

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 at least a month at room temperature.

HBV is the most common known cause of chronic viremia, with more than 200 million chronically infected persons estimated worldwide. HBV infection is an established cause of acute and chronic hepatitis and cirrhosis. It is the cause of up to 80% of hepatocellular carcinomas, and is second only to tobacco among known human carcinogens. More than 250,000 persons die worldwide each year 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

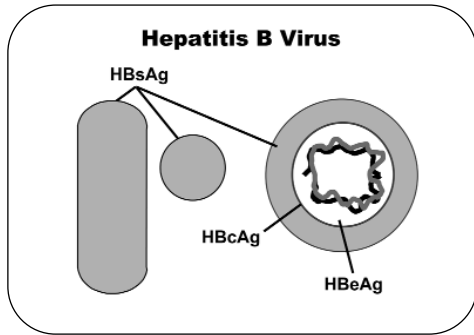
Hepatitis B Virus

- Hepadnaviridae family (DNA)
- Numerous antigenic components
- Humans are only known host
- May retain infectivity for at least 1 month at room temperature

Hepatitis B Virus Infection

- >200 million chronically infected worldwide
- Established cause of chronic hepatitis and cirrhosis
- Human carcinogen—cause of up to 80% of hepatocellular carcinomas

Hepatitis B



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 60 to 150 days (average, 90 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.

Hepatitis B Clinical Features

- Incubation period 60-150 days (average 90 days)
- Nonspecific prodrome of malaise, fever, headache, myalgia
- Illness not specific for hepatitis B
- At least 50% of infections asymptomatic

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 10% 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 weeks after

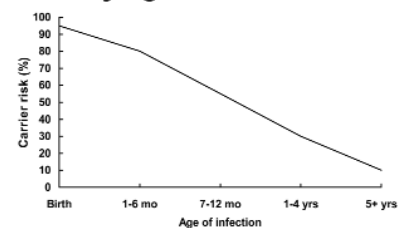
Hepatitis B Complications

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

Chronic Hepatitis B Virus Infection

- Chronic viremia
- Responsible for most mortality
- Overall risk 10%
- Higher risk with early infection

Risk of Chronic HBV Carriage by Age of Infection



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

*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 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 |

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

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 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.

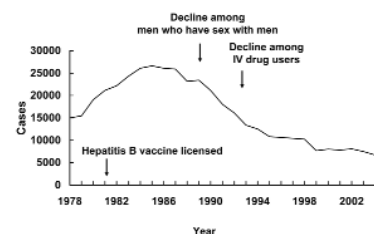
The incidence of reported hepatitis B peaked in the mid-1980s, with about 26,000 cases reported each year. Reported cases have declined since that time, and fell below 10,000 cases for the first time in 1996. The decline in cases during the 1980s and early 1990s is generally attributed to reduction of 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 6,741 cases of hepatitis B were reported in 2004.

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 1–1.25 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, 1978-2004



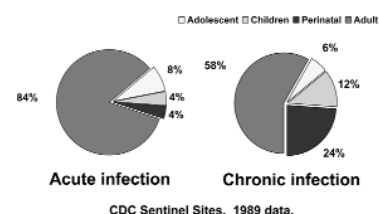
15

HBV Disease Burden in the United States*

New infections	78,000/yr
Current carriers	>1 million
New carriers	>5,000/yr
Death	5,000/yr

*2001 estimates

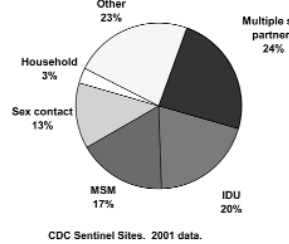
Age of Infection of Acute and Chronic Hepatitis B Virus Infection



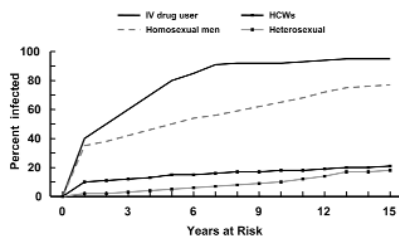
CDC Sentinel Sites. 1989 data.

Hepatitis B

Risk Factors for Hepatitis B



Hepatitis B Virus Infection by Duration of High-Risk Behavior



The most common risk factor for HBV infection in the United States is sexual contact, either heterosexual (37%), or among men who have sex with men (17%). Injection-drug use accounts for 20% of cases, and 3% of cases occur by household contact with a chronically infected person. In the early 1990s, healthcare workers accounted for approximately 1% of HBV infections. With widespread use of hepatitis B vaccine, HBV infection among healthcare workers is now very uncommon.

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 institutions for the developmentally disabled.	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 workers – frequent blood contact.	1-2	15-30
	Staff of institutions for the mentally retarded.	1	10-25
	Heterosexuals with multiple partners.	0.5	5-20
Low-Risk	Healthcare workers – 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.

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 human carriers. 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, and was the first licensed vaccine in the United States produced by recombinant DNA technology. 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** >15 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 11–15 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 (11–19 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, 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	0	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 age 0, 1, and 6 months.

‡ Two 1.0 mL doses administered at one site, on a 4-dose schedule at age 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 whose 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 anterolateral 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 infants using a needle of at least 7/8 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. Nevertheless, immune memory remains intact for more than 15 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 an 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, nor is routine serologic testing to assess immune status of vaccinees indicated.** 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, 1-2, and 6-18 months. Infants whose mothers are HBsAg positive or whose HBsAg status is unknown should receive the third dose by 6 months of age.

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) beginning at or shortly after birth. 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 12–15 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 9, *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 <6 weeks of age
- May be used in infants whose mothers are HBsAg positive or status is unknown

Hepatitis B

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

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 [11–19 Years of Age]

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 11–12 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).

Adolescents 11–19 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 4–6 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 11–15 years of age. This alternative schedule is for two 10-mcg doses of Recombivax HB separated by 4–6 months. Seroconversion rates and postvaccination anti-HBs antibody titers were similar using this schedule or the standard schedule of three 5-mcg doses of Recombivax HB. This alternative schedule is approved only for adolescents 11–15 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 4–6 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 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

Hepatitis B

Adult Hepatitis B Vaccine Candidates

- Men who have sex with men
- Heterosexual with multiple partners
- Persons diagnosed with an STD
- Prostitutes
- Injection drug users
- Inmates of long-term correctional facilities
- Persons receiving hemodialysis
- Healthcare workers

Adults who are at increased risk of HBV infection from sexual transmission include **men who have sex with other men, heterosexuals with multiple sex partners, persons diagnosed with a recently acquired sexually transmitted disease, and prostitutes.**

Injection-drug users who share needles are at very high risk for HBV infection. All injection-drug users who are susceptible to HBV should be vaccinated as soon as possible after their drug use begins.

Inmates of long-term correctional facilities are at increased risk of HBV infection because of injection-drug use, homosexual activity, or other factors. The prison setting provides an access point for vaccination of inmates with histories of high-risk behavior.

Persons undergoing hemodialysis are at increased risk of HBV infection because of contact with large amounts of blood. Although the hepatitis B vaccine is less effective in these patients, it is recommended for all susceptible hemodialysis patients.

The risk of **healthcare workers** contracting HBV infection depends on how often they are exposed to blood or blood products through percutaneous and permucosal exposures. Any healthcare or public safety worker may be at risk for HBV exposure, depending on the tasks performed. If those tasks involve contact with blood or blood-contaminated body fluids, such workers should be vaccinated. Risk is often highest during training periods. Therefore, it is recommended that vaccination be completed during training in schools of medicine, dentistry, nursing, laboratory technology, and other allied health professions.

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. 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

Twinrix

- **Combination hepatitis A vaccine (pediatric dose) and hepatitis B (adult dose)**
- **Schedule: 0, 1, 6 months**
- **Approved for persons ≥ 18 years**

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 Chapter 14, Hepatitis A, for details.

Other Groups Who May Be Candidates for Hepatitis B Vaccine

The special behavioral and medical problems encountered in **institutions for the developmentally disabled** make this a high-risk setting, and clients and staff should be vaccinated. The risk of HBV infection in these institutions is related to contact with blood and also with bites and contact with skin lesions and other body fluids that contain HBV. Clients and staff of group and foster homes where a chronically infected person is known to be present should also be vaccinated.

In certain U.S. populations, such as **Alaska Natives, Pacific Islanders, and immigrants and refugees from HBV-endemic areas**, HBV infection is highly endemic and transmission occurs primarily during childhood. In such groups, vaccination of all infants is particularly important. Immigrants and refugees from areas with highly endemic HBV disease should be screened for HBV upon resettlement in the United States. If a chronically infected person (carrier) is identified, all susceptible household members should be vaccinated. Even if no carriers are found, vaccination is recommended for susceptible children younger than 7 years of age because of the high rate of interfamilial spread of HBV.

Adoptees, orphans, and unaccompanied minors from countries of high or intermediate HBV endemicity should be screened for HBsAg, and, if positive, their household members should be vaccinated.

Household members and sex partners of HBV carriers should be tested and, if susceptible (i.e., neither anti-HBs positive [immune] or HBsAg positive [acutely or chronically infected]), should be vaccinated.

Adults and children who plan to travel to areas outside the United States that have high rates of HBV infection should be vaccinated if they plan to stay in these areas for more than 6 months and have close contact with the local population. Persons traveling for shorter durations who may have sexual contact with local persons in areas where HBV infection is common should also be vaccinated. Persons traveling abroad who will perform medical procedures in areas where HBV infection is common are at very high risk.

Other Hepatitis B Vaccine Candidates

- Staff of institutions for developmentally disabled
- Alaska Natives, Pacific Islanders
- Immigrants/refugees*
- Adoptees, orphans, unaccompanied minors*
- Household members and sex partners of HBV carriers
- Extended travel to areas of high endemicity
- Recipients of certain blood products

*from countries of high or intermediate HBV endemicity

Prevaccination Serologic Testing

- Not indicated before routine vaccination of infants or children
- May be considered when vaccinating adolescents in groups with high rates of HBV infection
 - Alaska Natives
 - Pacific Islanders
 - children of immigrants from endemic countries
 - family members of HBV carriers

Postvaccination Serologic Testing

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

Recipients of certain blood products, such as persons with hemophilia, are at high risk of infection. Vaccination should be initiated at the time their specific clotting disorder is identified.

Persons who have casual contact with chronically infected persons at schools and offices are at low risk of HBV infection from such contact, and vaccine is not recommended for this group. Unless special circumstances exist, such as behavior problems (biting or scratching) or medical conditions (severe skin disease) that might facilitate transmission, vaccination of contacts of carriers in child care centers is not indicated. However, routine vaccination of all persons 18 years of age and younger is recommended.

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. Screening is usually cost-effective, and should be considered, in 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, Alaska natives, Pacific Islanders, children of immigrants from endemic-disease countries, and family members of HBsAg-positive persons. 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 knowing their immune status, such as dialysis patients and staff, and persons in whom a suboptimal response may be anticipated, such as those who have received vaccine in the buttock. Testing is also recommended for sex partners of HBsAg-positive persons. When necessary, postvaccination testing should be performed 1–2 months after completion of the vaccine series.

All infants born to HBsAg-positive women should be tested 3–12 months after their final (third or fourth) dose of hepatitis B vaccine (i.e., at 9–18 months of age). If HBsAg is not present and anti-HBs antibody is present, children can be considered to be protected.

In 1997, ACIP and the Hospital Infection Control Practices Advisory Committee published comprehensive recommendations for the immunization of healthcare workers. One of the recommendations was that **healthcare workers who have contact with patients or blood and are at ongoing risk for injuries with sharp instruments or needles should be routinely tested for antibody after vaccination.** However, a catch-up program of serologic testing for healthcare providers vaccinated prior to December 1997 was not recommended. These persons should be tested as necessary if they have a significant exposure to HBV (see postexposure prophylaxis section below).

Routine postvaccination testing is **not** recommended for persons at low risk of exposure, such as public safety workers and healthcare workers 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 workers and others for whom postvaccination serologic testing is recommended should be retested 1–2 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

Postvaccination Serologic Testing

Healthcare workers who have contact with patients or blood should be tested for antibody after vaccination

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

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

probable parenteral exposure to HBsAg-positive blood (see postexposure prophylaxis table on page 228).

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, 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) 9–15 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 1–2 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 4–6 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, below).

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 1–2 months and 6 months, respectively, after the first. Testing for HBsAg and anti-HBs is recommended at 9–18 months of age (3–12 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 1–2 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 9–18 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 1–2 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

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**

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 (see http://www.cdc.gov/nip/vfc/acip_recs/1003hepb.pdf). **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 below.

Recommended Postexposure Prophylaxis for Exposure to Hepatitis B Virus

Vaccination and antibody status of exposed person*		Treatment		
		Source HBsAg** Positive	Source HBsAg** Negative	Source unknown or not available for testing
Unvaccinated		HBIG† X 1 and initiate IIB vaccine series	Initiate IIB vaccine series	Initiate IIB vaccine series
Previously Vaccinated	Known Responder §	No treatment	No treatment	No treatment
	Known nonresponder †	HBIG X 1 and initiate revaccination or IIBIG X 2 ††	No treatment	If known high-risk source, treat as if source were IIBsAg positive
	Antibody response unknown	Test exposed person for anti-HBs† – If adequate §, no treatment is necessary – If inadequate ‡, administer HBIG X 1 and vaccine booster	No treatment	Test exposed person for anti-HBs† – If adequate §, no treatment is necessary – If inadequate ‡, administer vaccine booster and recheck titer in 1-2 months

* Persons who have previously been infected with HBV are immune to reinfection and do not require postexposure prophylaxis
 ** Hepatitis B surface antigen
 † Hepatitis B immune globulin; dose is 0.06 mL/kg administered intramuscularly
 § A responder is a person with adequate levels of serum antibody to HBsAg (i.e., anti-HBs ≥10 mIU/mL)
 ‡ A nonresponder is a person with inadequate response to vaccination (i.e., serum anti-IIBs <10 mIU/mL)
 †† The option of giving one dose of HBIG and reinitiating the vaccine series is preferred for nonresponders who have not completed a second 3-dose vaccine series. For persons who previously completed a second vaccine series but failed to respond, two doses of HBIG are preferred.
 ¶ Antibody to HBsAg

Source: *MMWR* 2001; 50(RR-11) pg 22

Susceptible Sex Partners of Persons with Acute or Chronic HBV Infection

For susceptible sex partners of persons with acute HBV infection, a single dose of HBIG (0.06 mL/kg) given within 14 days of the last sexual contact is recommended. If the last sexual contact was more than 14 days previously, hepatitis B vaccination should be initiated, although the amount of protection afforded by postexposure prophylaxis given this late is not known. For sex partners of persons with chronic HBV infection, postexposure prophylaxis with hepatitis B vaccine alone is recommended. HBIG is not recommended in this situation. Postvaccination anti-HBs antibody testing should be considered for sex partners of persons with chronic HBV infection.

Household Contacts of Persons with Acute HBV Infection

Infants whose mother or primary caregiver has acute HBV infection are at increased risk of developing chronic HBV infection because of close contact. An unvaccinated infant whose mother or primary caregiver has acute HBV infection should receive HBIG (0.5 mL) along with the first dose of the hepatitis B vaccine series. HBIG is not needed for infants who have received two doses of vaccine or who are scheduled to receive the second dose of vaccine. The second vaccine dose should be given and/or vaccination should be completed on schedule. Household contacts of persons with acute HBV infection who have had a blood exposure to the infected person (e.g., sharing a toothbrush or razor) should receive HBIG and begin the vaccine series. Routine hepatitis B vaccination should be considered for nonsexual household contacts who do not have a blood exposure to the infected person, especially for children and adolescents.

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 Adverse Reactions

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

Hepatitis B Vaccine Contraindications and Precautions

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

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.

Contraindications and Precautions to Vaccination

A severe allergic reaction 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.

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.

Selected References

American Academy of Pediatrics. Hepatitis B. In: Pickering L, ed. *Red Book: 2003 Report of the Committee on Infectious Diseases*. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2003:318–36.

Ascherio A, Zhang SM, Hernan MA, et al. Hepatitis B vaccination and the risk of multiple sclerosis. *N Engl J Med* 2001;344:327–32.

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 1: Immunization of infants, children, and adolescents. *MMWR* 2005;54(No. RR-16):1–32.

CDC. Immunization of health-care workers: recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Hospital Infection Control Practices Advisory Committee (HICPAC). *MMWR* 1997;46(No. RR-18):1–42.

CDC. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. *MMWR* 2001;50(No. RR-11):1–42.

Confavreux C, Suissa S, Saddier P, et al. Vaccinations and the risk of relapse in multiple sclerosis. *N Engl J Med* 2001;344:319–26.

Margolis HS, Alter MJ, Hadler SC. Viral hepatitis. In: Evans AS, Kaslow RA, eds. *Viral Infections of Humans. Epidemiology and Control*. 4th edition. New York, NY: Plenum Medical Book Company, 1997.

Lewis E, Shinefield HR, Woodruff BA, et al. Safety of neonatal hepatitis B vaccine administration. *Pediatr Infect Dis J* 2001;20:1049–54.

Mast E, Mahoney F, Kane M, Margolis H. Hepatitis B vaccine. In: Plotkin SA, Orenstein WA, eds. *Vaccines*. 4th edition. Philadelphia, PA: Saunders; 2003:299–337.

Poland GA, Jacobson RM. Clinical practice: prevention of hepatitis B with the hepatitis B vaccine. *N Engl J Med* 2004;351:2832–8.