level of HBsAg present in the serum.

HBeAg is a useful marker associated strongly with the number of infective HBV particles in the serum and a higher risk of infectivity.

Anti-HBs (surface antibody) is a protective, neutralizing antibody. The presence of anti-HBs following acute HBV infection generally indicates recovery and immunity against reinfection. Anti-HBs can also be acquired as an immune response to hepatitis B vaccine or passively transferred by administration of hepatitis B immune globulin (HBIG). When using radioimmunoassay (RIA), a minimum of 10 sample ratio units should be used to designate immunity. With enzyme immunoassay (EIA), the manufacturer's recommended positive should be considered an appropriate measure of immunity. The level of anti-HBs may also be expressed in milli-international units/mL (mIU/mL). Ten mIU/mL is considered to indicate a protective level of immunity.

Medical Management

There is no specific therapy for acute HBV infection. Treatment is supportive. Interferon is the most effective treatment for chronic HBV infection and is successful in 25% to 50% of cases.

Persons with acute or chronic HBV infections should prevent their blood and other potentially infective body fluids from contacting other persons. They should not donate blood or share toothbrushes or razors with household members.

In the hospital setting, patients with HBV infection should be managed with standard precautions.

Epidemiology

Reservoir

Although other primates have been infected in laboratory conditions, HBV infection affects only humans. No animal or insect hosts or vectors are known to exist.

Transmission

The virus is transmitted by parenteral or mucosal exposure to HBsAg-positive body fluids from persons who have acute or chronic HBV infection. The highest concentrations of virus are in blood and serous fluids; lower titers are found in other fluids, such as saliva and semen. Saliva can be a vehicle of transmission through bites; however, other types of exposure to saliva, including kissing, are unlikely modes of transmission. There appears to be no transmission of HBV via tears, sweat, urine, stool, or droplet nuclei.

Hepatitis B Epidemiology

- | | |
|-------------------|---|
| • Reservoir | Human |
| • Transmission | Bloodborne Subclinical cases transmit |
| • Communicability | 1-2 months before and after onset of symptoms Chronic carriers |

In the United States, the most important route of transmission is by sexual contact, either heterosexual or homosexual, with an infected person. Fecal-oral transmission does not appear to occur. However, transmission occurs among men who have sex with men, possibly via contamination from asymptomatic rectal mucosal lesions.

Direct percutaneous inoculation of HBV by needles during injection-drug use is an important mode of transmission. Transmission of HBV may also occur by other percutaneous exposure, including tattooing, ear piercing, and acupuncture, as well as needlesticks or other injuries from sharp instruments sustained by medical personnel. These exposures account for only a small proportion of reported cases in the United States. Breaks in the skin without overt needle puncture, such as fresh cutaneous scratches, abrasions, burns, or other lesions, may also serve as routes for entry.

Contamination of mucosal surfaces with infective serum or plasma may occur during mouth pipetting, eye splashes, or other direct contact with mucous membranes of the eyes or mouth, such as hand-to-mouth or hand-to-eye contact when hands are contaminated with infective blood or serum. Transfer of infective material to skin lesions or mucous membranes via inanimate environmental surfaces may occur by touching surfaces of various types of hospital equipment. Contamination of mucosal surfaces with infective secretions other than serum or plasma could occur with contact involving semen.

Perinatal transmission from mother to infant at birth is very efficient. If the mother is positive for both HBsAg and HBeAg, 70%–90% of infants will become infected in the absence of postexposure prophylaxis. The risk of perinatal transmission is about 10% if the mother is positive only for HBsAg. As many as 90% of these infected infants will become chronically infected with HBV.

The frequency of infection and patterns of transmission vary in different parts of the world. Approximately 45% of the global population live in areas with a high prevalence of chronic HBV infection (8% or more of the population is HBsAg positive), 43% in areas with a moderate prevalence (2% to 7% of the population is HBsAg positive), and 12% in areas with a low prevalence (less than 2% of the population is HBsAg positive).

In China, Southeast Asia, most of Africa, most Pacific Islands, parts of the Middle East, and the Amazon Basin, 8% to 15% of the population carry the virus. The lifetime risk of HBV infection is greater than 60%, and most infections are acquired at birth or during early childhood, when the risk of developing chronic infections is greatest. In these areas, because most infections are asymptomatic, very little acute

Hepatitis B Perinatal Transmission*

- If mother positive for HBsAg and HBeAg
 - 70%-90% of infants infected
 - 90% of infected infants become chronically infected
- If positive for HBsAg only
 - 10% of infants infected
 - 90% of infected infants become chronically infected

*in the absence of postexposure prophylaxis

Global Patterns of Chronic HBV Infection

- High ($\geq 8\%$): 45% of global population
 - lifetime risk of infection $>60\%$
 - early childhood infections common
- Intermediate (2%-7%): 43% of global population
 - lifetime risk of infection 20%-60%
 - infections occur in all age groups
- Low ($<2\%$): 12% of global population
 - lifetime risk of infection $<20\%$
 - most infections occur in adult risk groups

disease related to HBV occurs, but rates of chronic liver disease and liver cancer among adults are very high. In the United States, Western Europe, and Australia, HBV infection is a disease of low endemicity. Infection occurs primarily during adulthood, and only 0.1% to 0.5% of the population are chronic carriers. Lifetime risk of HBV infection is less than 20% in low prevalence areas.

Communicability

Persons with either acute or chronic HBV infection should be considered infectious any time that HBsAg is present in the blood. When symptoms are present in persons with acute HBV infection, HBsAg can be found in blood and body fluids for 1–2 months before and after the onset of symptoms.

Secular Trends in the United States

Hepatitis has been reportable in the United States for many years. Hepatitis B became reportable as a distinct entity during the 1970s, after serologic tests to differentiate different types of hepatitis became widely available.

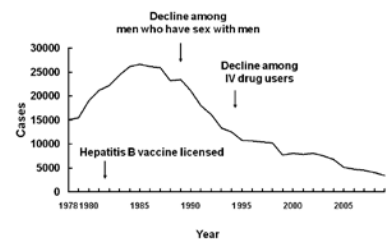
The incidence of reported hepatitis B peaked in the mid-1980s, with about 26,000 cases reported each year. Reported cases have declined since that time, and fell below 10,000 cases for the first time in 1996. The decline in cases during the 1980s and early 1990s is generally attributed to reduction of transmission among men who have sex with men and injection-drug users as a result of HIV prevention efforts.

During 1990–2004, incidence of acute hepatitis B in the United States declined 75%. The greatest decline (94%) occurred among children and adolescents, coincident with an increase in hepatitis B vaccine coverage. A total of 3,405 cases of hepatitis B were reported in 2009.

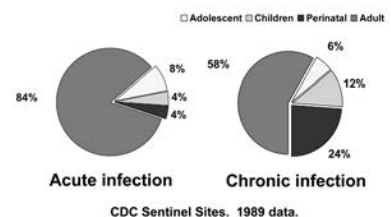
Reported cases of HBV infection represent only a fraction of cases that actually occur. In 2001, a total of 7,844 cases of acute hepatitis B were reported to CDC. Based on these reports, CDC estimates that 22,000 acute cases of hepatitis B resulted from an estimated 78,000 new infections. An estimated 700,000 to 1.4 million persons in the United States are chronically infected with HBV, and an additional 5,000–8,000 persons become chronically infected each year.

Before routine childhood hepatitis B vaccination was recommended, more than 80% of acute HBV infections occurred among adults. Adolescents accounted for approximately 8% of infections, and children and infants infected through perinatal transmission accounted for approximately 4% each. Perinatal transmission accounted for a disproportionate 24% of chronic infections.

Hepatitis B—United States, 1978-2009

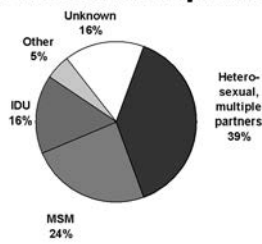


Age of Infection of Acute and Chronic Hepatitis B Virus Infection



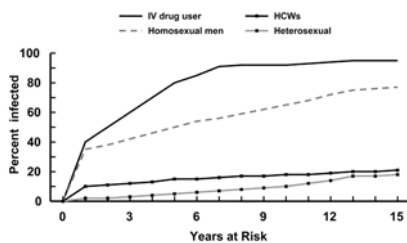
Hepatitis B

Risk Factors for Hepatitis B



MMWR 2006;55(RR-16):6-7

Hepatitis B Virus Infection by Duration of High-Risk Behavior



In the United States in 2005, the highest incidence of acute hepatitis B was among adults aged 25–45 years. Approximately 79% of persons with newly acquired hepatitis B infection are known to engage in high-risk sexual activity or injection-drug use. Other known exposures (i.e., occupational, household, travel, and healthcare-related) together account for 5% of new infections. Approximately 16% of persons deny a specific risk factor for infection.

Although HBV infection is uncommon among adults in the general population (the lifetime risk of infection is less than 20%), it is highly prevalent in certain groups. Risk for infection varies with occupation, lifestyle, or environment (see table). Generally, the highest risk for HBV infection is associated with lifestyles, occupations, or environments in which contact with blood from infected persons is frequent. In addition, the prevalence of HBV markers for acute or chronic infection increases with increasing number of years of high-risk behavior. For instance, an estimated 40% of injection-drug users become infected with HBV after 1 year of drug use, while more than 80% are infected after 10 years.

Prevalence of Hepatitis B in Various Population Groups

| Population Group | | Prevalence of Serologic Markers of HBV Infection | |
|-------------------|--|--|-----------------|
| | | HBsAg (%) | All Markers (%) |
| High-Risk | Immigrants/refugees from areas of high HBV endemicity. | 13 | 70-85 |
| | Clients in mental health institutions. | 10-20 | 35-80 |
| | Users of illicit parenteral drugs. | 7 | 60-80 |
| | Homosexually active men. | 6 | 35-80 |
| | Patients of hemodialysis units. | 3-10 | 20-80 |
| | Household contacts of HBV carriers. | 3-6 | 30-60 |
| Intermediate-Risk | Prisoners (male). | 1-8 | 10-80 |
| | Healthcare providers – frequent blood contact. | 1-2 | 15-30 |
| | Staff of mental health institutions. | 1 | 10-25 |
| | Heterosexuals with multiple partners. | 0.5 | 5-20 |
| Low-Risk | Healthcare providers – no or infrequent blood contact. | 0.3 | 3-10 |
| | Healthy adults (first-time volunteer blood donors). | 0.3 | 3-5 |

Hepatitis B Prevention Strategies

Hepatitis B vaccines have been available in the United States since 1981. However, the impact of vaccine on HBV disease has been less than optimal.

The apparent lack of impact from the vaccine can be attributed to several factors. From 1981 until 1991, vaccination was targeted to persons in groups at high risk of acquiring HBV infection. A large proportion of persons with HBV infection (25% to 30%) deny having any risk factors for the disease. These persons would not be identified by a targeted risk factor screening approach.

The three major risk groups (heterosexuals with contact with infected persons or multiple partners, injection-drug users, and men who have sex with men) are not reached effectively by targeted programs. Deterrents to immunization of these groups include lack of awareness of the risk of disease and its consequences, lack of effective public or private sector programs, and vaccine cost. Difficulty in gaining access to these populations is also a problem. Further, success in providing vaccine to persons in high-risk groups has been limited because of rapid acquisition of infection after beginning high-risk behaviors, low initial vaccine acceptance, and low rates of completion of vaccinations.

A comprehensive strategy to eliminate hepatitis B virus transmission was recommended in 1991; it includes prenatal testing of pregnant women for HBsAg to identify newborns who require immunoprophylaxis for prevention of perinatal infection and to identify household contacts who should be vaccinated, routine vaccination of infants, vaccination of adolescents, and vaccination of adults at high risk for infection. Recommendations to further enhance vaccination of adults at increased risk of HBV infection were published in 2006.

Hepatitis B Vaccine

Characteristics

A plasma-derived vaccine was licensed in the United States in 1981. It was produced from 22-nm HBsAg particles purified from the plasma of chronically infected humans. The vaccine was safe and effective but was not well accepted, possibly because of unsubstantiated fears of transmission of live HBV and other bloodborne pathogens (e.g., human immunodeficiency virus). This vaccine was removed from the U.S. market in 1992.

Recombinant hepatitis B vaccine was licensed in the United States in July 1986. A second, similar vaccine was licensed in August 1989.

Strategy to Eliminate Hepatitis B Virus Transmission—United States

- Prevent perinatal HBV transmission
- Routine vaccination of all infants
- Vaccination of children in high-risk groups
- Vaccination of adolescents
- Vaccination of adults in high-risk groups

Hepatitis B Vaccine

- | | |
|------|---|
| 1965 | Discovery of Australian antigen |
| 1973 | Successful HBV infection of chimpanzees |
| 1981 | Licensure of plasma-derived vaccine |
| 1986 | Licensure of recombinant vaccine |
| 1991 | Universal infant vaccination |
| 1996 | Universal adolescent vaccination |

Hepatitis B

Hepatitis B Vaccine

- **Composition** Recombinant HBsAg
- **Efficacy** 95% (Range, 80%-100%)
- **Duration of Immunity** at least 20 years
- **Schedule** 3 Doses
- **Booster doses not routinely recommended**

Hepatitis B Vaccine Formulations

- **Recombivax HB (Merck)**
 - 5 mcg/0.5 mL (pediatric)
 - 10 mcg/1 mL (adult)
 - 40 mcg/1 mL (dialysis)
- **Engerix-B (GSK)**
 - 10 mcg/0.5 mL (pediatric)
 - 20 mcg/1 mL (adult)

Recombinant vaccine is produced by inserting a plasmid containing the gene for HBsAg into common baker's yeast (*Saccharomyces cerevisiae*). Yeast cells then produce HBsAg, which is harvested and purified. The recombinant vaccine contains more than 95% HBsAg protein (5 to 40 mcg/mL); yeast-derived proteins may constitute up to 5% of the final product, but no yeast DNA is detectable in the vaccine. HBV infection cannot result from use of the recombinant vaccine, since no potentially infectious viral DNA or complete viral particles are produced in the recombinant system. Vaccine HBsAg is adsorbed to aluminum hydroxide.

Hepatitis B vaccine is produced by two manufacturers in the United States, Merck (Recombivax HB) and GlaxoSmithKline Pharmaceuticals (Engerix-B). Both vaccines are available in both pediatric and adult formulations. Although the antigen content of the vaccines differs, vaccines made by different manufacturers are interchangeable, except for the two-dose schedule for adolescents aged 11 through 15 years. Only Merck vaccine is approved for this schedule. Providers must always follow the manufacturer's dosage recommendations.

Both the pediatric and adult formulations of Recombivax HB are approved for use in any age group. For example, the adult formulation of Recombivax HB may be used in children (0.5 mL) and adolescents (0.5 mL). However, pediatric Engerix-B is approved for use only in children and adolescents younger than 20 years of age. The adult formulation of Engerix-B is not approved for use in infants and children but may be used in both adolescents (11 through 19 years of age) and adults.

Engerix-B contains aluminum hydroxide as an adjuvant. It does not contain thimerosal as a preservative but contains a trace of thimerosal as residual from the manufacturing process. The vaccine is supplied in single-dose vials and syringes. Recombivax HB contains aluminum hydroxyphosphate sulfate as an adjuvant. None of the formulations of Recombivax HB contain thimerosal or any other preservative. The vaccine is supplied in single-dose vials.

Immunogenicity and Vaccine Efficacy

After three intramuscular doses of hepatitis B vaccine, more than 90% of healthy adults and more than 95% of infants, children, and adolescents (from birth to 19 years of age) develop adequate antibody responses. However, there is an age-specific decline in immunogenicity. After age 40 years, approximately 90% of recipients respond to a three-dose series, and by 60 years, only 75% of vaccinees develop

protective antibody titers. The proportion of recipients who respond to each dose varies by age (see table).

Protection* by Age Group and Dose

| Dose | Infants [†] | Teens and Adults [§] |
|------|----------------------|-------------------------------|
| 1 | 16% - 40% | 20% - 30% |
| 2 | 80% - 95% | 75% - 80% |
| 3 | 98% - 100% | 90% - 95% |

*Anti-HBs antibody titer of 10 mIU/mL or higher

[†] Preterm infants less than 2kg have been shown to respond to vaccination less often

[§] Factors that may lower vaccine response rates are age 40 years or older, male gender, smoking, obesity, and immune deficiency

The vaccine is 80% to 100% effective in preventing infection or clinical hepatitis in those who receive the complete course of vaccine. Larger vaccine doses (2 to 4 times the normal adult dose) or an increased number of doses are required to induce protective antibody in a high proportion of hemodialysis patients and may also be necessary in other immunocompromised persons.

The recommended dosage of vaccine differs depending on the age of the recipient and type of vaccine (see table). Hemodialysis patients should receive a 40-mcg dose in a series of three or four doses. Recombivax HB has a special dialysis patient formulation that contains 40 mcg/mL.

Recommended doses of currently licensed formulations of hepatitis B vaccine, by age group and vaccine type

| Age Group | Single-Antigen Vaccine | | | | Combination Vaccine | | | | | |
|---|------------------------|-------------|-----------------|-------------|---------------------|-------------|------------|-------------|------------|-------------|
| | Recombivax HB | | Engerix-B | | Comvax | | Pediatrix | | Twinrix | |
| | Dose (µg)* | Volume (mL) | Dose (µg)* | Volume (mL) | Dose (µg)* | Volume (mL) | Dose (µg)* | Volume (mL) | Dose (µg)* | Volume (mL) |
| Infants (<1 yr) | 5 | 0.5 | 10 | 0.5 | 5 | 0.5 | 10 | 0.5 | N/A** | N/A |
| Children (1-10 yrs) | 5 | 0.5 | 10 | 0.5 | 5 | 0.5 | 10 | 0.5 | N/A | N/A |
| Adolescents | | | | | | | | | | |
| 11-15 yrs | 10 [†] | 1.0 | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| 11-19 yrs | 5 | 0.5 | 10 | 0.5 | N/A | N/A | N/A | N/A | N/A | N/A |
| Adults (≥20 yrs) | 10 | 1.0 | 20 | 1.0 | N/A | N/A | N/A | N/A | 20 | 1.0 |
| Hemodialysis patients and other immunocompromised persons | | | | | | | | | | |
| <20 yrs [§] | 5 | 0.5 | 10 | 0.5 | N/A | N/A | N/A | N/A | N/A | N/A |
| ≥20 yrs | 40 [‡] | 1.0 | 40 [‡] | 2.0 | N/A | N/A | N/A | N/A | N/A | N/A |

* Recombinant hepatitis B surface antigen protein dose.

[†] Adult formulation administered on a 2-dose schedule.

[§] Higher doses might be more immunogenic, but no specific recommendations have been made.

[¶] Dialysis formulation administered on a 3-dose schedule at 0, 1, and 6 months.

[‡] Two 1.0 mL doses administered at one site, on a 4-dose schedule at 0, 1, 2, and 6 months.

** Not applicable.

Hepatitis B Vaccine Long-Term Efficacy

- Immunologic memory established following vaccination
- Exposure to HBV results in anamnestic anti-HBs response
- Chronic infection rarely documented among vaccine responders

Hepatitis B Vaccine

Routine booster doses are **NOT** routinely recommended for any group

Hepatitis B Vaccine Routine Infant Schedule

| Dose | Usual Age | Minimum Interval |
|-----------|--------------|------------------|
| Primary 1 | Birth | - - - |
| Primary 2 | 1- 2 months | 4 weeks |
| Primary 3 | 6-18 months* | 8 weeks** |

* infants who mothers are HBsAg+ or whose HBsAg status is unknown should receive the third dose at 6 months of age
 ** at least 16 weeks after the first dose

The deltoid muscle is the recommended site for hepatitis B vaccination in adults and children, while the antero-lateral thigh is recommended for infants and neonates. Immunogenicity of vaccine in adults is lower when injections are given in the gluteus. Hepatitis B vaccine should be administered to newborns using a needle of at least 5/8 inch length and to older children and adults of at least 1 inch length. Hepatitis B vaccine administered by any route or site other than intramuscularly in the anterolateral thigh or deltoid muscle should not be counted as valid and should be repeated unless serologic testing indicates that an adequate response has been achieved.

Available data show that vaccine-induced antibody levels decline with time. However, immune memory remains intact for more than 20 years following immunization, and both adults and children with declining antibody levels are still protected against significant HBV infection (i.e., clinical disease, HBsAg antigenemia, or significant elevation of liver enzymes). Exposure to HBV results in anamnestic anti-HBs response that prevents clinically significant HBV infection. Chronic HBV infection has only rarely been documented among vaccine responders.

For adults and children with normal immune status, booster doses of vaccine are not recommended. Routine serologic testing to assess immune status of vaccinees is not recommended. The need for booster doses after longer intervals will continue to be assessed as additional information becomes available.

For hemodialysis patients, the need for booster doses should be assessed by annual testing of vaccinees for antibody levels, and booster doses should be provided when antibody levels decline below 10 mIU/mL.

Vaccination Schedule and Use

Infants and Children

Hepatitis B vaccination is recommended for all infants soon after birth and before hospital discharge. Infants and children younger than 11 years of age should receive 0.5 mL (5 mcg) of pediatric or adult formulation Recombivax HB (Merck) or 0.5 mL (10 mcg) of pediatric Engerix-B (GlaxoSmithKline). Primary vaccination consists of three intramuscular doses of vaccine. The usual schedule is 0, 1 to 2, and 6 to 18 months. Infants whose mothers are HBsAg positive or whose HBsAg status is unknown should receive the last (third or fourth) dose by 6 months of age (12 to 15 months if Comvax is used).

Because the highest titers of anti-HBs are achieved when the last two doses of vaccine are spaced at least 4 months apart, schedules that achieve this spacing are preferable.

However, schedules with 2-month intervals between doses, which conform to schedules for other childhood vaccines, have been shown to produce good antibody responses and may be appropriate in populations in which it is difficult to ensure that infants will be brought back for all their vaccinations. However, the third dose must be administered at least 8 weeks after the second dose, and should follow the first dose by at least 16 weeks. For infants, the third dose should not be given earlier than 24 weeks of age. It is not necessary to add doses or restart the series if the interval between doses is longer than recommended.

Preterm infants born to HBsAg-positive women and women with unknown HBsAg status must receive immunoprophylaxis with hepatitis B vaccine and hepatitis B immune globulin (HBIG) within 12 hours of birth. See the section on Postexposure Prophylaxis for additional information. Preterm infants with low birthweight (i.e., less than 2,000 grams) have a decreased response to hepatitis B vaccine administered before 1 month of age. However, by chronologic age 1 month, preterm infants, regardless of initial birthweight or gestational age, are as likely to respond as adequately as full-term infants. Preterm infants of low birthweight whose mothers are HBsAg negative can receive the first dose of the hepatitis B vaccine series at chronologic age 1 month. Preterm infants discharged from the hospital before chronologic age 1 month can also be administered hepatitis B vaccine at discharge if they are medically stable and have gained weight consistently. The full recommended dose should be used. Divided or reduced doses are not recommended.

Comvax

Hepatitis B vaccine is available in combination with *Haemophilus influenzae* type b (Hib) vaccine as Comvax (Merck). Each dose of Comvax contains 7.5 mcg of PRP-OMP Hib vaccine (PedvaxHIB), and 5 mcg of hepatitis B surface antigen. The dose of hepatitis B surface antigen is the same as that contained in Merck's pediatric formulation. The immunogenicity of the combination vaccine is equivalent to that of the individual antigens administered at separate sites.

Comvax is licensed for use at 2, 4, and 12 through 15 months of age. It may be used whenever either antigen is indicated and the other antigen is not contraindicated. However, the vaccine must not be administered to infants younger than 6 weeks of age because of potential suppression of the immune response to the Hib component (see Chapter 7, *Haemophilus influenzae* type b, for more details). Comvax must not be used for doses at birth or 1 month of age for a child on a 0, 1, 6 month hepatitis B vaccine schedule. Although it is not labeled for this indication by FDA, ACIP recommends that Comvax may be used in infants whose mothers are HBsAg positive or whose HBsAg status is unknown.

Third Dose of Hepatitis B Vaccine

- Minimum of 8 weeks after second dose, and
- At least 16 weeks after first dose, and
- For infants, at least 24 weeks of age

Preterm Infants

- Birth dose and HBIG if mother HBsAg positive
- Preterm infants <2,000 grams have a decreased response to vaccine administered before 1 month of age
- Delay first dose until chronologic age 1 month if mother HBsAg negative

COMVAX

- Hepatitis B-Hib combination
- Use when either antigen is indicated
- Cannot use before 6 weeks of age
- May be used in infants whose mothers are HBsAg positive or status is unknown

Pediarix

- DTaP – Hep B – IPV combination
- Approved for 3 doses at 2, 4 and 6 months
- Not approved for booster doses
- Licensed for children 6 weeks to 7 years of age

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Pediarix

- May be used interchangeably with other pertussis-containing vaccines if necessary
- Can be given at 2, 4, and 6 months to infants who received a birth dose of hepatitis B vaccine (total of 4 doses)
- May be used in infants whose mothers are HBsAg positive or status unknown

Hepatitis B Vaccine Adolescent Vaccination

- Routine vaccination recommended through age 18 years
- Integrate into routine adolescent immunization visit
- Flexible schedules

Pediarix

In 2002, the Food and Drug Administration approved Pediarix (GlaxoSmithKline), the first pentavalent (5-component) combination vaccine licensed in the United States. Pediarix contains DTaP (Infanrix), hepatitis B (Engerix-B), and inactivated polio vaccines. In prelicensure studies, the proportion of children who developed a protective level of antibody, and the titer of antibody, were at least as high among children receiving the vaccine antigens given together as Pediarix as among children who received separate vaccines.

The minimum age for the first dose of Pediarix is 6 weeks, so it cannot be used for the birth dose of the hepatitis B series. Pediarix is approved for the first three doses of the DTaP and IPV series, which are usually given at about 2, 4, and 6 months of age; it is not approved for fourth or fifth (booster) doses of the DTaP or IPV series. However, Pediarix is approved for use through 6 years of age. A child who is behind schedule can still receive Pediarix as long as it is given for doses 1, 2, or 3 of the series, and the child is younger than 7 years of age.

A dose of Pediarix inadvertently administered as the fourth or fifth dose of the DTaP or IPV series does not need to be repeated.

Pediarix may be used interchangeably with other pertussis-containing vaccines if necessary (although ACIP prefers the use of the same brand of DTaP for all doses of the series, if possible). It can be given at 2, 4, and 6 months to infants who received a birth dose of hepatitis B vaccine (total of 4 doses of hepatitis B vaccine). Although not labeled for this indication by FDA, Pediarix may be used in infants whose mothers are HBsAg positive or whose HBsAg status is unknown.

Adolescents

Routine hepatitis B vaccination is recommended for all children and adolescents through age 18 years. All children not previously vaccinated with hepatitis B vaccine should be vaccinated at 11 or 12 years of age with the age-appropriate dose of vaccine. When adolescent vaccination programs are being considered, local data should be considered to determine the ideal age group to vaccinate (i.e., preadolescents, young adolescents) to achieve the highest vaccination rates. The vaccination schedule should be flexible and should take into account the feasibility of delivering three doses of vaccine to this age group. Unvaccinated older adolescents should be vaccinated whenever possible. Those in groups at risk for HBV infection (e.g., Asian and Pacific Islanders, sexually active) should be identified and vaccinated in settings serving

this age group (i.e., schools, sexually transmitted disease clinics, detention facilities, drug treatment centers).

Persons younger than 20 years of age should receive 0.5 mL (5 mcg) of pediatric or adult formulation Recombivax HB (Merck) or 0.5 mL (10 mcg) of pediatric formulation Engerix-B (GlaxoSmithKline). The adult formulation of Engerix-B may be used in adolescents, but the approved dose is 1 mL (20 mcg).

The usual schedule for adolescents is two doses separated by no less than 4 weeks, and a third dose 4 to 6 months after the second dose. If an accelerated schedule is needed, the minimum interval between the first two doses is 4 weeks, and the minimum interval between the second and third doses is 8 weeks. However, the first and third doses should be separated by no less than 16 weeks. Doses given at less than these minimum intervals should not be counted as part of the vaccination series.

In 1999, the Food and Drug Administration approved an alternative hepatitis B vaccination schedule for adolescents 11 through 15 years of age. This alternative schedule is for two 1.0-mL (10 mcg) doses of Recombivax HB separated by 4 to 6 months. Seroconversion rates and postvaccination anti-HBs antibody titers were similar using this schedule or the standard schedule of three 5-mcg doses of RecombivaxHB. This alternative schedule is approved only for adolescents 11 through 15 years of age, and for Merck's hepatitis B vaccine. The 2-dose schedule should be completed by age 16 years.

Adults (20 Years of Age and Older)

Routine preexposure vaccination should be considered for groups of adults who are at increased risk of HBV infection. Adults 20 years of age and older should receive 1 mL (10 mcg) of pediatric or adult formulation Recombivax HB (Merck) or 1 mL (20 mcg) of adult formulation Engerix-B (GlaxoSmithKline). The pediatric formulation of Engerix-B is not approved for use in adults.

The usual schedule for adults is two doses separated by no less than 4 weeks, and a third dose 4 to 6 months after the second dose. If an accelerated schedule is needed, the minimum interval between the first two doses is 4 weeks, and the minimum interval between the second and third doses is 8 weeks. However, the first and third doses should be separated by no less than 16 weeks. Doses given at less than these minimum intervals should not be counted as part of the vaccination series. It is not necessary to restart the series or add doses because of an extended interval between doses.

Hepatitis B Vaccine Adolescent and Adult Schedule

| <u>Dose</u> | <u>Usual Interval</u> | <u>Minimum Interval</u> |
|-------------|-----------------------|-------------------------|
| Primary 1 | --- | --- |
| Primary 2 | 1 month | 4 weeks* |
| Primary 3 | 5 months | 8 weeks* |

*third dose must be separated from first dose by at least 16 weeks

Alternative Adolescent Vaccination Schedule

- Two 1.0-mL (10 mcg) doses of Recombivax HB separated by 4-6 months
- Approved only for adolescents 11-15 years of age
- Only applies to Merck hepatitis B vaccine

Adults at Risk for HBV Infection

- Sexual exposure
 - sex partners of HBsAg-positive persons
 - sexually active persons not in a long-term, mutually monogamous relationship*
 - persons seeking evaluation or treatment for a sexually transmitted disease
 - men who have sex with men

*persons with more than one sex partner during the previous 6 months

Adults at Risk for HBV Infection

- Percutaneous or mucosal exposure to blood
 - current or recent IDU
 - household contacts of HBsAg-positive persons
 - residents and staff of facilities for developmentally disabled persons
 - healthcare and public safety workers with risk for exposure to blood or blood-contaminated body fluids
 - persons with end-stage renal disease
 - persons with diabetes mellitus

Adults at Risk for HBV Infection

- Others groups
 - international travelers to regions with high or intermediate levels (HBsAg prevalence of 2% or higher) of endemic HBV infection
 - persons with HIV infection

Hepatitis B vaccination is recommended for all unvaccinated adults at risk for HBV infection and for all adults requesting protection from HBV infection. Acknowledgment of a specific risk factor should not be a requirement for vaccination.

Persons at risk for infection by sexual exposure include sex partners of HBsAg-positive persons, sexually active persons who are not in a long-term, mutually monogamous relationship (e.g., persons with more than one sex partner during the previous 6 months), persons seeking evaluation or treatment for a sexually transmitted disease, and men who have sex with men.

Persons at risk for infection by percutaneous or mucosal exposure to blood include current or recent injection-drug users (IDU), household contacts of HBsAg-positive persons, residents and staff of facilities for developmentally disabled persons, healthcare and public safety workers with risk for exposure to blood or blood-contaminated body fluids and persons with end-stage renal disease, including predialysis, hemodialysis, peritoneal dialysis, and home dialysis patients.

Adults with diabetes mellitus (type 1 or type 2) are at increased risk of HBV infection, probably because of breaches in infection control during assisted blood glucose monitoring (e.g., reuse of single patient finger stick devices). In October 2011, ACIP recommended that all previously unvaccinated adults 19 through 59 years of age with diabetes mellitus (type 1 and type 2) be vaccinated against hepatitis B as soon as possible after a diagnosis of diabetes is made. ACIP also recommended that unvaccinated adults aged 60 years of age or older with diabetes may be vaccinated at the discretion of the treating clinician after assessing their risk and the likelihood of an adequate immune response to vaccination.

Others groups at risk include international travelers to regions with high or intermediate levels (HBsAg prevalence of 2% or higher) of endemic HBV infection and persons with HIV infection.

In settings in which a high proportion of adults have risks for HBV infection (e.g., sexually transmitted disease/human immunodeficiency virus testing and treatment facilities, drug-abuse treatment and prevention settings, healthcare settings targeting services to IDUs, healthcare settings targeting services to MSM, and correctional facilities), ACIP recommends universal hepatitis B vaccination for all unvaccinated adults. In other primary care and specialty medical settings in which adults at risk for HBV infection receive care, healthcare providers should inform all patients about the health benefits of vaccination, including risks for HBV infection and persons for whom vaccination is recommended, and vaccinate adults

who report risks for HBV infection and any adults requesting protection from HBV infection.

Twinrix

In 2001, the Food and Drug Administration approved a combination hepatitis A and hepatitis B vaccine (Twinrix, GlaxoSmithKline). Each dose of Twinrix contains 720 ELISA units of hepatitis A vaccine (equivalent to a pediatric dose of Havrix), and 20 mcg of hepatitis B surface antigen protein (equivalent to an adult dose of Engerix-B). The vaccine is administered in a three-dose series at 0, 1, and 6 months. Appropriate spacing of the doses must be maintained to assure long-term protection from both vaccines. The first and third doses of Twinrix should be separated by at least 6 months. The first and second doses should be separated by at least 4 weeks, and the second and third doses should be separated by at least 5 months. In 2007, the FDA approved an alternative Twinrix schedule of doses at 0, 7, and 21–31 days and a booster dose 12 months after the first dose. It is not necessary to restart the series or add doses if the interval between doses is longer than the recommended interval.

Twinrix is approved for persons aged 18 years and older, and can be used in persons in this age group with indications for both hepatitis A and hepatitis B vaccines. Because the hepatitis B component of Twinrix is equivalent to a standard dose of hepatitis B vaccine, the schedule is the same whether Twinrix or single-antigen hepatitis B vaccine is used. Single-antigen hepatitis A vaccine can be used to complete a series begun with Twinrix and vice versa. See the Hepatitis A chapter for details.

Serologic Testing of Vaccine Recipients

Prevaccination Serologic Testing

The decision to screen potential vaccine recipients for prior infection depends on the cost of vaccination, the cost of testing for susceptibility, and the expected prevalence of immune persons in the population being screened. Prevaccination testing is recommended for all foreign-born persons (including immigrants, refugees, asylum seekers, and internationally adopted children) born in Africa, Asia, the Pacific Islands, and other regions with endemicity of HBV infection; for household, sex, and needle-sharing contacts of HBsAg-positive persons; men who have sex with men, injection drug users, and for certain persons receiving cytotoxic or immunosuppressive therapy. Screening is usually cost-effective, and should be considered for groups with a high risk of HBV infection (prevalence of HBV markers 20% or higher), such as men who have sex with men, injection-drug users, and incarcerated persons.

Prevaccination Serologic Testing

- Not indicated before routine vaccination of infants or children
- Recommended for
 - all persons born in Africa, Asia, the Pacific Islands, and other regions with HBsAg prevalence of 2% or higher
 - household, sex, and needle-sharing contacts of HBsAg-positive persons
 - men who have sex with men
 - injection drug users
 - certain persons receiving cytotoxic or immunosuppressive therapy

Postvaccination Serologic Testing

- Not routinely recommended following vaccination of infants, children, adolescents, or most adults
- Recommended for:
 - chronic hemodialysis patients
 - other immunocompromised persons
 - persons with HIV infection
 - sex partners of HBsAg+ person
 - infants born to HBsAg+ women
 - certain healthcare workers

Postvaccination Serologic Testing

Healthcare personnel who have contact with patients or blood should be tested for anti-HBs (antibody to hepatitis B surface antigen) 1 to 2 months after completion of the 3-dose series

Management of Nonresponse to Hepatitis B Vaccine

- Complete a second series of three doses
- Should be given on the usual schedule of 0, 1 and 6 months
- Retest 1-2 months after completing the second series

Screening is usually not cost-effective for groups with a low expected prevalence of HBV serologic markers, such as health professionals in their training years.

Serologic testing is not recommended before routine vaccination of infants and children.

Postvaccination Serologic Testing

Testing for immunity following vaccination is not recommended routinely but should be considered for persons whose subsequent management depends on knowledge of their immune status, such as chronic hemodialysis patients, other immunocompromised persons and persons with HIV infection. Testing is also recommended for sex partners of HBsAg-positive persons. When necessary, postvaccination testing should be performed 1 to 2 months after completion of the vaccine series.

Infants born to HBsAg-positive women should be tested for HBsAg and antibody to HBsAg (anti-HBs) after completion of at least 3 doses of the hepatitis B vaccine series, at age 9 through 18 months (generally at the next well-child visit). If HBsAg is not present and anti-HBs antibody is present, children can be considered to be protected.

Healthcare personnel who have contact with patients or blood and are at ongoing risk for injuries with sharp instruments or needlesticks should be routinely tested for antibody after 1 to 2 months after completion of the 3-dose series. However, a catch-up program of serologic testing for healthcare personnel is not recommended. These persons should be tested as necessary if they have a significant exposure to HBV (see postexposure prophylaxis section).

Routine postvaccination testing is not recommended for persons at low risk of exposure, such as public safety workers and healthcare personnel without direct patient contact.

Vaccine Nonresponse

Several factors have been associated with nonresponse to hepatitis B vaccine. These include vaccine factors (e.g., dose, schedule, injection site) and host factors. Older age (40 years and older), male sex, obesity, smoking, and chronic illness have been independently associated with nonresponse to hepatitis B vaccine. Further vaccination of persons who fail to respond to a primary vaccination series administered in the deltoid muscle produces adequate response in 15% to 25% of vaccinees after one additional dose and in 30% to 50% after three additional doses.

Persons who do not respond to the first series of hepatitis B vaccine should complete a second three-dose vaccine series.

The second vaccine series should be given on the usual 0, 1, 6-month schedule. A 0, 1, 4-month accelerated schedule may also be used. Revaccinated healthcare personnel and others for whom postvaccination serologic testing is recommended should be retested 1 to 2 months after completion of the second vaccine series.

Fewer than 5% of persons receiving six doses of hepatitis B vaccine administered by the appropriate schedule in the deltoid muscle fail to develop detectable anti-HBs antibody. Some persons who are anti-HBs negative following six doses may have a low level of antibody that is not detected by routine serologic testing ("hyporesponder"). However, one reason for persistent nonresponse to hepatitis B vaccine is that the person is chronically infected with HBV. Persons who fail to develop detectable anti-HBs after six doses should be tested for HBsAg. Persons who are found to be HBsAg positive should be counseled accordingly. Persons who fail to respond to two appropriately administered three-dose series, and who are HBsAg negative should be considered susceptible to HBV infection and should be counseled regarding precautions to prevent HBV infection and the need to obtain HBIG prophylaxis for any known or probable parenteral exposure to HBsAg-positive blood (see the postexposure prophylaxis table in this chapter).

It is difficult to interpret the meaning of a negative anti-HBs serologic response in a person who received hepatitis B in the past and was not tested after vaccination. Without postvaccination testing 1 to 2 months after completion of the series, it is not possible to determine if persons testing negative years after vaccination represent true vaccine failure (i.e., no initial response), or have anti-HBs antibody that has waned to below a level detectable by the test. The latter is the most likely explanation, because up to 60% of vaccinated people lose detectable antibody (but not protection) 9 to 15 years after vaccination.

One management option is to assume true vaccine failure and administer a second series to these persons. Serologic testing for anti-HBs antibody should be repeated 1 to 2 months after the sixth dose.

A second, probably less expensive option is to administer a single dose of hepatitis B vaccine and test for hepatitis B surface antibody in 4 to 6 weeks. If the person is anti-HBs antibody positive, this most likely indicates a booster response in a previous responder, and no further vaccination (or serologic testing) is needed. If the person is anti-HBs antibody negative after this "booster" dose, a second series should be completed (i.e., two more doses). If the person is still seronegative after six total doses, he or she should be managed as a nonresponder (see Postexposure Management, on the next page).

Persistent Nonresponse to Hepatitis B Vaccine

- <5% of vaccinees do not develop anti-HBsAg after 6 valid doses
- May be nonresponder or "hyporesponder"
- Check HBsAg status
- If exposed, treat as nonresponder with postexposure prophylaxis

Postexposure Management

Hepatitis B vaccine is recommended as part of the therapy used to prevent hepatitis B infection following exposure to HBV. Depending on the exposure circumstance, the hepatitis B vaccine series may be started at the same time as treatment with hepatitis B immune globulin (HBIG).

HBIG is prepared by cold ethanol fraction of plasma from selected donors with high anti-HBs titers; it contains an anti-HBs titer of at least 1:100,000, by RIA. It is used for passive immunization for accidental (percutaneous, mucous membrane) exposure, sexual exposure to an HBsAg-positive person, perinatal exposure of an infant, or household exposure of an infant younger than 12 months old to a primary caregiver with acute hepatitis B. Most candidates for HBIG are, by definition, in a high-risk category and should therefore be considered for vaccine as well.

Immune globulin (IG) is prepared by cold ethanol fractionation of pooled plasma and contains low titers of anti-HBs. Because titers are relatively low, IG has no valid current use for HBV disease unless hepatitis B immune globulin is unavailable.

Infants born to women who are HBsAg-positive (i.e., acutely or chronically infected with HBV) are at extremely high risk of HBV transmission and chronic HBV infection. Hepatitis B vaccination and one dose of HBIG administered within 24 hours after birth are 85%–95% effective in preventing both acute HBV infection and chronic infection. Hepatitis B vaccine administered alone beginning within 24 hours after birth is 70%–95% effective in preventing perinatal HBV infection.

HBIG (0.5 mL) should be given intramuscularly (IM), preferably within 12 hours of birth. Hepatitis B vaccine should be given IM in three doses. The first dose should be given at the same time as HBIG, but at a different site. If vaccine is not immediately available, the first injection should be given within 7 days of birth. The second and third doses should be given 1 to 2 months and 6 months, respectively, after the first. Testing for HBsAg and anti-HBs is recommended at 9 to 18 months of age (3 to 12 months after the third dose) to monitor the success of therapy. If the mother's HBsAg status is not known at the time of birth, the infant should be vaccinated within 12 hours of birth.

HBIG given at birth does not interfere with the administration of other vaccines administered at 2 months of age. Subsequent doses of hepatitis B vaccine do not interfere with the routine pediatric vaccine schedule.

Infants born to HBsAg-positive women and who weigh less than 2,000 grams at birth should receive postexposure

prophylaxis as described above. However, the initial vaccine dose (at birth) should not be counted in the 3-dose schedule. The next dose in the series should be administered when the infant is chronologic age 1 month. The third dose should be given 1 to 2 months after the second, and the fourth dose should be given at 6 months of age. These infants should be tested for HBsAg and anti-HBs at 9 to 18 months of age.

Women admitted for delivery whose HBsAg status is unknown should have blood drawn for testing. While test results are pending, the infant should receive the first dose of hepatitis B vaccine (without HBIG) within 12 hours of birth. If the mother is found to be HBsAg positive, the infant should receive HBIG as soon as possible but not later than 7 days of age. If the infant does not receive HBIG, it is important that the second dose of vaccine be administered at 1 or 2 months of age.

Preterm infants (less than 2,000 grams birthweight) whose mother's HBsAg status is unknown should receive hepatitis B vaccine within 12 hours of birth. If the maternal HBsAg status cannot be determined within 12 hours of birth HBIG should also be administered because of the immune response is less reliable in preterm infants weighing less than 2,000 grams. As described above, the vaccine dose administered at birth should not be counted as part of the series, and the infant should receive three additional doses beginning at age 1 month. The vaccine series should be completed by 6 months of age.

Few data are available on the use of Comvax or Pediarix in infants born to women who have acute or chronic infection with hepatitis B virus (i.e., HBsAg-positive). Neither vaccine is licensed for infants whose mothers are known to be acutely or chronically infected with HBV. However, ACIP has approved off-label use of Comvax and Pediarix in children whose mothers are HBsAg positive, or whose HBsAg status is unknown. Comvax and Pediarix should never be used in infants younger than 6 weeks of age. Either vaccine may be administered at the same time as other childhood vaccines given at 6 weeks of age or older.

After a percutaneous (needle stick, laceration, bite) or permucosal exposure that contains or might contain HBV, blood should be obtained from the person who was the source of the exposure to determine their HBsAg status. Management of the exposed person depends on the HBsAg status of the source and the vaccination and anti-HBs response status of the exposed person. Recommended postexposure prophylaxis is described in the table on the next page.

Prevention of Perinatal Hepatitis B Virus Infection

- Begin treatment within 12 hours of birth
- Hepatitis B vaccine (first dose) and HBIG at different sites
- Complete vaccination series at 6 months of age
- Test for response at 9-18 months of age

Recommended postexposure prophylaxis for percutaneous or permucosal exposure to hepatitis B virus — Advisory Committee on Immunization Practices, United States

| Vaccination and antibody response status of exposed person | Treatment | | |
|--|--|----------------------------|--|
| | Source HBsAg-positive | Source HBsAg-negative | Source not tested or status unknown |
| Unvaccinated | HBIG x 1; initiate HB vaccine series | Initiate HB vaccine series | Initiate HB vaccine series |
| Previously vaccinated | | | |
| Known responder | No treatment | No treatment | No treatment |
| Known nonresponder | | | |
| After 3 doses | HBIG x 1 and initiate revaccination | No treatment | If known high-risk source, treat as if source were HBsAg-positive |
| After 6 doses | HBIG x 2 (separated by 1 month) | No treatment | If known high-risk source, treat as if source were HBsAg-positive |
| Antibody response unknown | Test exposed person for anti-HBs If adequate,* no treatment If inadequate,* HBIG x 1 and vaccine booster | No treatment | Test exposed person for anti-HBs If adequate,* no treatment If inadequate,* initiate revaccination |

Abbreviations: HBsAg = Hepatitis B surface antigen; HBIG = hepatitis B immune globulin; anti-HBs = antibody to hepatitis B surface antigen; HB = hepatitis B. **Source:** Adapted from CDC. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). Part II: immunization of adults. *MMWR* 2006;55(No. RR-16).

* A seroprotective (adequate) level of anti-HBs after completion of a vaccination series is defined as anti-HBs ≥10 mIU/mL; a response < 10 mIU/mL is inadequate and is not a reliable indicator of protection.

Source: *MMWR* 2011;60(RR-7)42.

Non-Occupational Exposure to an HBsAg-Positive Source

Persons who have written documentation of a complete hepatitis B vaccine series and who did not receive postvaccination testing should receive a single vaccine booster dose. Persons who are in the process of being vaccinated but who have not completed the vaccine series should receive the appropriate dose of HBIG and should complete the vaccine series. Unvaccinated persons should receive both HBIG and hepatitis B vaccine as soon as possible after exposure (preferably within 24 hours). Hepatitis B vaccine may be administered simultaneously with HBIG in a separate injection site.

Household, sex, and needle-sharing contacts of HBsAg-positive persons should be identified. Unvaccinated sex partners and household and needle-sharing contacts should be tested for susceptibility to HBV infection and should receive the first dose of hepatitis B vaccine immediately after collection of blood for serologic testing. Susceptible persons should complete the vaccine series using an age-appropriate vaccine dose and schedule. Persons who are not fully vaccinated should complete the vaccine series.

Non-Occupational Exposure to a Source with Unknown HBsAg Status

Persons with written documentation of a complete hepatitis B vaccine series require no further treatment. Persons who are not fully vaccinated should complete the vaccine series. Unvaccinated persons should receive the hepatitis B vaccine series with the first dose administered as soon as possible after exposure, preferably within 24 hours.

Contraindications and Precautions to Vaccination

A severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose of hepatitis B vaccine is a contraindication to further doses of vaccine. Such allergic reactions are rare.

Persons with moderate or severe acute illness should not be vaccinated until their condition improves. However, a minor illness, such as an upper respiratory infection, is not a contraindication to vaccination.

Specific studies of the safety of hepatitis B vaccine in pregnant women have not been performed. However, more than 20 years of experience with inadvertent administration to pregnant women have not identified vaccine safety issues for either the woman or the fetus. In contrast, if a pregnant woman acquires HBV infection, it may cause severe disease in the mother and chronic infection in the newborn baby. Therefore, hepatitis B vaccine may be administered to a pregnant woman who is otherwise eligible for it.

Hepatitis B vaccine does not contain live virus, so it may be used in persons with immunodeficiency. However, response to vaccination in such persons may be suboptimal.

Adverse Reactions Following Vaccination

The most common adverse reaction following hepatitis B vaccine is pain at the site of injection, reported in 13%–29% of adults and 3%–9% of children. Mild systemic complaints, such as fatigue, headache, and irritability, have been reported in 11% to 17% of adults and 0% to 20% of children. Fever (up to 99.9°F [37.7°C]) has been reported in 1% of adults and 0.4% to 6.4% of children. Serious systemic adverse reactions and allergic reactions are rarely reported following hepatitis B vaccine. There is no evidence that administration of hepatitis B vaccine at or shortly after birth increases the number of febrile episodes, sepsis evaluations, or allergic or neurologic events in the newborn period.

Hepatitis B vaccine has been alleged to cause or exacerbate multiple sclerosis (MS). A 2004 retrospective study in a

Hepatitis B Vaccine Contraindications and Precautions

- Severe allergic reaction to a vaccine component or following a prior dose
- Moderate or severe acute illness

Hepatitis B Vaccine Adverse Reactions

| | Adults | Infants and Children |
|--|---------|----------------------|
| Pain at injection site | 13%-29% | 3%-9% |
| Mild systemic complaints (fatigue, headache) | 11%-17% | 0%-20% |
| Temperature \leq 99.9°F (37.7°C) | 1% | 0.4%-6% |
| Severe systemic reactions | rare | rare |

British population found a slight increase in risk of MS among hepatitis B vaccine recipients. However, large population-based studies have shown no association between receipt of hepatitis B vaccine and either the development of MS or exacerbation of the course of MS in persons already diagnosed with the disease.

Vaccine Storage and Handling

Hepatitis B vaccines should be stored refrigerated at 35°–46°F (2°–8°C), but not frozen. Exposure to freezing temperature destroys the potency of the vaccine.

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