



Chapter 10: Hepatitis B

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Health Care Providers

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AT A GLANCE

This chapter discusses pathogenesis, clinical features, epidemiology, vaccination, and surveillance of hepatitis B.

Overview

Keep in mind



The 14th edition of the "Pink Book" was published August 2021. Vaccine-specific recommendations may be outdated. Refer to the CDC website for updated [Hepatitis B Vaccination Information for Healthcare Providers](#).

Hepatitis B

- Epidemic jaundice described by Hippocrates in 5th century BCE
- First recorded cases in 1883 following administration of smallpox vaccine containing human lymph
- Transmission via blood further emphasized in 1943
- HBsAg first described in 1965
- Plasma-derived HepB vaccine licensed in 1981 replaced in 1986 with recombinant HepB vaccines

Viral hepatitis is a term commonly used for several diseases that are clinically similar but etiologically and epidemiologically distinct. 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. Hepatitis D, or 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 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 Paul 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 and helped to clarify the natural history of the disease. Ultimately, HBsAg, the surface protein of HBV, was manufactured in quantity and now comprises the immunogen in highly effective vaccines for prevention of HBV infection.

A plasma-derived Hepatitis B (HepB) vaccine was first licensed for use in the United States in 1981. The vaccine was safe and effective but was not well accepted, possibly because of unsubstantiated fears of transmission of live HBV and other blood-borne pathogens. Recombinant HepB vaccines replaced plasma-derived HepB vaccines beginning in 1986. Plasma-derived HepB vaccines are no longer used in the United States.

Hepatitis B Virus (HBV)

Hepatitis B Virus

- Hepadnaviridae family (DNA)
- Multiple serologic markers for infection
- Classified by serologic subtype and genotype, which vary geographically
- Infectious for at least 7 days on surfaces

HBV is a small, double-stranded DNA virus in the family Hepadnaviridae. Serologic markers for HBV infection include HBsAg, antibody to HBsAg (anti-HBs), immunoglobulin class M (IgM) antibodies to hepatitis B core antigen (IgM anti-HBc), and immunoglobulin class G (IgG) anti-HBc (IgG anti-HBc). At least one serologic marker is present during the different phases of infection. Hepatitis B e antigen (HBeAg) can be detected in persons with acute or chronic HBV infection; the presence of HBeAg correlates with viral replication, high viral levels of HBV DNA, and high infectivity; antibody to HBeAg (anti-HBe) usually correlates with the decrease of replicating virus, although reversion to HBeAg positivity can occur.

HBV has been classified by two separate systems: serologic subtype and genotype. Nine serologic subtypes based on the heterogeneity of HBsAg have been described. Ten HBV genotypes, designated A through J, have been described. HBV serotypes and genotypes vary geographically. HBV genotypes are associated with the modes of HBV transmission (vertical versus horizontal) and with the risk of certain outcomes of chronic infection, such as cirrhosis and hepatocellular carcinoma (HCC). For example, in Alaska, HBV genotype F is associated with HCC in children as well as adults younger than age 30 years, while in Asia as well as Alaska, HBV genotype C has been associated with a significantly higher risk of HCC than other genotypes. Infection or immunization with one HBV genotype generally confers immunity to all genotypes.

HBV remains infectious for at least 7 days on environmental surfaces and is transmissible in the absence of visible blood.

Pathogenesis

Hepatitis B Pathogenesis

- Transmission by parenteral or mucosal exposure
- Replicates in hepatocytes
- Unique reverse transcription replication

HBV is transmitted by parenteral or mucosal exposure to HBsAg-positive body fluids from persons who have acute or chronic HBV infection. It replicates in hepatocytes through a unique reverse transcription process.

Clinical Features

Hepatitis B Clinical Features

- Incubation period 60 to 90 days
- Clinical signs and symptoms more common in adults
- Prodromal phase lasts 3 to 10 days; abrupt onset of fever, malaise, anorexia, nausea, abdominal discomfort, and dark urine before jaundice
- Icteric phase lasts 1 to 3 weeks; jaundice, light or gray stools, hepatic tenderness, hepatomegaly
- Convalescent phase lasts weeks to months; malaise and fatigue persist while jaundice, anorexia, and other symptoms disappear
- Most adults recover while most infants progress to chronic infection

The clinical course of acute hepatitis B is indistinguishable from that of other types of acute viral hepatitis. The incubation period typically ranges from 60 to 90 days. Clinical signs and symptoms occur more often in adults than in infants or children; infants and young children usually are asymptomatic. Approximately 50% of adults who have acute infections are asymptomatic.

The preicteric, or prodromal, phase from initial symptoms to onset of jaundice usually lasts 3 to 10 days. It is nonspecific and is characterized by abrupt onset of fever, malaise, anorexia, nausea, abdominal discomfort, 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. In contrast, as many as 90% of HBV infections in infants progress to chronic infection. Perinatal transmission from mother to infant at birth (vertical transmission) is highly efficient. Prior to the widespread availability of postexposure prophylaxis, the proportion of infants born to HBsAg-positive women that acquired HBV infection was approximately 30% for those born to HBeAg-negative mothers and 85% for those born to HBeAg-positive mothers. With postexposure prophylaxis, comprised of HepB vaccine and hepatitis B immune globulin (HBIG) at birth, followed by completion of the HepB vaccine series, 0.7% through 1.1% of infants develop infection; infants born to mothers with high viral loads are at greatest risk for infection despite receipt of HepB vaccine and HBIG.

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Complications

Hepatitis B Complications

- Fulminant hepatitis in about 1% to 2% of acutely infected adults

While most acute HBV infections in adults result in complete recovery, fulminant hepatitis occurs in about 1% to 2% of acutely infected persons. 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

Chronic Hepatitis B Virus Infection (HBV)

- Proportion of persons with acute HBV that progress to chronic HBV
 - As many as 90% of infants
 - 30% to 50% of children between age 1 and 5 years
 - 5% of adults
- Often asymptomatic
- Responsible for most HBV-related morbidity and mortality
- 25% of persons infected as children and 15% of persons infected as adults will die prematurely

The proportion of persons with acute HBV infection who progress to chronic infection varies with age and immune status. As many as 90% of infants who acquire HBV infection from their mothers at birth or in infancy become chronically infected. Of children who become infected with HBV between age 1 and 5 years, 30% to 50% become chronically infected. The risk of acquiring chronic HBV infection when infected during adulthood is approximately 5%. Acute HBV progresses to chronic HBV in approximately 40% of hemodialysis patients and up to 20% of patients with immune deficiencies.

Persons with chronic infection are often asymptomatic and may not be aware 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 HCC. Approximately 25% of persons who become chronically infected during childhood and 15% of those who become chronically infected after childhood will die prematurely from cirrhosis or liver cancer.

An estimated 257 million persons worldwide are living with HBV infection. HBV infection is an established cause of acute and chronic hepatitis and cirrhosis. The frequency of infection and patterns of transmission vary in different parts of the world. 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 has chronic HBV infection. In these high-prevalence areas, 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 has chronic HBV infection.

Laboratory Testing



Diagnosis is based on clinical, laboratory, and epidemiologic findings. HBV infection cannot be differentiated based on 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 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 exposure to HBV. The presence of HBsAg indicates that a person is infectious, regardless of whether the infection is acute or chronic. Transient HBsAg positivity can occur up to 18 days following vaccination (up to 52 days among hemodialysis patients) and is clinically insignificant.

Anti-HBs 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 HepB vaccine or passively transferred by administration of HBIG. The level of anti-HBs considered as a protective level of immunity when following a complete vaccination series is 10 mIU/mL. Persons who recover from natural HBV infection are typically positive for both anti-HBs and anti-HBc, whereas persons who respond to HepB vaccine are positive only for anti-HBs.

Anti-HBc 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 generally persists for life. Persons who are HBsAg-negative and anti-HBc-positive can experience reactivation of infection during chemotherapy or immunosuppressive therapy, with reappearance of HBsAg.

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.

HBeAg is a marker that is associated with a high number of infective HBV particles in the serum and a higher risk of infectivity. Anti-HBe correlates with a reduction of replicating virus and lower infectivity, although reversion to HBeAg positivity can occur.

HBV DNA assays are used to monitor response to treatment, assess the likelihood of perinatal HBV transmission, and detect the presence of occult HBV infection (i.e., infection in someone who tests HBsAg-negative). In resource-limited settings, HBeAg may replace the use of HBV DNA for some purposes, e.g., assessment of perinatal HBV transmission risk.

Medical Management



There is no specific therapy for acute HBV infection. Treatment is supportive. Guidelines for management of chronic HBV infection in children and adults, including disease monitoring and antiviral therapy, are available from the American Association for the Study of Liver Diseases (AASLD, <https://www.AASLD.org>). Antiviral therapy, while not curative, can reduce the level of HBV DNA and quiet liver inflammation. Following the AASLD Guidelines/Guidance, antiviral therapy should generally be initiated in patients with chronic HBV infection who have high levels of virus and active liver inflammation characterized by elevated liver transaminase levels. These persons are at high risk for liver-related morbidity.

AASLD suggests antiviral therapy to reduce perinatal HBV transmission when maternal HBV DNA is greater than 200,000 IU/mL starting in the third trimester. Maternal therapy is generally discontinued at birth to 3 months postpartum.

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 health care settings, patients with HBV infection should be managed with standard precautions.

Epidemiology

Hepatitis B Epidemiology

- Reservoir
 - Human
 - Some primates
- Transmission
 - Body fluids (highest concentration in blood and serous fluids)
- Temporal Pattern
 - No temporal pattern

- Communicability
 - Persons with acute or chronic HBV infection are infectious any time HBsAg present in blood
 - Persons with acute HBV infection can have HBsAg in blood 1-2 months before and after onset of symptoms

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Occurrence ▼

HBV infection occurs worldwide. The frequency of infection varies in different parts of the world but is more common in some countries in Asia, Africa, South America, and the Caribbean.

Reservoir ▼

HBV infection affects humans. Additionally, some primates (chimpanzee, gorilla, orangutan, gibbon) in Africa and Southeast Asia are infected with HBV.

Transmission ▼

HBV 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, tears, urine, and semen. Semen is a vehicle for sexual transmission and saliva can be a vehicle of transmission through bites; other types of exposure (e.g., to saliva through kissing) are unlikely modes of transmission. HBsAg is also found in other body fluids (e.g., breast milk, bile, feces, nasopharyngeal washings, and sweat). However, most body fluids are not efficient vehicles of transmission (unless they contain blood) because they contain low quantities of infectious HBV.

In the United States, the most important routes of transmission are injection-drug use, perinatal, and sexual contact with an infected person. Fecal-oral transmission does not appear to occur. However, transmission occurs among men who have sex with men (MSM), possibly via contamination from asymptomatic rectal mucosal lesions. In the 2000s and 2010s, outbreaks of hepatitis B occurred in long-term care facilities (e.g., assisted living facilities and nursing homes) as the result of inadequate infection control practices related to blood glucose monitoring. Transmission occurs in households from persons who have immigrated from endemic areas and who have chronic HBV infection.

Temporal Pattern ▼

HBV infection is reported throughout the year. There is no known temporal pattern.

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 to 2 months before and after the onset of symptoms.

Direct, percutaneous inoculation of HBV by needles during injection-drug use is an important mode of transmission. 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. Exposures such as transfusion of blood or blood products, hemodialysis, use of meters and lancets for blood glucose monitoring, insulin pens, and needle-stick or other sharps injuries sustained by health care personnel (HCP) have all resulted in HBV transmission. Outbreaks have been reported among patients in dialysis centers in many countries through failure to adhere to recommended infection control practices. Past outbreaks have been traced to tattoo parlors, acupuncturists, and barbers.

Secular Trends in the United States

Hepatitis B Secular Trends in the United States

- Acute HBV infection
 - Before vaccine, about 9.6 per 100,000 cases
 - Following vaccine, about 1 per 100,000 cases in 2018 (~90% decrease)
 - During 2009 through 2013, KY, TN, and WV experienced 114% increase associated with injection-drug use
 - Incidence greatest for persons 40 through 49 years and lowest for persons 19 years or younger
- Chronic HBV infection
 - Estimated 850,000 to 2.2 million persons infected in the U.S.; most immigrated from endemic countries

Hepatitis B became nationally notifiable as a distinct entity during the 1970s after serologic tests to differentiate different types of hepatitis became widely available.

In 2018, a total of 3,322 cases of acute hepatitis B were reported to CDC, for an overall incidence rate of 1.0 cases per 100,000 population. After adjusting for under-ascertainment and under-reporting, an estimated 21,600 acute hepatitis B cases occurred in 2018. The rate of reported acute HBV infections declined approximately 90% since recommendations for HepB vaccination were first issued, from 9.6 cases per 100,000 population in 1982 to 1.0 cases per 100,000 population in 2018.

During 2009 through 2013, the combined incidence of acute HBV infection in three states (Kentucky, Tennessee, and West Virginia) increased 114% and was associated with increasing injection-drug use. Incidence is greatest for persons age 40 through 49 years (2.5 per 100,000 population); persons age 19 years or younger have the lowest incidence (0.02 cases per 100,000 population), likely a result of routine infant vaccination.

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. Generally, the highest risk for HBV infection is associated with lifestyles, occupations, or environments in which contact with blood from infected persons is frequent. Chronic HBV infection has been identified in 3.5% to 20.0% of persons who inject drugs (PWID) in a variety of settings, and 22.6% of PWID have evidence of past infection.

An estimated 850,000 to 2.2 million persons in the United States are chronically infected with HBV. Most persons in the United States with chronic HBV infection have immigrated from endemic countries in the world. While screening persons who immigrate for HBsAg, anti-HBc and anti-HBs is recommended, it is not enforced. Therefore, clinicians and public health workers should screen all persons born in countries with high endemicity of HBV virus.

Among children born during 2015–2016, 75.0% received the HepB vaccine birth dose administered from birth through age 3 days. This was an increase from 71.8% for children born during 2013–2014. By age 24 months, 91.0% of children had received at least 3 doses of HepB vaccine. In 2017, 25.8% of adults age 19 years or older had received at least 3 doses of HepB vaccine; the coverage was 34.3% and 16.6% for adults age 19 through 49 years and age 50 years or older, respectively. Among HCP with direct patient contact, 70% had received at least 3 doses of HepB vaccine.

Hepatitis B Prevention Strategies

HepB vaccination is the mainstay of hepatitis B prevention efforts. A comprehensive strategy to eliminate HBV transmission includes universal vaccination of infants beginning at birth, routine vaccination of previously unvaccinated children less than age 19 years, and vaccination of adults at risk for HBV infection, including those requesting protection from HBV without acknowledgement of a specific risk factor. It also includes universal testing of pregnant women for HBsAg to identify newborns who require immunoprophylaxis for prevention of perinatal infection and to pregnant women who can benefit from antiviral therapy to reduce perinatal transmission.

Hepatitis B Vaccine

Hepatitis B Vaccines

- DTaP-HepB-IPV (Pediatrix)
- DTaP-IPV-Hib-HepB (Vaxelis)
- HepA-HepB (Twinrix)
- HepB (Engerix-B, Heplisav-B, and Recombivax HB)

The first recombinant HepB vaccine, Recombivax HB, was licensed in the United States in 1986. A second recombinant vaccine, Engerix-B, was licensed in 1989. Recombivax HB and Engerix-B are available in both pediatric and adult formulations. A third recombinant vaccine with a novel

adjuvant, Heplisav-B, was licensed in 2017 for use in adults age 18 years or older. 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.

There are two combination vaccines that contain HepB vaccine. DTaP-HepB-IPV (Pediarix) is licensed for children age 6 weeks through 6 years. HepA-HepB (Twinrix) is licensed for persons age 18 years or older. A third combination vaccine, DTaP-IPV-Hib-HepB (Vaxelis), is licensed in the United States.

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Characteristics

Hepatitis B Vaccine Characteristics

- Administered by intramuscular injection
- Contain yeast protein
- Contain aluminum adjuvant (Engerix-B and Recombivax HB) or synthetic adjuvant (Heplisav-B)
- Some presentations contain latex
- Ingredients in combination vaccines differ; all contain antibiotics

Recombinant HepB vaccine is produced by inserting a plasmid containing the gene for HBsAg into yeast (*Saccharomyces cerevisiae* or *Hansenula polymorpha*); HepB vaccines contain yeast protein. HepB vaccines are administered by intramuscular injection. Each dose of HepB vaccine contains aluminum as an adjuvant or, for Heplisav-B, a small synthetic immunostimulatory oligodeoxynucleotide 1018 adjuvant. Each dose of DTaP-HepB-IPV contains antibiotics neomycin and polymyxin B; each dose of DTaP-IPV-Hib-HepB contains neomycin, polymyxin B, and streptomycin; each dose of HepA-HepB contains neomycin. HepB vaccines contain no preservative. Presentations of HepB vaccines contain latex rubber. Specific ingredients in combination vaccines containing HepB vaccine differ.

Recombivax HB and Engerix-B are available in both pediatric and adult formulations and are typically administered as a 3-dose series on a 0, 1, 6 month schedule. Although their antigen content differs, the two vaccines are interchangeable except for a 2-dose series for adolescents age 11 through 15 years, for which only Recombivax HB is approved. Heplisav-B is administered as a 2-dose series on a 0, 1 month schedule and is approved for persons age 18 years or older.

Vaccination Schedule and Use

Hepatitis B Vaccination Schedule

- Infants: See Hepatitis B vaccine schedule for infants
- Adolescents: All children and adolescents through age 18 years not previously vaccinated
 - 3-dose series at 0, 1, 6 months
 - Adolescents age 11 through 15 years may use 2-dose series of Recombivax HB separated by 4 to 6 months
- Adults: All unvaccinated adults at risk for or requesting protection from HBV infection
 - 2-dose series at 0 and 1 month (Heplisav-B) or 3-dose series at 0, 1 and 6 months (Engerix-B and Recombivax HB)
 - 3-dose series at 0, 1 and 6 months (Twinrix)
 - 3-dose series with doses at 0, 7, 21-30 days, and booster 12 months after dose 1 (Twinrix, accelerated)

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Infants and Children

HepB vaccination is recommended for all medically stable infants weighing at least 2,000 grams within 24 hours of birth. Only single-component vaccine should be used for the birth dose and doses administered before age 6 weeks. The usual schedule is 0, 1 through 2, and 6 through 18 months.

All pregnant women found to be HBsAg-positive should have their sera tested for HBV DNA. If HBV DNA levels are greater than 200,000 IU/mL, Tenofovir (preferable) or lamivudine should be administered to the pregnant woman starting at the beginning of the third

trimester and continued one to three months after birth. Infants born to mothers who are HBsAg-positive should receive the HepB vaccine birth dose and HBIG within 12 hours of birth. HepB vaccine and HBIG should be administered in separate limbs. For infants weighing less than 2,000 grams, the birth dose should not be counted as part of the vaccine series because of potentially reduced immunogenicity; 3 additional doses of vaccine (for a total of 4 doses) should be administered beginning when the infant reaches age 1 month. Infants whose mothers are HBsAg-positive should receive the last dose by age 6 months but not before age 24 weeks.

Infants born to mothers whose HBsAg status is unknown should receive the HepB birth dose within 12 hours of birth. Infants weighing less than 2,000 grams should also receive HBIG within 12 hours of birth. The mother's HBsAg status should be assessed as soon as possible. If the mother is determined to be HBsAg-positive, infants weighing at least 2,000 grams should also receive HBIG as soon as possible but no later than age 7 days. As with infants born to HBsAg-positive mothers, for infants weighing less than 2,000 grams, the birth dose should not be counted as part of the vaccine series because of potentially reduced immunogenicity; 3 additional doses of vaccine (for a total of 4 doses) should be administered beginning when the infant reaches age 1 month. Infants with mothers whose HBsAg status is unknown should receive the last dose by age 6 months but not before age 24 weeks.

Preterm infants weighing less than 2,000 grams have a decreased response to HepB vaccine administered before 1 month of age. However, by chronologic age 1-month preterm infants, regardless of initial birth weight or gestational age, are as likely to respond as adequately as full-term infants. Preterm infants of low birth weight whose mothers are HBsAg-negative can receive the first dose of HepB vaccine at chronologic age 1 month. Preterm infants discharged from the hospital before chronologic age 1 month can receive HepB vaccine at discharge if they are medically stable and have gained weight consistently, even if they are less than 2,000 grams.

The third HepB dose must be administered at least 8 weeks after the second dose, and at least 16 weeks after the first dose. The minimum interval between the first and second dose is 4 weeks.

Hepatitis B vaccine schedules for infants (≥2,000 g birthweight), by maternal HBsAg status

Maternal HBsAg Status	Single-antigen vaccine dose	Single-antigen vaccine age indications	Single-antigen + combination vaccine [†] dose	Single-antigen + combination vaccine [†] age indications
Positive	1	Birth (≤12 hrs)	1	Birth (≤12 hrs)
	HBIG [§]	Birth (≤12 hrs)	HBIG [§]	Birth (≤12 hrs)
	2	1-2 mos	2	2 mos
	3	6 mos [¶]	3	4 mos
	N/A	N/A	4	6 mos [¶]
Unknown*	1	Birth (≤12 hrs)	1	Birth (≤12 hrs)
	2	1-2 mos	2	2 mos
	3	6 mos [¶]	3	4 mos
	N/A	N/A	4	6 mos [¶]
Negative	1	Birth (≤24 hrs)	1	Birth (≤24 hrs)
	2	1-2 mos	2	2 mos
	3	6-18 mos [¶]	3	4 mos
	N/A	N/A	4	6 mos [¶]

* Mothers should have blood drawn and tested for HBsAg as soon as possible after admission for delivery; if the mother is found to be HBsAg positive, the infant should receive HBIG as soon as possible but no later than age 7 days.

[†] Pediarix and Vaxelis should not be administered before age 6 weeks.

[§] HBIG should be administered at a separate anatomical site from vaccine.

[¶] The final dose in the vaccine series should not be administered before age 24 weeks (164 days).

Hepatitis B vaccine schedules for infants (<2,000 g birthweight), by maternal HBsAg status

Maternal HBsAg Status	Single-antigen vaccine dose	Single-antigen vaccine age indications	Single-antigen + combination vaccine [†] dose	Single-antigen + combination vaccine [†] age indications
Positive	1	Birth (≤12 hrs)	1	Birth (≤12 hrs)
	HBIG [§]	Birth (≤12 hrs)	HBIG [§]	Birth (≤12 hrs)
	2	1 mos	2	2 mos
	3	2-3 mos	3	4 mos
	4	6 mos [¶]	4	6 mos [¶]
Unknown*	1	Birth (≤12 hrs)	1	Birth (≤12 hrs)
	HBIG [§]	Birth (≤12 hrs)	HBIG [§]	Birth (≤12 hrs)
	2	1 mos	2	2 mos
	3	2-3 mos	3	4 mos
	4	6 mos [¶]	4	6 mos [¶]
Negative	1	Hospital discharge or age 1 mo	1	Hospital discharge or age 1 mo

Maternal HBsAg Status	Single-antigen vaccine dose	Single-antigen vaccine age indications	Single-antigen + combination vaccine [†] dose	Single-antigen + combination vaccine [†] age indications
	2	2 mos	2	2 mos
	3	6–18 mos [¶]	3	4 mos
	N/A	N/A	4	6 mos [¶]

[†] Pediarix and Vaxelis should not be administered before age 6 weeks.

[§] HBIG should be administered at a separate anatomical site from vaccine.

[¶] The final dose in the vaccine series should not be administered before age 24 weeks (164 days).

DTaP-HepB-IPV (Pediarix)

DTaP-HepB-IPV vaccine is approved for use as a 3-dose series for children age 6 weeks through 6 years. It is administered to infants at age 2, 4, and 6 months. The minimum intervals for DTaP-HepB-IPV vaccine are determined by the DTaP component. The 3 doses must be separated by at least 4 weeks between doses. Because the minimum age for the first dose of DTaP-HepB-IPV vaccine is 6 weeks, this vaccine cannot be used for the birth dose of HepB vaccine. The final dose of DTaP-HepB-IPV vaccine should be administered at age 24 weeks or older, the minimum age for completion of the HepB vaccine series. When DTaP-HepB-IPV vaccine is used to provide 3 doses at age 2, 4, and 6 months (based on the DTaP and IPV schedules), this will result in a 4-dose HepB vaccine series, which is acceptable.

DTaP-IPV-Hib-HepB (Vaxelis)

DTaP-IPV-Hib-HepB is approved for use as a 3-dose series for children age 6 weeks through 4 years. It is administered to infants at age 2, 4, and 6 months. The minimum intervals for DTaP-IPV-Hib-HepB vaccine are determined by the DTaP component. The 3 doses must be separated by at least 4 weeks between doses. Because the minimum age for the first dose of DTaP-IPV-Hib-HepB vaccine is 6 weeks, this vaccine cannot be used for the birth dose of HepB vaccine. The final dose of DTaP-IPV-Hib-HepB vaccine should be administered at age 24 weeks or older, the minimum age for completion of the HepB vaccine series. When DTaP-IPV-Hib-HepB vaccine is used to provide 3 doses at age 2, 4, and 6 months (based on the DTaP and IPV schedules), this will result in a 4-dose HepB vaccine series, which is acceptable.

Adolescents

Routine HepB vaccination is recommended for all children and adolescents through age 18 years. All children not previously vaccinated with HepB vaccine should be vaccinated.

An alternative HepB vaccination schedule for adolescents age 11 through 15 years consists of 2 adult doses of Recombivax HB separated by 4 to 6 months. The 2-dose series should be completed by the 16th birthday.

Adults

HepB vaccine 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 is not a requirement for vaccination.

Adults recommended for HepB vaccination include:

- Persons at risk for infection by sexual exposure, including sex partners of HBsAg-positive persons, persons with more than one sex partner during the previous 6 months, persons seeking evaluation or treatment for a sexually transmitted infection (STI), and MSM
- Household contacts of persons who are HBsAg-positive. They should be screened first for HBsAg, anti-HBc and anti-HBs.
- Persons at risk for infection by percutaneous or mucosal exposure to blood, including current or recent PWID, household contacts of HBsAg-positive persons, residents and staff of facilities for developmentally disabled persons, health care and public safety workers with risk for exposure to blood or blood-contaminated body fluids
- Persons with end-stage renal disease, including predialysis, hemodialysis, peritoneal dialysis, and home dialysis patients
- Persons with diabetes age 19 through 59 years; persons with diabetes age 60 years or older at the discretion of the treating clinician
- Persons with hepatitis C infection or chronic liver disease, including those with cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level greater than twice the upper limit of normal
- Persons traveling internationally to regions with high or intermediate levels (HBsAg prevalence of 2% or higher) of endemic HBV infection, including those who may engage in high-risk behaviors or provide health care while traveling
- Persons with human immunodeficiency virus (HIV) infection

- Persons who are incarcerated
- All other persons seeking protection from HBV infection

In settings in which a high proportion of adults have risks for HBV infection (e.g., STI/HIV testing and treatment facilities, substance use disorder treatment and prevention settings, health care settings targeting services to PWID or MSM, and correctional facilities), ACIP recommends HepB vaccination for all unvaccinated adults. In other primary care and specialty medical settings in which adults at risk for HBV infection receive care, health care providers should inform all patients about the health benefits of vaccination, risks for HBV infection, and persons for whom vaccination is recommended, and should vaccinate any adults who report risks for HBV infection or request protection from HBV infection.

Heplisav-B

Heplisav-B is approved for use in persons age 18 years or older. The schedule is 2 doses separated by 1 month. Even though Heplisav-B cannot be combined with a different HepB vaccine (e.g., Engerix-B, Recombivax HB, Twinrix) to complete a series, any 2 Heplisav-B doses separated by 4 weeks constitutes a complete HepB vaccine series, even if other doses of Engerix-B, Recombivax HB, or Twinrix, are administered before, after, or between the 2 doses of Heplisav-B, regardless of the interval between these other vaccines and Heplisav-B.

HepA-HepB (Twinrix)

The vaccine is administered in a 3-dose series on a 0, 1, 6 months schedule. Dose 1 and dose 3 should be separated by at least 6 months. Dose 1 and dose 2 should be separated by at least 4 weeks, and dose 2 and dose 3 should be separated by at least 5 months. An alternative Twinrix schedule consists of doses at 0, 7, 21–30 days, and a booster dose at 12 months after the first dose. Because the HepB component of Twinrix is equivalent to a standard adult dose of HepB vaccine, Twinrix can be administered on a single-antigen HepB vaccine schedule; the minimum interval recommendations will be met. Single-antigen HepB vaccine can be used to complete a series begun with Twinrix or vice versa.

Immunogenicity and Vaccine Efficacy

Hepatitis B Vaccine Efficacy

- Over 90% of infants, children, adolescents, and healthy adults <40 years develop protective antibody response following complete series
- 80 to 100% effective in preventing infection or clinical hepatitis following complete series
- Larger doses or increased number of doses necessary for dialysis patients and immunocompromised persons
- Booster doses not recommended for immunocompetent persons

More than 90% of infants, children, and adolescents and more than 90% of healthy adults younger than age 40 years develop a protective antibody response following a complete HepB vaccine series. However, there is an age-specific decline in immunogenicity. By 60 years, only 75% develop protective antibody titers. In adults receiving Heplisav-B, 90 to 100% develop adequate antibody after the 2-dose series.

Infants born to women who are HBsAg-positive are at high risk of HBV transmission and chronic HBV infection. HepB vaccination and 1 dose of HBIG administered within 24 hours after birth are 85% to 95% effective in preventing chronic HBV infection. HepB vaccine administered alone beginning within 24 hours after birth is 70% to 95% effective in preventing perinatal HBV infection.

HepB vaccine is 80% to 100% effective in preventing infection or clinical hepatitis in those who receive the complete vaccine series. Larger vaccine doses (2 to 4 times the normal adult dose) or an increased number of doses are required to induce protective antibody in most dialysis patients age 20 years or older and may also be necessary for other immunocompromised persons age 20 years or older. The recommended dosage of vaccine differs depending on the age of the recipient and type of vaccine.

Available data show that vaccine-induced antibody levels decline with time. However, immune memory remains intact for more than 30 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 those who responded to vaccine.

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

For dialysis patients who did respond to vaccine, the need for booster doses should be assessed by annual testing of vaccine recipients for antibody levels, and a booster dose should be provided when antibody levels decline below 10 mIU/mL.

Seroconversion rates and postvaccination anti-HBs titers are similar among adolescents age 11 through 15 years vaccinated using the 2 adult-dose Recombivax HB schedule compared to those vaccinated using 3 doses.

Serologic Testing of Vaccine Recipients

Serologic Testing

Prevaccination

- Consists of testing for HBsAg, anti-HBs, and anti-HBc
- Recommended for:
 - Household, sexual, or needle-sharing contacts of HBsAg-positive persons
 - HIV-positive persons
 - Persons with elevated ALT/AST of unknown etiology
 - Hemodialysis patients
 - MSM
 - Past or current PWID

Postvaccination

- Not routinely recommended
- Recommended for:
 - Infants born to HBsAg+ women or women with unknown HBsAg status
 - HCP and public safety workers
 - Hemodialysis patients
 - HIV-infected persons
 - Other immunocompromised persons
 - Sex partners of HBsAg+ persons
- Results:
 - Anti-HBs \geq 10 mIU/mL = Immune
 - Anti-HBs $<$ 10 mIU/mL = Revaccinate

Prevaccination Serologic Testing

Vaccination of persons immune to HBV because of current or previous infection or HepB vaccination does not increase the risk for adverse events. However, in populations that have high rates of previous HBV infection, prevaccination testing might reduce costs by avoiding vaccination of persons who are already immune. Prevaccination testing consists of testing for HBsAg, anti-HBs, and anti-HBc. Serologic testing should not be a barrier to vaccination of susceptible persons, especially in populations that are difficult to access. Testing is not a requirement for vaccination, and in settings where testing is not feasible, vaccination of recommended persons should continue. The first dose of HepB vaccine should typically be administered immediately after collection of the blood for serologic testing. Prevaccination testing is recommended for household, sexual, or needle-sharing contacts of HBsAg-positive persons; HIV-positive persons; persons with elevated ALT/AST of unknown etiology; hemodialysis patients; MSM; and past or current PWID.

Serologic testing is not recommended before routine vaccination of infants, children, or adolescents.

Postvaccination Serologic Testing

Testing for immunity following vaccination is not recommended routinely. However, testing is recommended for persons whose subsequent management depends on knowledge of their immune status, including infants born to HBsAg-positive mothers or mothers whose HBsAg status remains unknown (e.g., when a parent or person with lawful custody safely surrenders an infant confidentially shortly after birth), HCP and public safety workers, hemodialysis patients and others who might require outpatient hemodialysis (e.g., predialysis, peritoneal dialysis, and home dialysis), HIV-infected persons, other immunocompromised persons (e.g., hematopoietic stem-cell transplant recipients or persons receiving chemotherapy), and sex partners of HBsAg-positive persons.

Testing should be performed 1 to 2 months after administration of the final dose of the vaccine series using a method that allows determination of a protective concentration of anti-HBs (greater than or equal to 10 mIU/mL). Persons found to have anti-HBs concentrations of greater than or equal to 10 mIU/mL after the primary vaccine series are considered to be immune. Immunocompetent persons have long-term protection and do not need further periodic testing to assess anti-HBs levels. Immunocompromised persons might need annual testing to assess anti-HBs concentrations.

Persons found to have anti-HBs concentrations less than 10 mIU/mL after the primary vaccine series should be revaccinated. Administration of all doses in the second series, on an appropriate schedule, followed by anti-HBs testing 1 to 2 months after the final dose, is usually more practical than serologic testing after one or more doses of vaccine (except for when revaccinating infants born to HBsAg-positive mothers).

Infants born to HBsAg-positive women or HBsAg-unknown women whose status is not determined should be tested for HBsAg and anti-HBs 1 to 2 months after completion of the final dose of the HepB vaccine series, at age 9 through 12 months (generally at the next well-child visit following completion of the HepB vaccine series). If HBsAg is not present and anti-HBs antibody is greater than or equal to 10 mIU/mL, children can be considered to be protected.

HCP who have contact with blood and body fluids of patients who might be infected with HBV, or who are at ongoing risk for injuries with sharp instruments or needlesticks, should be tested for antibody 1 to 2 months after completion of the hepatitis B vaccine series. Increasingly, HCP with documentation of routine HepB vaccination received the series in infancy or as catch-up vaccination in adolescence without postvaccination testing, but they may be tested as a condition of employment. Antibody to vaccine antigen wanes over time, although protection persists in immunocompetent vaccine recipients who responded initially. A negative anti-HBs serologic response in HCP who received HepB vaccine in the distant past will not distinguish between failure to respond to the initial vaccination series (lack of protection) and response to the initial vaccination series with subsequent waning of antibody (protected). Health care institutions may measure anti-HBs upon hire or matriculation for HCP who have documentation of a complete HepB vaccine series in the past (e.g., as part of routine infant or adolescent vaccination). HCP with anti-HBs less than 10 mIU/mL should receive one or more additional doses of HepB vaccine and retesting. Institutions that decide to not measure anti-HBs upon hire or matriculation for HCP who have documentation of a complete HepB vaccine series in the past should ensure timely assessment and postexposure prophylaxis following an exposure.

Vaccine Nonresponse

Vaccine Nonresponse

- Persons who do not respond to the first HepB series should complete a second series on a 0, 1, 6 month schedule
- Retest anti-HBs 1–2 months after completion of second series

Several factors have been associated with nonresponse to HepB vaccine. These include vaccine factors (e.g., dose, schedule, injection site) and host factors (e.g., older age, male sex). Older age (40 years and older), male sex, obesity, diabetes, smoking, and chronic illness have been independently associated with nonresponse to HepB vaccine. Additional vaccine doses for persons who receive postvaccination testing and who fail to respond to a primary vaccination series administered in the deltoid muscle produce adequate response in 15% to 25% of these persons after 1 additional dose and in 30% to 50% after 3 additional doses.

Persons who do not respond to the first series of HepB vaccine should complete a second vaccine series. The second vaccine series should be given on the usual 0, 1, 6 month schedule. HCP 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 6 doses of HepB vaccine administered by the appropriate schedule in the deltoid muscle fail to develop detectable anti-HBs antibody. One reason for persistent nonresponse to HepB vaccine is chronic infection with HBV. Persons who fail to develop detectable anti-HBs after 6 doses should be tested for HBsAg and anti-HBc. Persons who are found to be HBsAg-positive should be counseled accordingly and linked to care with providers experienced in the management of chronic HBV infection. Persons who fail to respond to two appropriately administered series and who are HBsAg-negative should be considered susceptible to HBV infection and should be counseled regarding precautions to prevent HBV infection. They should also be counseled about the need to obtain HBIG prophylaxis for exposure to HBsAg-positive blood.

Occupational Postexposure Management

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

Postexposure Management of Health Care Personnel after Occupational Exposure to Blood and Body Fluids, by Health Care Personnel HepB Vaccination and Response Status

HepB Vaccination and Response Status	Postexposure testing results for source patient (HBsAg)	Postexposure testing results for HCP (anti-HBs)	HBIG* postexposure prophylaxis	Vaccination postexposure prophylaxis	Postvaccination Serologic Testing [†]
Documented responder[§] after complete series (3 or more doses)	No action needed	No action needed	No action needed	No action needed	No action needed
Documented nonresponder[¶] after 2 complete series	Positive/ unknown	**	2 doses HBIG separated by 1 month	No action needed	No action needed
	Negative	No action needed	No action needed	No action needed	No action needed
Response unknown after a complete series	Positive/ unknown	less than 10mIU/mL**	1 dose HBIG	Initiate revaccination	Yes
	Negative	less than 10mIU/mL	None	Initiate revaccination	Yes
	Any result	greater than or equal to 10 mIU/mL	No action needed	No action needed	No action needed
Unvaccinated/incompletely vaccinated or vaccine refusers	Positive/ unknown	**	1 dose HBIG	Complete vaccination	Yes
	Negative	No action needed	None	Complete vaccination	Yes

Postexposure Management of Health Care Personnel after Occupational Exposure to Blood and Body Fluids

*HBIG should be administered intramuscularly as soon as possible after exposure when indicated. The effectiveness of HBIG when administered greater than 7 days after percutaneous, mucosal, or nonintact skin exposures is unknown. HBIG and HepB vaccine should be administered in separate anatomic injection sites.

[†]Should be performed 1 to 2 months after the last dose of the HepB vaccine series (and 4 to 6 months after administration of HBIG to avoid detection of passively administered anti-HBs) using a quantitative method that allows detection of the protective concentration of anti-HBs (greater than or equal to 10 mIU/mL).

[§]A responder is defined as a person with anti-HBs greater than or equal to 10 mIU/mL after 3 or more doses of HepB vaccine.

[¶]A nonresponder is defined as a person with anti-HBs less than 10 mIU/mL after 2 complete series of HepB vaccine.

**HCP who have anti-HBs less than 10 mIU/mL, or who are unvaccinated or incompletely vaccinated, and sustain an exposure to a source patient who is HBsAg-positive or has unknown HBsAg status, should undergo baseline testing for HBV infection as soon as possible after exposure and follow-up testing approximately 6 months later. Initial baseline tests consist of total anti-HBc; testing at approximately 6 months consists of HBsAg and total anti-HBc.

Non-Occupational Exposure

Persons who have written documentation of a complete HepB vaccine series and who did not receive postvaccination testing should receive a single vaccine booster dose after non-occupational exposure to an HBsAg-positive source. Persons who are in the process of being vaccinated but who have not completed the vaccine series should complete the vaccine series and receive the appropriate dose of HBIG as soon as possible. Studies are limited on the maximum interval after exposure during which postexposure prophylaxis is effective, but the interval is unlikely to exceed 7 days for percutaneous exposure and 14 days for sexual exposures. Unvaccinated persons should receive both HBIG and a dose of HepB vaccine as soon as possible after exposure (preferably within 24 hours) and complete the HepB vaccine series according to the appropriate schedule. HepB vaccine may be administered simultaneously with HBIG in a separate injection site, i.e., separate limb.

Contraindications and Precautions to Vaccination

Hepatitis B Vaccine Contraindications and Precautions

- Contraindication
 - Severe allergic reaction to vaccine component or following a prior dose
 - History of hypersensitivity to yeast
- Precaution
 - Moderate or severe acute illness

As with other vaccines, a history of a severe allergic reaction (anaphylaxis) to a vaccine component or following a prior dose is a contraindication to further doses. Moderate or severe acute illness (with or without fever) in a patient is considered a precaution to vaccination, although persons with minor illness may be vaccinated.

In 2011, the Institute of Medicine concluded that the evidence convincingly supports a causal relationship between HepB vaccine and anaphylaxis in yeast-sensitive persons. HepB vaccination is contraindicated for persons with a history of hypersensitivity to yeast or any other vaccine component. The estimated incidence of anaphylaxis among HepB vaccine recipients is 1.1 per million vaccine doses administered.

Some presentations of HepB vaccines contain latex, which may cause allergic reactions.

Vaccination is not contraindicated in persons with a history of multiple sclerosis, Guillain-Barré syndrome, autoimmune disease (e.g., systemic lupus erythematosus or rheumatoid arthritis) or other chronic diseases.

Contraindications to combination vaccines that contain HepB vaccine include the contraindications to the individual component vaccines (e.g., DTaP, hepatitis A); specific ingredients differ by vaccine.

[Expand All](#)

Vaccination during Pregnancy

Pregnancy is not a contraindication to HepB vaccination. Limited data suggest that developing fetuses are not at risk for adverse events when HepB vaccine is administered to pregnant women. Available vaccines contain noninfectious HBsAg and should cause no risk of infection to the fetus.

Pregnant women who are identified as being at risk for HBV infection during pregnancy (e.g., persons with more than one sex partner during the previous 6 months, persons who have been evaluated or treated for an STI, recent or current PWID, or persons who have had an HBsAg-positive sex partner) should be vaccinated.

Heplisav-B is not recommended in pregnancy, based on a lack of available safety data.

Vaccine Safety

Hepatitis B Vaccine Safety

- Pain
 - 3% to 29%
- Erythema
 - 3%
- Swelling
 - 3%
- Fever
 - 1% to 6%
- Headache
 - 3%

In prelicensure trials, adverse events following HepB vaccination were most commonly injection site reactions and mild systemic reactions. Commonly reported mild adverse events from postmarketing data include pain (3% to 29%), erythema (3%), swelling (3%), fever (1% to 6%), and headache (3%).

In rare instances, other illnesses have been reported after HepB vaccination, including Guillain-Barré syndrome, chronic fatigue syndrome, neurologic disorders (e.g., leukoencephalitis, optic neuritis, and transverse myelitis), rheumatoid arthritis, type 1 diabetes, and autoimmune disease. However, no causal association between those conditions or any other chronic illness and HepB vaccine has been demonstrated. Reviews by scientific panels have also found no causal association between HepB vaccination and multiple sclerosis.

Reported episodes of alopecia (hair loss) after rechallenge with HepB vaccine suggest that vaccination might very rarely trigger alopecia. "Rechallenge" in this context means the same adverse event occurs twice, each time after sequential doses of vaccine. Some cases were transient. However, a population-based study found no statistically significant association between alopecia and Hep B vaccination.

Vaccine Storage and Handling

HepB vaccine should be maintained at refrigerator temperature between 2°C and 8°C (36°F and 46°F). Manufacturer package inserts contain additional information. For complete information on best practices and recommendations, please refer to [CDC's Vaccine Storage and Handling](#)

Surveillance and Reporting of Hepatitis B

Hepatitis B infection is nationally notifiable in the United States. For information on guidance for state and local health department staff who are involved in surveillance activities for vaccine-preventable diseases, please consult the [Manual for the Surveillance of Vaccine-Preventable Diseases](#).

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