Hepatitis B virus immunization in adults

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INTRODUCTION

There are more than 2 billion individuals with serologic evidence of hepatitis B virus (HBV) infection worldwide [1]. In 2015, the World Health Organization (WHO) estimated that there were 257 million individuals with chronic hepatitis B infection globally, of whom 887,000 died within that year due to chronic hepatitis B-associated cirrhosis and hepatocellular carcinoma [2]. Despite advances in antiviral therapy, it was estimated that only 10.5 percent of patients with chronic hepatitis B were aware of their infection, and less than 2 percent were on treatment [2]. Thus, primary prevention by vaccination to increase herd immunity remains the main focus of controlling HBV infection.

This topic will review the approach to hepatitis B immunization in adults. The use of hepatitis B vaccination in infants, children, and adolescents and the use of other prevention strategies are presented separately. (See "Hepatitis B virus immunization in infants, children, and adolescents" and "Epidemiology, transmission, and prevention of hepatitis B virus infection".)

VACCINATION FOR HBV PREVENTION

HBV infection can potentially be eradicated through global vaccination.

Globally, vaccine coverage for infants (based upon completion of the third dose of the conventional hepatitis B vaccine) has increased from 3 percent in 1992 to 85 percent in 2019 [2-5]. However, even in countries that actively advocate universal vaccination, coverage is less than

100 percent. As an example, the vaccine coverage rate for completion of third-dose hepatitis B vaccine in Taiwan increased from 88.9 percent in 1985 [6] to 98.1 percent in 2018 [7].

In the United States, vaccine coverage among adults remains low. In 2017, hepatitis B vaccination coverage (≥3 doses of the conventional hepatitis B vaccine) among adults was approximately 25.8 percent for adults aged ≥19 years, 34.3 percent among adults aged 19 to 49 years, and 16.6 percent among adults aged ≥50 years [8]. In select high-risk adults ≥19 years of age, such as travelers and patients with chronic liver disease, coverage was slightly higher (32 and 30 percent, respectively). Despite this suboptimal vaccine coverage, the incidence of acute hepatitis B has decreased by almost 90 percent in the United States (from 8.5 per 100,000 in 1990 to 1.0 per 100,000 in 2018). The rates are generally low among the young because of childhood vaccinations while the rate is highest among individuals between 40 and 49 years of age at 2.6 cases per 100,000 people [9]. New infections also continue to be seen in young adults who use injection drugs [10]. (See "Epidemiology, transmission, and prevention of hepatitis B virus infection", section on 'Epidemiology of chronic HBV'.)

While vaccination represents the cornerstone of public health measures to eradicate HBV, 5 to 10 percent of individuals do not respond to currently available vaccines. Thus, other public health measures, including health education and infection control measures, remain important. (See "Epidemiology, transmission, and prevention of hepatitis B virus infection".)

There are also concerns that individuals who are immune to hepatitis B from vaccination will be susceptible to infection from HBV S escape mutants [11]. However, despite some reports of an increasing incidence of S escape mutant detection, the overall prevalence of hepatitis B is decreasing. More detailed discussions of hepatitis B S escape mutants can be found below. (See "Epidemiology, transmission, and prevention of hepatitis B virus infection" and 'Vaccine-induced HBV S escape mutants' below.)

TYPES OF VACCINES

The development of hepatitis B vaccine is considered one of the major achievements of modern medicine. This section will review available vaccines. A discussion of novel approaches to vaccination is found below. (See 'New developments' below.)

Single-antigen vaccines — There are three different classes of single-antigen recombinant hepatitis B vaccines; these are derived from yeast, mammalian cells, or plasma. The most commonly used vaccines are the yeast-derived vaccines. Mammalian-derived vaccines are used

in select countries outside of the United States. (See 'Yeast-derived' below and 'Mammalian cell-derived' below.)

The plasma-derived vaccine was the first-generation hepatitis B vaccine and had excellent efficacy and safety. However, derivation from plasma left lingering concerns regarding the potential to transmit bloodborne infections [12]. Given these concerns and the reduced cost of recombinant vaccines [13], most countries no longer use plasma-derived vaccines.

Yeast-derived — The recombinant hepatitis B vaccines using yeast-derived hepatitis B surface antigen (HBsAg) first became available in the 1980s. Yeast-derived vaccines are produced by cloning of the HBV S gene in yeast cells. They contain nonglycosylated HBV small S protein as the envelope antigen, which must be released from the yeast cells during the manufacturing process [14]. These vaccines do not contain antigens of the pre-S regions. (See "Characteristics of the hepatitis B virus and pathogenesis of infection".)

The United States Advisory Committee on Immunization Practices (ACIP) recommends the use of the following vaccine formulations [15,16]:

- Recombinant hepatitis B vaccines (conventional)
  - Recombivax HB (10 mcg HBsAg/mL)
  - Engerix-B (20 mcg HBsAg/mL)
- Recombinant hepatitis B vaccine (CpG-adjuvanted)
  - Heplisav-B (20 mcg HBsAg/0.5 mL)

Recombivax HB and Engerix-B (referred to as conventional hepatitis B vaccines) became available in 1983 and 1989, respectively [17] and are used worldwide [18]. They use an aluminum adjuvant and typically require three doses over a six-month period to provide protection (table 1). These vaccines used to contain very small amounts of thimerosal, but those formulations were discontinued.

In November 2017, a new recombinant hepatitis B vaccine (designated HepB-CpG; sold as Heplisav-B) received approval for use in adults 18 years of age and older [19]. This vaccine consists of recombinant HBsAg with a novel immunostimulatory adjuvant [20,21]. The vaccine is administered as two intramuscular doses given one month apart [22]. In the European Union, this vaccine was approved for use in February 2021 [23]. The accelerated regimen used with this vaccine has the advantage of providing more rapid immune protection and increases the likelihood of completing the vaccine series.

In the United States, HepB-CpG is approved by the US Food and Drug Administration (FDA) for adults aged 18 and older; however, there are no clinical studies on pregnant women, and Heplisav should be avoided in pregnancy [22]. In addition, the safety and effectiveness in children and patients receiving hemodialysis have not been established. More detailed information on the approach to vaccination in these populations is presented elsewhere. (See "Hepatitis B virus immunization in infants, children, and adolescents" and 'Patients on dialysis and immunocompromised hosts' below.)

The conventional recombinant hepatitis B vaccines are extremely safe, and the overall seroconversion rate is >90 percent in healthy adults using the definition of >10 milli-international units/mL hepatitis B surface antibody (anti-HBs) as a positive response. The rate of protection decreases with increasing age from more than 90 percent in children and young adults, to 86 percent in the fourth decade, and 47 percent in the sixth decade [24]. The response rate is slightly lower in obese individuals, smokers, and men, and significantly lower in patients with diabetes, cirrhosis, chronic renal failure, organ transplant recipients, children with celiac disease, and immunosuppressed patients. In patients on chronic hemodialysis, the response rate to hepatitis B vaccines is 50 to 60 percent [25]. Despite the lower seroconversion rate, the risk of hepatitis B infection is 70 percent lower in the vaccinated patients when compared with nonvaccinated patients undergoing chronic hemodialysis [26].

Clinical trials comparing HepB-CpG (the recombinant vaccine that uses a novel immunostimulatory adjuvant) with the recombinant hepatitis B vaccine Engerix-B found that seroprotective anti-HBs levels (>10 milli-international units/mL) were achieved in 90 to 100 percent of patients receiving HepB-CpG versus 70 to 90 percent of those receiving Engerix-B [20,27-29]. These studies included healthy adults, as well as those over age 40 and patients with type 2 diabetes mellitus, who tend to have a lower response rate. One of the studies compared 4376 persons who received the HepB-CpG vaccine with 2289 persons who received Engerix-B [29]. In the per-protocol analysis, the proportion of subjects with seroprotective anti-HBs after two doses of HepB-CpG versus three doses of Engerix-B were 95.4 versus 81.3 percent in the overall cohort, respectively. The response rates for HepB-CpG were higher in all subgroups (100 versus 93 percent in subjects aged 18 to 29 years; 91.6 versus 72.6 percent in subjects aged 60 to 70 years; 90.0 versus 65.1 percent among diabetics; 94.7 versus 75.4 percent in obese individuals; and 95.9 versus 78.6 percent among smokers); however, the biggest differences were in those known to have a poorer response to conventional hepatitis B vaccine. In a retrospective study of patients with chronic liver disease and other comorbidities, the likelihood of achieving an immune response was 2.7 times higher in those who received Heplisav-B compared to those who received Engerix-B (adjusted odds ratio 2.74, 95% CI 1.31-5.71) [30].

A discussion of adverse reactions to the different vaccines is found below. (See 'Adverse reactions' below.)

Mammalian cell-derived — Mammalian cell-derived vaccines contain pre-S epitopes in addition to the S antigen [31]. A recombinant hepatitis B vaccine (trivalent), sold as Prehevbrio, was approved for use in the United States in December 2021 [32]. The vaccine contains the small (S), middle (pre-S2), and large (pre-S1) hepatitis B surface antigens, copurified from genetically modified Chinese hamster ovary cells, and an alum adjuvant. This vaccine has also been used in Israel.

In clinical trials of young adults and children, the trivalent vaccine was found to produce anti-HBs titers ≥10 milli-international units/mL at rates similar to the monovalent vaccine (eg, Engerix) [32,33]. However, in older adults, the immunogenicity of the trivalent vaccine appears to be superior. In a randomized trial of 1607 adults, the percentage of participants ≥45 years of age who achieved an anti-HBs titer of ≥10 milli-international units/mL 24 weeks after completing the vaccine series was greater in those receiving the trivalent versus the monovalent vaccine (89.4 versus 73.1 percent, respectively; difference 16.4 percent, 95% CI 12.2-20.7) [34]. The side effect profile of the trivalent vaccine was similar to that of the monovalent vaccine, but the frequency of side effects, such as injection site pain, tenderness, and myalgias, was higher.

Combination vaccines — Hepatitis B vaccine has been successfully combined with several other vaccines, such as hepatitis A vaccine and a vaccine that combines diphtheria, tetanus, acellular pertussis, and inactivated poliovirus. The immunogenicity of these multivalent vaccines is similar to that of the univalent vaccines. These combination vaccines reduce the number of injections, resulting in higher compliance.

Hepatitis A-hepatitis B vaccine (HepA-HepB vaccine; Twinrix) includes both recombinant hepatitis B vaccine and hepatitis A vaccine and is approved for use in adults in the United States and Europe and in children in some countries [35-37]. Approval was based upon data from 1551 study participants from 11 clinical trials who received HepA-HepB vaccine on a 0-, 1-, and 6-month schedule. An immune response against hepatitis A and B was observed in 99.9 and 98.5 percent of vaccinees, respectively. An accelerated dosing schedule (with doses given at 0, 7, and 21 to 30 days, and a booster at 12 months) has also been approved. Its main potential advantage is convenience and improved compliance for those who require vaccination against both hepatitis viruses.

A more detailed discussion of the combination diphtheria-tetanus toxoids-acellular pertussis-recombinant hepatitis B inactivated poliovirus vaccine (DTaP-HepB-IPV; Pediarix) is found

elsewhere. (See "Hepatitis B virus immunization in infants, children, and adolescents", section on 'Vaccine formulations' and "Standard immunizations for children and adolescents: Overview", section on 'Routine schedule'.)

APPROACH TO VACCINATION

Indications — Vaccination with a complete HBV series has few adverse events and can result in immunity in >90 percent of healthy adults aged <40 years, although the response can decrease with age [15]. (See 'Types of vaccines' above.)

Our approach to HBV vaccination depends in part upon the patient population, and is consistent with recommendations from the United States Advisory Committee on Immunization Practices (ACIP) [38]:

- **Adults at high risk for HBV infection** – We recommend HBV vaccination for adults who are at high risk for acquiring HBV infection, regardless of age. Persons at high risk for acquiring HBV infection are summarized in the table (table 2) and discussed in detail in a separate topic review.(See "Epidemiology, transmission, and prevention of hepatitis B virus infection".)

  In low prevalence areas, sexual intercourse and injection drug use are the major routes of spread in adults. As an example, United States surveillance data from 2019 found that, when risk data was available, injection drug use or having multiple sexual partners were reported in 35 and 23 percent of acute HBV cases, respectively [39].

- **Adults <60 years of age without risk factors for HBV** – We suggest routine hepatitis B vaccination for adults <60 years of age without risk factors for HBV infection. The ACIP updated their guidelines to recommend routine hepatitis B vaccination for this population in March 2022 [38,40].

  Prior to that, vaccination was only recommended for adults if they had risk factors for HBV infection or were seeking protection from HBV. This change in recommendation stems from the low rate of HBV immunity among adults in the United States, an increase in incidence of acute HBV infection among adults in their 40s in recent years, and the fact that many people may not recognize they are at risk of HBV infection [38].

- **Adults ≥ 60 years of age without known risk factors for HBV** – Providers should discuss the risks and benefits of hepatitis B vaccination with those ≥60 years of age without known risk factors for HBV. Although the ACIP does not suggest routine hepatitis B vaccination for

such persons, vaccination should be administered to anyone seeking protection from HBV infection.

In some adults, prevaccination testing should be performed to screen for prior or active HBV; however, prevaccination screening is not mandatory if it is perceived to hinder or to delay vaccination, and the first dose of the vaccine can be administered pending the results. A more detailed discussion of prevaccination screening and the approach to vaccination in persons with isolated antibody to hepatitis B core antigen (anti-HBc) are discussed below. (See 'Prevaccination screening' below and 'Patients who have isolated anti-HBc' below.)

Universal hepatitis B vaccination is recommended for all neonates, regardless of maternal hepatitis B surface antigen (HBsAg) status. For infants born to HBsAg-positive mothers, hepatitis B immune globulin is also indicated. Detailed discussions of childhood HBV immunization and prevention of mother-to-child transmission, including the use of antiviral therapy for mothers with high serum HBV DNA, are presented elsewhere. (See "Hepatitis B virus immunization in infants, children, and adolescents" and "Hepatitis B and pregnancy", section on 'Prevention of mother-to-child transmission'.)

Prevaccination screening — In the United States, screening for HBV is indicated for all adults ≥18 years of age, regardless of risk, unless there is documentation of receiving a complete vaccine series and having an appropriate response to vaccination [41]. Previously, screening was only recommended for those at high risk for acquiring HBV and those at risk for severe outcomes (eg, persons initiating immunosuppressive therapy) (table 3) [42,43]. In other countries, the approach to screening depends upon the prevalence of HBV and the availability of resources. Screening for HBV is discussed in detail elsewhere. (See "Hepatitis B virus: Screening and diagnosis in adults", section on 'Approach to screening and testing'.)

Some individuals may choose to defer vaccination until after the results of the screening tests have been obtained. While this approach is reasonable for certain individuals (eg, those who are likely to follow-up on the results and subsequent vaccination if needed), screening should not present a barrier to vaccination. Thus, for those who have not been vaccinated or the history of vaccination is unknown, we typically administer the first dose at the time of screening and complete the series in those who warrant vaccination (table 4). Administration of hepatitis B vaccine to individuals who are infected or immune will not result in any adverse outcomes.

Patients who have isolated anti-HBc — We do not routinely vaccinate immunocompetent persons with isolated antibody to anti-HBc (total or IgG positive and HBsAg and anti-HBs negative) if they have risk factors for HBV infection (eg, born in an endemic area, engage in

high-risk behaviors). Such patients likely had prior HBV exposure and will not respond to vaccination.

By contrast, we administer the full series of the hepatitis B vaccine to patients with isolated anti-HBc who are from low endemic areas and have no risk factors for HBV, given the possibility of a false-positive result [44]. We also vaccinate immunocompromised patients who have isolated anti-HBc, including those with HIV, since studies suggest these patients may have resolved HBV infection and loss of anti-HBs, and would respond to vaccination [45]. A more detailed discussion of the etiology of isolated anti-HBc is found elsewhere. (See "Hepatitis B virus: Screening and diagnosis in adults", section on 'Isolated anti-HBc'.)

Choice of vaccine

For most persons — For most persons, any one of the available vaccines is appropriate and effective, and the choice of vaccine is often dictated by local guidelines and availability. (See 'Types of vaccines' above.)

In general, we prefer one of the three available recombinant yeast-derived, single-antigen vaccines that are available for persons over 18 years of age. The one exception is pregnant persons, for whom conventional hepatitis B vaccines (Engerix-B or Recombivax HB) should still be used. (See 'During pregnancy' below.)

The ACIP does not indicate a preference regarding which yeast-derived vaccine to use for nonpregnant persons [16,40]. However, if there is a choice of vaccine, our approach is as follows:

- We continue to use the recombinant hepatitis B vaccines that use an aluminum adjuvant (Engerix-B, Recombivax HB) for most persons. There is extensive experience with these vaccines, and they are safe and immunogenic in most healthy adults. They are widely available and at lower cost than the newer vaccines. (See 'Yeast-derived' above.)

- We consider the recombinant hepatitis B vaccine that uses a novel immunostimulatory adjuvant (HepB-CpG) for adults who are unlikely to follow up with the three-dose series and those who need rapid protection against HBV. This vaccine is also reasonable for health care workers who did not respond to the conventional vaccine (Engerix-B, Recombivax HB) or who have failed a second single- or double-dose revaccination attempt.

  HepB-CpG can also be considered for those who are less likely to respond to HBV vaccines (eg, patients on dialysis, immunocompromised persons). However, the decision to vaccinate with HepB-CpG should be made on a case-by-case basis. Although HepB-CpG

appears more immunogenic, data are more limited compared with Engerix-B and Recombivax HB, and its safety and efficacy in these patient populations have not been established. (See 'Adverse reactions' below and 'Single-antigen vaccines' above.)

More detailed discussions of hepatitis B vaccination in specific populations are presented in separate topic reviews. (See "Immunizations in patients with end-stage kidney disease", section on 'Hepatitis B virus vaccine' and "Prevention of hepatitis B virus infection in adults with HIV", section on 'Vaccination' and "Immunizations in solid organ transplant candidates and recipients", section on 'Hepatitis B' and "Immunizations in hematopoietic cell transplant candidates and recipients", section on 'Hepatitis B' and "Immunizations in adults with cancer", section on 'Hepatitis B vaccine' and "Immunizations for adults with chronic liver disease", section on 'Hepatitis B vaccine'.)

People should complete the vaccine series using the same type of vaccine if possible (table 1). If this is not feasible (eg, due to vaccine availability), vaccination should not be deferred. The single-antigen vaccines can be used interchangeably, except that a two-dose vaccine series should only be used when both doses consist of HepB-CpG [16]. Vaccine series that consist of a combination of a dose of HepB-CpG and a dose of another HBV vaccine should consist of three total vaccine doses:

- The vaccine series should generally adhere to the typical three-dose schedule with minimum intervals of 4 weeks between doses 1 and 2, 8 weeks between doses 2 and 3, and 16 weeks between doses 1 and 3.
- Two doses of HepB-CpG administered at least four weeks apart are sufficient, even if the patient received a single earlier dose of other hepatitis B vaccines.

Doses administered at less than the minimum interval should be repeated. Additional information on vaccine administration is found below. (See 'Vaccine administration' below.)

In the United States, a mammalian cell-derived recombinant hepatitis B vaccine (trivalent), which includes pre-S1 and pre-S2 antigens and alum, was approved for use in December 2021. Although this vaccine appears to be more immunogenic in those >45 years of age [34], the advantage of using this vaccine versus one of the available yeast-derived vaccines is unclear. When compared with HepB-CpG, it requires three versus two doses, and it is associated with a higher frequency of side effects than Engerix-B. In addition, there are no data on the use of this vaccine in children, pregnant persons, or persons on dialysis. More detailed information on the efficacy of this vaccine is described above. (See 'Mammalian cell-derived' above.)

During pregnancy — If hepatitis B vaccination is indicated during pregnancy, one of the conventional recombinant vaccines (eg, Recombivax HB, Engerix-B) should be used. These hepatitis B vaccines have no teratogenic effects and can be administered during pregnancy [46,47]. A combined hepatitis A virus (HAV) recombinant HBV vaccine is also available and safe for pregnant individuals who have indications for vaccination against both viruses. (See "Immunizations during pregnancy".)

HepB-CpG and the mammalian cell-derived recombinant hepatitis B vaccine (trivalent) should not be used during pregnancy given the paucity of efficacy and safety data in this population.

VACCINE ADMINISTRATION

This section will review administration of the recombinant hepatitis B vaccines. Additional information regarding the different types of vaccines is found above. (See 'Types of vaccines' above.)

Dose regimens — Three yeast-derived recombinant hepatitis B vaccines have been licensed in the United States. The two conventional hepatitis B vaccines (Engerix-B and Recombivax HB) use an aluminum adjuvant, whereas the most recently approved vaccine (referred to as HepB-CpG, sold as Heplisav-B) uses a novel immunostimulatory adjuvant. The dosing schedules for these vaccines, as well as the combination vaccine that includes hepatitis A vaccine, are described in the table (table 1).

The regimen for mammalian cell-derived recombinant vaccines is similar to conventional hepatitis B vaccines, with a total of three doses administered over six months (at 0, 1, and 6 months).

Vaccines should be administered intramuscularly since deposition of the vaccine into adipose tissue results in a lower seroconversion rate [48]. Thus, the deltoid is the preferred site in adults, while the vastus lateralis is preferred in infants. Longer needles should be used in overweight individuals.

Missed doses — An interruption in the vaccination schedule does not require restarting the entire series of vaccination or adding extra doses [49,50]. If the vaccination series is interrupted after the first dose (table 1), the second dose should be administered as soon as possible [51]. For those receiving a three-dose series, the second and third doses should be separated by an interval of at least two months. If only the third dose is delayed, it should be administered when convenient.

Longer than recommended intervals between doses do not reduce final antibody concentrations, although protection might not be attained until the recommended number of doses has been administered [52-56]. In some patients, protective hepatitis B surface antibody (anti-HBs) titers may be attained after only one or two doses of vaccine; however, completion of the full course of vaccine is recommended to maximize the anti-HBs titer and the duration that anti-HBs can be detected. In general, the duration in which anti-HBs titer remains above protective level >10 milli-international units/mL is proportional to the peak titer achieved after completion of vaccination [57].

Patients on dialysis and immunocompromised hosts — Patients on dialysis and immunocompromised patients can receive the conventional hepatitis B vaccine or HepB-CpG. However, the safety and efficacy of HepB-CpG have not been established in these patients. (See 'Choice of vaccine' above.)

If the conventional hepatitis B vaccine is used, patients on hemodialysis should receive a higher dose of the vaccine (40 mcg of hepatitis B surface antigen [HBsAg] for Recombivax HB or Engerix-B) than patients not receiving hemodialysis (10 to 20 mcg depending upon the vaccine formulation) (table 1). Nonresponders should receive a second course of the hepatitis B vaccine using the double dose or a course of HepB-CpG, though data on efficacy are not available.

The approach to using the conventional hepatitis B vaccine in other immunocompromised patients and patients with cirrhosis is less clear, and there is no consensus. Some providers administer the usual dose of hepatitis B vaccine (ie, 10 mcg of HBsAg for Recombivax HB or 20 mcg of HBsAg for Engerix-B) for the initial series and use the double dose when the vaccine series is repeated in nonresponders (table 1). However, others use the double dose for the initial series, and then again in those who do not respond.

Additional information on dosing and administration in patients with end-stage kidney disease and in select immunocompromised hosts is found elsewhere. (See "Immunizations in patients with end-stage kidney disease", section on 'Hepatitis B virus vaccine' and "Prevention of hepatitis B virus infection in adults with HIV", section on 'Vaccination' and "Immunizations in solid organ transplant candidates and recipients", section on 'Hepatitis B' and "Immunizations in hematopoietic cell transplant candidates and recipients", section on 'Hepatitis B' and "Immunizations in adults with cancer", section on 'Hepatitis B vaccine' and "Immunizations for adults with chronic liver disease", section on 'Hepatitis B vaccine'.)

Postvaccination testing

Indications — For most persons, routine postvaccination testing to document anti-HBs seroconversion is unnecessary since the recombinant hepatitis B vaccines generally have a response rate of >90 percent. (See 'Single-antigen vaccines' above.)

However, postvaccination testing one to two months after completing the primary vaccination series is indicated in select persons with ongoing risk, as well as those who are less likely to respond to vaccination. This includes:

- Health care and public safety workers. (See "Immunizations for health care providers", section on 'Hepatitis B vaccine'.)
- Patients on chronic hemodialysis, as well as those who may require chronic dialysis in the future. (See "Immunizations in patients with end-stage kidney disease".)
- Sex partners of HBsAg-positive persons.
- Immunocompromised patients (including those with HIV infection). (See "Prevention of hepatitis B virus infection in adults with HIV", section on 'Response to vaccination'.)
- Newborns of HBsAg-positive mothers who are vaccinated at birth. The timing of postvaccination testing in this setting is discussed in detail elsewhere. (See "Hepatitis B virus immunization in infants, children, and adolescents", section on 'Postvaccination serology'.)

For persons who have had an adequate response to vaccinations (anti-HBs ≥10 milli-international units/mL), annual monitoring of anti-HBs is indicated for adults on hemodialysis, as well as for immunocompromised persons with ongoing risk. The need for booster doses and the management of nonresponders are discussed below. (See 'When a booster dose should be administered' below and 'Nonresponders' below.)

The level of 10 milli-international units/mL was arbitrarily chosen; however, clinical studies suggest that vaccinees with anti-HBs titer above this level are protected [58]. The significance of this titer was illustrated in a five-year follow-up study of 773 gay men vaccinated in 1980; the acute infection rate was seven times when the anti-HBs titer decreased below the level of 10 milli-international units/mL [59].

Nonresponders

- **Approach to revaccination** – Individuals who do not respond to the initial vaccine series should complete a second vaccine series with a single-antigen vaccine. In general, any of the recombinant yeast-derived vaccine formulations can be used. However, HepB-CpG is

not approved for use in children, pregnant women, and patients undergoing dialysis. (See 'Choice of vaccine' above and 'Patients on dialysis and immunocompromised hosts' above.)

If the conventional vaccine is used, revaccination with a double dose is reasonable for persons with impaired immune response (eg, those with HIV infection, patients on chronic hemodialysis, patients with cirrhosis awaiting liver transplantation), though high quality data in support of double versus usual dose for revaccination is lacking. A more detailed discussion of revaccination in patients with HIV is presented in a separate topic review. (See "Prevention of hepatitis B virus infection in adults with HIV", section on 'Management based upon vaccine response'.)

Retesting for anti-HBs should be performed one month after the second vaccination series. For patients receiving the conventional vaccine, the second three-dose course is successful in about 50 to 70 percent of patients [51,60]. The efficacy of HepB-CpG in nonresponders has not been established.

Nonresponders to the second course of vaccine should be tested for HBsAg and hepatitis B core antibody (anti-HBc), as some may have had undiagnosed chronic HBV infection [61]. (See "Immunizations for health care providers", section on 'Hepatitis B vaccine' and "Prevention of hepatitis B virus infection in adults with HIV", section on 'Response to vaccination'.)

Individuals who fail to respond to a second vaccine series that has been appropriately administered, and test negative for HBsAg and anti-HBc, are unlikely to benefit from further vaccination. Although these individuals may still mount an immune response and recover from HBV infection, nonresponders should be educated on how to prevent HBV infection, including the need for hepatitis B immune globulin (HBIG) after an exposure to blood or other body fluids of a person who is HBsAg positive. (See "Epidemiology, transmission, and prevention of hepatitis B virus infection", section on 'Prevention' and "Prevention of hepatitis B virus and hepatitis C virus infection among health care providers", section on 'Post-exposure management'.)

- **Reasons for lack of response** – There are three main groups of vaccine nonresponders:
  - **Underlying medical conditions** – Patients with underlying medical conditions, such as chronic kidney disease and immunosuppressed states, may have a reduced response to vaccination. In patients undergoing hemodialysis, the response rate to conventional hepatitis B vaccines containing 10 to 20 mcg of HBsAg is between 50 and 60 percent [25]. This can be improved to above 70 percent by increasing the HBsAg to 40 mcg (table 1) [62]. The response rate can also be improved by intradermal administration

of the vaccine [25]. However, intradermal injections are technically difficult, and inadvertent subcutaneous injections can result in diminished efficacy. The current policy for patients with chronic renal failure is to vaccinate them before commencement of hemodialysis. In the United States, higher doses of vaccine are recommended for patients who are already on hemodialysis or who are immunocompromised. (See "Treatment of chronic hepatitis B in patients with HIV".)

- **Genetic factors** – Healthy individuals in whom the lack of response appears to be genetically determined. Immunogenetic studies have demonstrated that certain individuals lack a dominant response gene that controls the production of anti-HBs. The absence of this gene may be marked by two extended human leukocyte antigen (HLA) haplotypes [63]. In a study from the United States, an increased incidence of individuals homozygous for the extended HLA haplotype B8, SC01, DR3 was found among nonresponders [63]. Among the responders, individuals homozygous for this haplotype developed a lower antibody level compared with heterozygotes. In another study of 52 nonresponders from Sweden, the HLA haplotype (DQB1*0604; DQA1*0102DRB1*1302) was more frequent in nonresponders [64]. However, the same HLA haplotypes could be found among responders and nonresponders, suggesting that factors other than immunogenetics may be related to nonresponse to hepatitis B vaccine.

  Individuals with celiac disease also appear to have a diminished response to HBV vaccination, possibly because of HLA haplotypes that predispose to both celiac disease and hepatitis B vaccine nonresponse [65,66].

- **Technical errors** – Some individuals may fail to respond as a result of technical errors. In some patients, the vaccine may not have been administered appropriately (eg, intragluteal injection, into fat rather than muscles). Another example is inappropriate storage conditions, such as inadvertent freezing of vaccines during shipment.

When a booster dose should be administered — The approach to booster doses depends upon the population.

Immunocompetent individuals — Routine booster doses of HBV vaccine are not recommended [18,67,68], and in most individuals, there is no reason to document vaccine response after vaccination. (See 'Postvaccination testing' above.)

However, in the event that someone had an anti-HBs checked (eg, in the setting of routine screening), and the anti-HBs level is <10 milli-international units/mL, it is reasonable to give a booster dose of vaccine and repeat titers, or repeat the vaccine series.

The response to hepatitis B vaccination is >90 percent in immunocompetent persons, and among those who respond to the initial vaccine series, protection has been estimated to persist for up to 30 years [57,59,69-74]. For most patients, protection from clinical disease is felt to occur even in the setting of declining or undetectable anti-HBs levels, due to the priming of memory cells, which are capable of eliciting an anamnestic response when challenged, as well as long-lasting cellular immunity [25,52,57,74,75].

In a cohort study conducted in Taiwan that included 6950 students vaccinated at birth, the hepatitis B serological status was assessed 6 to 18 years after vaccination [75]. Anti-HBs was positive in 44.3 percent of the subjects. A subgroup of 657 subjects who were negative for both HBsAg and anti-HBs at age 15 years received a booster dose of the vaccine; a titer of ≥10 milli-international units/mL was seen in approximately 93 percent six weeks after receiving the booster dose. However, there was no difference in the HBsAg seropositive rates after three years between those who received or did not receive a booster vaccine (0 versus 0.8 percent, respectively).

In a study of 493 Alaskan Natives, a protective effect of anti-HBs was demonstrated in 87 percent of individuals 22 years after vaccination [76]. Of the remaining 13 percent, none developed acute HBV. A follow-up study that included 243 patients who responded to the initial series found that 51 percent had an anti-HBs ≥10 milli-international units/mL 30 years after vaccination [57]. Eighty-five persons who had an anti-HBs <10 milli-international units/mL received a booster dose of vaccine, and 75 (88 percent) developed an anti-HBs ≥10 milli-international units/mL, confirming that immune memory is present in the majority of persons whose anti-HBs titer has declined to undetectable. In addition, among a subset of 44 persons who were evaluated 32 years after vaccination, all had evidence of tumor necrosis factor-alpha, interleukin 10, or interleukin 6 production by HBV surface antigen-specific T cells, regardless of their anti-HBs level [74].

Although these studies support that immune memory is present in the majority of persons who lose protective levels of antibody, others have demonstrated that a small proportion of the vaccinated population lose both the protective levels of anti-HBs and an anamnestic response [77-80]. Thus, there may be some benefit to a booster dose or a repeat vaccine series if a previously vaccinated person is subsequently found to have an anti-HBs <10 milli-international units/mL.

Individuals who are immunocompromised or receiving hemodialysis — Booster doses should be administered to the following patient groups if the antibody level declines to <10 milli-international units/mL:

- Patients on hemodialysis, since vaccine-induced protection may persist only as long as the antibody level is ≥10 milli-international units/mL [25]. (See "Immunizations in patients with end-stage kidney disease".)

- Immunocompromised persons with an ongoing risk for exposure [81]. (See "Epidemiology, transmission, and prevention of hepatitis B virus infection", section on 'Transmission of HBV' and "Prevention of hepatitis B virus infection in adults with HIV".)

In such patients, serology should be repeated to ensure a response to the booster dose. The approach to nonresponders is discussed above. (See 'Nonresponders' above.)

Other populations — The need for a booster dose in previously vaccinated health care workers, and after a potential exposure to HBV, is discussed elsewhere. (See "Prevention of hepatitis B virus and hepatitis C virus infection among health care providers" and "Management of nonoccupational exposures to HIV and hepatitis B and C in adults", section on 'Exposure to hepatitis B virus'.)

ADVERSE REACTIONS

The most common adverse reaction associated with the conventional hepatitis B vaccines (Engerix-B and Recombivax HB) is soreness over the site of injection, which occurs in fewer than 25 percent of the vaccinees. Other adverse reactions reported by 1 to 3 percent of vaccinees include low-grade fever, malaise, headache, joint pain, and myalgia. These adverse reactions are usually mild and do not result in any serious clinical sequelae.

Several rare adverse events have been described in case reports, but the strength of these associations has not been clear. As an example, a series of reports on a possible association between hepatitis B vaccination and multiple sclerosis prompted the French government in October 1998 to suspend routine school-based vaccination for hepatitis B. However, at least six subsequent studies from the United States [82-87] failed to show a statistically significant temporal or causal association between hepatitis B vaccination and multiple sclerosis.

For the recombinant hepatitis B vaccine that uses the novel immunostimulatory adjuvant (HepB-CpG), the most common adverse reactions reported within seven days of vaccination were injection site pain (23 to 39 percent), fatigue (11 to 17 percent), and headache (8 to 17 percent) [22]. The percent of patients experiencing mild and serious events is similar between the HepB-CpG and Engerix-B vaccines (45.6 versus 45.7 percent and 5.4 versus 6.3 percent, respectively) [16]. An increased risk of myocardial infarction was observed in one of three trials, and new-onset autoimmune events, including polymyalgia rheumatica, ulcerative colitis, and

autoimmune thyroiditis, were observed in two of three trials (0.2 versus 0.03 percent for HepB-CpG and Engerix-B, respectively) [88]. However, no difference in myocardial infarction was seen in a prospective cohort study of approximately 70,000 people who received at least one dose of HepB-CpG or conventional hepatitis B vaccine [89].

VACCINE-INDUCED HBV S ESCAPE MUTANTS

HBV S gene mutants have been described in infants who were infected with HBV despite an adequate hepatitis B surface antibody (anti-HBs) response to hepatitis B vaccination. These mutants have been observed in many parts of the world including China, Singapore, Taiwan, Japan, Italy, and Africa [11,90-94]. The most common mutation involves a glycine to arginine substitution at codon 145 in the "a" determinant of hepatitis B surface antigen (HBsAg). This mutation decreases binding of HBsAg to anti-HBs and may explain why these infants develop "escape" infection. The G145R mutation has also been observed in liver transplant recipients who developed recurrent HBV infection despite hepatitis B immune globulin (HBIG) prophylaxis [95,96]. Other mutations in the "a" determinant have also been described but are of unclear significance.

Most reports found that the HBV S mutations were not detected in the maternal carriers, suggesting that the mutations were selected by immune pressure (vaccine and/or HBIG). A study from Taiwan demonstrated these mutants in infants who received hepatitis B vaccine without HBIG, indicating that the vaccine alone was sufficient to select the mutations [97]. These mutants can be detected in less than 5 percent of all infants who have received hepatitis B vaccination, and only 10 to 40 percent of the vaccine failures can be attributed to HBV S mutants. Experiments in chimpanzees confirmed that these mutants are infectious.

There are concerns that the vaccine escape mutants have become more prevalent over time, causing acute infections in individuals who were previously vaccinated [98-100]. A report from Taiwan found that the prevalence of HBV S mutants in HBV DNA-positive children increased from 8 percent (8 of 103) in 1984 to 19.6 percent (10 of 51) in 1989, peaked at 28 percent (9 of 32) in 1994, and remained at 23 percent (3 of 13) in 1999 [97]. However, long-term follow-up of vaccination programs have not observed a progressive decline in the efficacy of hepatitis B vaccines or an increase in the prevalence of HBV S mutants among the pediatric population. A report from Taiwan found that the prevalence of HBV S mutants among children <15 years of age surveyed every five years from 1984 to 2009 decreased from 0.67 to 0.30 percent, and prevalence of HBsAg decreased from 10.0 to 0.6 percent [101]. A subsequent update supported that selection of vaccine escape variants is rare and does not diminish the long-term effectiveness of available HBV vaccines; in this report, the prevalence of HBsAg among those

vaccinated at birth remained at about 0.5 percent, including young adults up to 30 years of age [102].

Based upon available data, the benefits of conventional hepatitis B vaccine far outweigh the concerns of HBV S escape mutants, and vaccination programs should not be deterred because of these concerns. However, continued monitoring is necessary to determine if the prevalence of these mutants is increasing and if the protective efficacy of conventional vaccines is maintained.

There are no available data to support the use of antiviral to reduce the risk of transmission among hepatitis B patients infected with S escape mutant. Hence, the indication to use antiviral should be the same as other patients with chronic hepatitis B infected with wild-type HBV.

NEW DEVELOPMENTS

The need for multiple dosing, the observation that 5 to 10 percent of vaccinees are nonresponders, and reports of vaccine escape HBV S gene mutants remain a challenge for the production of a better vaccine.

Ways to improve the application of the vaccine — Measures that can decrease the cost of manufacturing and delivering vaccines are particularly important in regions where facilities for parenteral administration are limited. Examples of vaccines in development that may achieve these goals include: single-dose vaccines that release combinations of viral surface proteins at different times, simulating multiple dosing; and administration of hepatitis B vaccine via oral, inhaled, and nasal routes [103-114].

Ways to enhance immunogenicity — A number of methods have been proposed to reduce the nonresponse rate of conventional vaccines.

- **Intradermal inoculation** – Intradermal inoculation appears to be more immunogenic than intramuscular injections, but is technically more difficult to administer and, if not administered properly, may decrease response rates [25,115,116].

  Several studies have evaluated intradermal versus intramuscular vaccination in patients with chronic kidney disease on dialysis (a group that generally has a suboptimal response to vaccination). A meta-analysis of 12 studies concluded that an initial response was more likely with the intradermal approach but the difference was no longer significant with follow-up (6 to 60 months) [117]. In one trial, the use of topical imiquimod in conjunction

with intradermal injection led to higher seroprotection rates as well as hepatitis B surface antibody (anti-HBs) titers [118].

In other studies, the increased efficacy of intradermal inoculation was also evident in intramuscular vaccine nonresponders. In one study, for example, 50 hemodialysis patients were revaccinated either intradermally or intramuscularly with a total dose of 80 mcg of recombinant vaccine [119]. Seroconversion rates at 20 months were much higher in the group vaccinated intradermally (54 versus 0 percent) [119]. Frequent low-dose intradermal administration of hepatitis B vaccine may maintain protective anti-HBs levels in hemodialyzed patients who did not have an adequate immune response to hepatitis B vaccine [116]. (See "Immunizations in patients with end-stage kidney disease".)

- **New adjuvants** – An adjuvanted recombinant hepatitis B vaccine (Heplisav-B) consisting of hepatitis B surface antigen (HBsAg) with an adjuvant immunostimulatory phosphorothioate oligodeoxyribonucleotide received approval in the United States for adults 18 years of age and older in 2017. (See 'Yeast-derived' above.)

  Another vaccine combines HBsAg with an adjuvant containing 3'-deacylated monophosphoryl lipid A and alum (AS04) to enhance the immunogenicity. This vaccine is approved in Europe for patients older than 15 years of age with renal insufficiency, including those who are prehemodialysis and those on hemodialysis. The use of the HBsAg/AS04 vaccine has been supported by several studies [120-123]. In one study involving 105 individuals aged 20 to 60 years who were nonresponders to commercially available hepatitis B vaccine, HBsAg/AS04 looked promising [120].

- **DNA vaccines** – Vaccines that contain naked DNA (plasmids that contain the HBV S gene) can be injected intramuscularly. HBsAg is expressed in the muscle cells. The intracellular production of HBsAg stimulates production of anti-HBs. In addition, the newly synthesized HBsAg may be degraded within the muscle cells to form peptides, which are expressed on the cell surface together with human leukocyte antigen (HLA) class I molecule stimulating the production of cytotoxic T-cells [124]. The protective efficacy of the HBV DNA vaccine was demonstrated in two chimpanzees that were vaccinated at birth and boosted at 6 and 24 weeks [125]. Although the production of anti-HBs was transient, both animals developed an anamnestic antibody response when challenged with an inoculum containing infectious doses of HBV at 33 weeks and did not develop any markers of HBV infection.

- **Pre-S+S vaccines** – HBV encodes three envelope proteins. The large S protein includes the pre-S1, pre-S2, and S regions; the middle S protein includes the pre-S2 and S regions; and

the small S protein encodes the S region only. All three regions contain immunogenic T and B cell epitopes. Studies have found that addition of pre-S1 and pre-S2 to S induced higher rates of response [126-129]. In the United States, one such vaccine was approved for use by the US Food and Drug Administration (FDA) in 2021; however, its role in clinical practice remains to be determined. (See 'Mammalian cell-derived' above and 'Choice of vaccine' above.)

POSTEXPOSURE MANAGEMENT

Issues related to HBV vaccination after a potential exposure are discussed separately. (See "Prevention of hepatitis B virus and hepatitis C virus infection among health care providers" and "Management of nonoccupational exposures to HIV and hepatitis B and C in adults", section on 'Exposure to hepatitis B virus'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hepatitis B vaccination" and "Society guideline links: Immunizations in children and adolescents" and "Society guideline links: Immunizations in adults" and "Society guideline links: Diagnosis of hepatitis B" and "Society guideline links: Travel medicine".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword[s] of interest.)

- Basics topic (see "Patient education: Hepatitis B (The Basics)")
- Beyond the Basics topic (see "Patient education: Hepatitis B (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Importance of vaccination** – There are more than 2 billion individuals with serologic evidence of hepatitis B virus (HBV) infection worldwide, and an estimated 250 to 270 million individuals are chronically infected. However, HBV infection can potentially be eradicated through global vaccination. (See 'Vaccination for HBV prevention' above.)
- **Types of vaccines** – There are several different recombinant vaccines available. The conventional yeast-derived hepatitis B vaccines (Engerix-B and Recombivax HB) use an aluminum adjuvant and are available worldwide. A recombinant vaccine with a novel immunostimulatory adjuvant (referred to as HepB-CpG, sold as Heplisav-B) and mammalian cell-derived vaccines are also available in some countries. Recombinant hepatitis B vaccines are also combined with other vaccines, such as the hepatitis A vaccine. (See 'Types of vaccines' above.)
- **Vaccination in children** – Universal vaccination is recommended for all neonates, regardless of maternal hepatitis B surface antigen (HBsAg) status. This is discussed in detail elsewhere. (See "Hepatitis B virus immunization in infants, children, and adolescents".)
- **Vaccination in adults** – For adults who are at high risk for acquiring HBV infection (table 2), we recommend HBV vaccination (**Grade 1B**).

  For adults <60 years of age without risk factors for HBV infection, we suggest routine hepatitis B vaccination (table 2) (**Grade 2C**).

  For those ≥60 years of age without risk factors for HBV infection, we discuss the risks and benefits of vaccination and vaccinate those seeking protection from HBV infection. (See 'Approach to vaccination' above.)

  - For most people, any one of the available vaccines is appropriate and effective, and the choice of vaccine may be dictated by local guidelines and availability. The one exception is pregnant persons, for whom conventional hepatitis B vaccines (Engerix-B or Recombivax HB) should still be administered. (See 'Choice of vaccine' above.)

Advantages of the HepB-CpG vaccine are two rather than three doses and improved immunogenicity compared to the conventional vaccines. However, there are less efficacy and safety data with HepB-CpG, particularly in patients who are on hemodialysis or are immunocompromised.

- Hepatitis B vaccines should be administered intramuscularly. The dose and schedule depend upon the type of vaccine and the patient population (table 1). An interruption in schedule does not require restarting the entire series or adding extra doses. (See 'Vaccine administration' above.)

- **Response to vaccination** – Postvaccination testing is only indicated in select persons with ongoing risk and/or those who are less likely to respond to the vaccine. A positive immune response to vaccination is defined as a hepatitis B surface antibody (anti-HBs) titer >10 milli-international units/mL. Postvaccination testing in not routinely performed in other patients since most respond to vaccination. (See 'Postvaccination testing' above.)

  If indicated, postvaccination testing should be performed one to two months after the last dose. Nonresponders to the initial series should complete a second series with a single-antigen vaccine. Individuals who fail to respond after a second series are unlikely to benefit from further vaccination. Such patients should be tested for HBsAg and hepatitis B core antibody (anti-HBc), as some may have undiagnosed chronic HBV infection. (See 'Nonresponders' above.)

- **Booster doses** – For most immunocompetent individuals, repeat anti-HBs testing and routine booster doses are **not** needed since immune memory is present in the majority of persons, even if they lose protective levels of antibody.

  However, in the event that someone had an anti-HBs checked (eg, in the setting of routine screening) and the anti-HBs level is <10 milli-international units/mL, we suggest a booster dose of vaccine and repeat titers, or a repeat vaccine series (**Grade 2C**). (See 'Immunocompetent individuals' above.)

  In patients on hemodialysis and in immunocompromised patients with ongoing risk, repeat anti-HBs testing should be performed on an annual basis. A booster dose is indicated if anti-HBs declines to <10 milli-international units/mL. (See 'Individuals who are immunocompromised or receiving hemodialysis' above.)

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Topic 3641 Version 38.0

GRAPHICS

Recommended doses of recombinant hepatitis B vaccines licensed in the United States for persons aged 18 years and older

	Age group and associated conditions	Volume (mL)	Dose HBsAg (mcg)	Recommended schedule
Single-antigen vaccines				
Recombivax HB				
Pediatric/adolescent formulation	18 through 19 years	0.5	5	0, 1, and 6 months
Adult formulation	≥20 years	1	10	
Dialysis formulation	Adults on hemodialysis and other immunocompromised adults aged ≥20 years	1	40	0, 1, and 6 months
Engerix-B	18 through 19 years	0.5	10	0, 1, and 6 months
	≥20 years	1	20	
	Adults on hemodialysis and other immunocompromised adults aged ≥20 years	2*	40	0, 1, 2, and 6 months
Heplisav-B¶ Δ	≥18 years	0.5	20	0 and 1 months
PreHevbrioΔ ◇	≥18 years	1	10	0, 1, and 6 months
Combination vaccine				
Twinrix (combined HepB-HepA vaccine)	≥18 years	1	20	Standard: 0, 1, and 6 months Accelerated: 0, 7, and 21 to 30 days, and 12 months

This table should be used in conjunction with UpToDate content on hepatitis B virus immunization in adults. Recommended doses for persons <18 years of age can be found in the UpToDate content on hepatitis B vaccines for children.

HBsAg: hepatitis B surface antigen; HepB: hepatitis B; HepA: hepatitis A.

* This is a double dose of the standard formulation of Engerix-B for patients ≥20 years of age (Engerix-B does not have a separate dialysis formulation).

¶ HepB-CpG (sold as Heplisav-B) is a recombinant yeast-derived vaccine that contains 3000 mcg of immunostimulatory phosphorothioate oligodeoxyribonucleotide as an adjuvant.

Δ There are insufficient data to inform vaccine-associated risks with Heplisav-B and PreHevbrio in pregnancy. Thus, providers should vaccinate pregnant persons needing HepB vaccination with Engerix-B, Recombivax HB, or Twinrix. In addition, data are not available to assess the effects of Heplisav-B and PreHevbrio on breastfed infants or on maternal milk production and excretion.

◇ The mammalian-derived recombinant hepatitis B vaccine (trivalent), sold as PreHevbrio, was approved for use in the United States in December 2021.

Data from:

1. *Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2018; 67:1.*
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Graphic 117603 Version 7.0

Target groups for hepatitis B virus (HBV) vaccination in the United States

Patient groups	Comments
Infants (birth to 1 year)	▪ The vaccination series should be started as soon as possible after birth, preferably within 12 hours.* ▪ For infants born to mothers who are HBsAg positive, HBIG should be administered at the same time as the birth dose HBV vaccine (at a different anatomic site). ▪ For infants born to mothers who are HBsAg positive and mothers whose HBsAg status cannot be determined, obtain HBsAg and anti-HBs after completion of HBV vaccination series (usually at age 9 to 12 months). Revaccination may be necessary.
Unvaccinated persons age 1 to 60 years, regardless of risk for HBV infection	▪ Catch-up immunization is recommended for persons age <60 years who were not vaccinated for HBV or whose HBV vaccination status is unknown.
Unvaccinated persons age ≥60 years who are at increased risk for acquiring HBV or developing severe HBV infection as well as those who wish to be vaccinated This includes individuals with: ▪ Chronic liver disease ▪ HIV infection ▪ HCV infection ▪ Percutaneous or mucosal risk for HBV exposure (eg, injection drug use, occupational risk, household contact of someone with HBsAg) ▪ Sexual risk for HBV (eg, sexual contact with someone who is HBsAg positive, persons who are sexually active and not in mutually monogamous relationships) ▪ Planned travel to countries with high (≥8%) or intermediate (2 to 7%) endemic prevalence of HBV infection ▪ Risk due to being incarcerated	▪ Among individuals who are at increased risk for HBV, post-vaccination serologic testing (anti-HBs) is warranted for certain groups (eg, those with HIV, health care and public safety personnel, persons who are predialysis or are undergoing dialysis, and sexual partners of persons who are HBsAg positive).

▪ Risk due to working or living in facilities for persons who are developmentally disabled ▪ Persons who are predialysis or are undergoing hemodialysis, peritoneal dialysis, or home dialysis	

This table lists target groups for HBV vaccination. More detailed information about groups at increased risk for HBV are presented in UpToDate content that discusses HBV epidemiology, screening, and immunization. For persons who are immunocompromised in all target groups, post-vaccination serology (anti-HBs) is recommended. Revaccination may be necessary. Refer to UpToDate content on HBV vaccination for details.

HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; HBIG: hepatitis B immune globulin; anti-HBs: antibody to HBsAg; HIV: human immunodeficiency virus; HCV: hepatitis C virus.

* Infants born to mothers who are HBsAg-positive and mothers whose HBsAg status cannot be determined should receive the first dose of HBV and HBIG as soon as possible after birth.

References:

1. *Abara WE, Qaseem A, Schillie S, et al. Hepatitis B vaccination, screening, and linkage to care: Best practice advice from the American College of Physicians and the Centers for Disease Control and Prevention. Ann Intern Med 2017; 167:794.*
2. *Schillie S, Vellozzi C, Reingold A, et al. Prevention of hepatitis B virus infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 2018; 67:1.*
3. *Terrault NA, Lok AS, McMahon BJ, et al. Update on prevention, diagnosis, and treatment and of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018; 67:1560.*
4. *United States Preventive Services Task Force, Krist AH, Davidson KW, et al. Screening for hepatitis B virus infection in adolescents and adults: US Preventive Services Task Force Recommendation Statement. JAMA 2020; 324:2415.*
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6. *Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and testing for hepatitis B virus infection: CDC recommendations – United States, 2023. MMWR Recomm Rep 2023; 72:1.*

Graphic 116656 Version 11.0

Groups at increased risk for hepatitis B virus

Individuals at risk for HBV due to vertical transmission (ie, mother to child transmission)
▪ Individuals born in regions with high (≥8%) or intermediate (≥2%) prevalence rates for HBV, including immigrants and adopted children* ▪ Infants born to pregnant persons who are HBsAg-positive¶ ▪ US-born persons not vaccinated as infants whose parents were born in regions with high HBV endemicity (≥8%)*
Individuals at risk due to horizontal transmission (ie, percutaneous or mucosal exposure to blood or body fluids contaminated with blood)Δ
▪ Household contacts of HBsAg-positive persons ▪ Needle sharing or sexual contacts of HBsAg-positive persons ▪ Individuals who have ever injected drugs ▪ Individuals with multiple sexual partners and/or history of sexually transmitted infections ▪ Men who have sex with men ▪ Inmates of correctional facilities or other detention settings ▪ Individuals with HIV infection◇ ▪ Individuals with current or past HCV infection§ ▪ Individuals with end-stage kidney disease on maintenance renal dialysis
Other individuals
▪ Individuals with elevated alanine aminotransferase or aspartate aminotransferase levels of unknown origin ▪ Individuals who request HBV testing

In the United States, screening for HBV includes[4]:

- **Risk-based screening** – For all individuals (including children and adolescents), screen those who have any of the risk factors listed in the table if they might have been susceptible during the period of increased risk¥. For those with ongoing risk factors (ie, for horizontal transmission) who remain susceptible, continue to test periodically.Δ
- **Universal screening** – For individuals ≥18 years of age, screen at least once in a lifetime. However, for those without risk factors for HBV, screening is generally not needed if there is documentation of completing a hepatitis B vaccine series and evidence of immunity (anti-HBs ≥10 milli-international units/mL) after vaccination.‡
- **Pregnancy screening** – Screen all pregnant people during each pregnancy, regardless of vaccination status of history of prior testing.

Refer to UpToDate content on screening and diagnosis of HBV, HBV immunization, and HBV and pregnancy for more detailed information on screening and vaccination.

HBV: hepatitis B virus; HBsAg: hepatitis B surface antigen; US: United States; HIV: human immunodeficiency virus; HCV: hepatitis C virus; anti-HBs: hepatitis B surface antibody; anti-HBc: hepatitis B core antibodies; HBIG: hepatitis B immune globulin.

* If HBsAg-positive persons are found in first-generation immigrants of a family, subsequent generations should be tested.

¶ To reduce the risk of perinatal transmission, infants born to HBsAg-positive mothers should receive HBIG and hepatitis B vaccine as soon as possible and within 12 hours of birth and then complete the hepatitis B series. Post-vaccination serology should be obtained at 9 to 12 months. Refer to the UpToDate topic that discusses HBV immunization in infants.

Δ In unvaccinated individuals with ongoing HBV risk through percutaneous or mucosal exposure, hepatitis B vaccine should be initiated at the time of screening; the need for subsequent doses will depend upon the results. Post-vaccination serology should be performed to ensure immunity. For at-risk persons who do not complete the vaccine series, repeat testing should be performed periodically (eg, every 1 to 2 years).

◇ The presence of HBV coinfection informs the choice of antiretroviral regimen. In addition, patients with HIV who are not immune should be vaccinated regardless of age or risk factors, since HBV infection has an accelerated course in coinfected patients.

§ Patients with chronic HBV are at risk for HBV reactivation with direct-acting antiviral therapy for hepatitis C. Refer to the UpToDate topic that provides an overview of the management of hepatitis C infection.

¥ Susceptible persons include those who have never been infected with HBV (ie, HBsAg-negative, total anti-HBc-negative, and anti-HBs-negative) and either did not complete a HepB vaccine series per the Advisory Committee on Immunization Practices recommendations or who are known to be vaccine nonresponders.

‡ For most patients who remain without risk factors for acquiring HBV, repeat screening is not warranted. However, screening prior to blood, plasma, organ, tissue, or semen donation is routinely performed, regardless of the person's prior history. In addition, screening is warranted prior to initiating immunosuppressive therapy (eg, corticosteroids, biologics, cancer chemotherapy, anti-rejection therapies) since persons with HBV are at risk for HBV reactivation. Refer to the UpToDate topic on HBV reactivation.

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1. *Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. MMWR Recomm Rep 2008; 57:1.*
2. *Abara WE, Qaseem A, Schillie S, et al. Hepatitis B vaccination, screening, and linkage to care: Best practice advice from the American College of Physicians and the Centers for Disease Control and Prevention. Ann Intern Med 2017; 167:794.*
3. *Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018; 67:1560.*
4. *Conners EE, Panagiotakopoulos L, Hofmeister MG, et al. Screening and testing for hepatitis B virus infection: CDC recommendations – United States, 2023. MMWR Recomm Rep 2023; 72:1.*

Graphic 55052 Version 18.0

Interpretation of the hepatitis B serologic panel

Tests	Results	Interpretation
HBsAg	Negative	Susceptible
anti-HBc	Negative	
anti-HBs	Negative	
HBsAg	Negative	Prior infection (inactive)
anti-HBc	Positive	
anti-HBs	Positive	
HBsAg	Negative	Immune due to hepatitis B vaccination*
anti-HBc	Negative	
anti-HBs	Positive	
HBsAg	Positive	Acutely infected
anti-HBc	Positive	
IgM anti-HBc	Positive	
anti-HBs	Negative	
HBsAg	Positive	Chronically infected
anti-HBc	Positive	
IgM anti-HBc	Negative	
anti-HBs	Negative	
HBsAg	Negative	Four interpretations possible¶
anti-HBc	Positive	
anti-HBs	Negative	

HBsAg: hepatitis B surface antigen; anti-HBc: hepatitis B core antibody; anti-HBs: hepatitis B surface antibody; IgM: immunoglobulin M; HBV: hepatitis B virus.

* Antibody response (anti-HBs) can be measured quantitatively or qualitatively. A protective antibody response is reported quantitatively as 10 or more milli-international units (≥10 mIU/mL) or qualitatively as positive. Postvaccination testing should be completed one to two months after the third vaccine dose for results to be meaningful.

¶ Four interpretations:

1. Might be recovering from acute HBV infection.
2. Might have had prior infection and test not sensitive enough to detect very low level of anti-HBs in serum.
3. Might be susceptible with a false positive anti-HBc.

4. Might be undetectable level of HBsAg present in the serum, and the person is actually chronically infected.

Centers for Disease Control and Prevention, Hepatitis B information for health professionals: Interpretation of hepatitis B serologic test results. Available from the CDC website.

Graphic 60827 Version 7.0

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