

HBV Screening and Diagnosis

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Module 1: [Screening and Diagnosis](#)

Lesson 2: [HBV Screening and Diagnosis](#)

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Indications and Rationale for Routine HBV Screening

Recommended Groups for Routine HBV Screening

The Centers for Disease Control and Prevention (CDC), the U.S. Preventive Services Task Force (USPSTF), the American Association for the Study of Liver Diseases (AASLD), and the American College of Physicians (ACP) all recommend performing routine screening for hepatitis B virus (HBV) infection in persons at increased risk of acquiring HBV infection.[1,2,3,4] The USPSTF recommendation was issued in 2014 as a grade B recommendation, meaning clinicians should offer or provide this service in practice.[2] The following list summarizes the groups considered to be high risk for HBV infection, in whom screening is recommended by the CDC. Certain indications for screening depend on country level HBV prevalence ([Table 1](#)).[3]

- Persons born in countries with a 2% or higher chronic HBV prevalence (defined as chronic infection and positive hepatitis B surface antigen [HBsAg])
- Persons born in the United States who were not vaccinated against HBV as an infant and whose parents were born in regions with high HBV endemicity (defined as an HBsAg prevalence of 8% or greater)
- Men who have sex with men
- Persons who inject drugs
- Persons with HIV infection
- Household and sexual contacts of persons with HBV infection
- Persons needing immunosuppressive therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatologic or gastroenterologic disorders
- Persons with end-stage renal disease, including persons receiving hemodialysis
- Donors of blood, plasma, organs, tissues, or semen
- Persons with elevated alanine aminotransferase levels of unknown etiology
- Pregnant women
- Infants born to mothers with HBV infection (HBsAg and anti-HBs only are recommended)
- Persons who are the sources of blood or body fluids resulting in an exposure (e.g. needlestick, sexual assault) that might require postexposure prophylaxis
- Unvaccinated persons traveling to countries with a chronic HBV infection prevalence of 2% or greater

Rationale for Routine HBV Screening of At-Risk Persons

There are multiple reasons why routinely screening for HBV infection in persons at increased risk of acquiring HBV infection. First, persons identified with chronic HBV can undergo evaluation for potential antiviral treatment; multiple safe and effective antiviral options are now available for persons who have an indication

for treatment.[\[4,5\]](#) Second, since chronic HBV infection can lead to cirrhosis and complications of cirrhosis, persons identified with chronic HBV infection can have an evaluation for cirrhosis; if the individual has cirrhosis, they can receive further evaluation, management, and prevention of cirrhosis-related complications.[\[4,5,6\]](#) Third, persons with chronic HBV can be evaluated to see if they have an indication for hepatocellular carcinoma surveillance; if indicated, regular surveillance for hepatocellular carcinoma can identify early stage cancer lesions in the liver that have potential for cure.[\[7\]](#) Fourth, persons diagnosed with chronic HBV can receive hepatitis A immunization (if nonimmune) and receive counseling on how to minimize damage, such as avoiding excess alcohol intake or excessive acetaminophen ingestion.[\[3\]](#) Last, but not least, identifying persons with chronic HBV can reduce the population spread of HBV through treatment of HBV and appropriate prevention measures, such as counseling for preventing HBV transmission to others.[\[4\]](#)

HBV Diagnostic Tests

A range of serologic tests are utilized to diagnose HBV infection and to determine whether a person lacks immunity to HBV. The following discusses the major serologic tests used for hepatitis B diagnosis. The interpretation of these tests, as well as the progression of these markers with acute HBV infection, resolved HBV infection, chronic HBV infection, and response to immunization are summarized in the section Interpretation of HBV Serologic Tests.

- Hepatitis B Surface Antigen (HBsAg)**[Play animation: Hepatitis B Surface Antigen \(HBsAg\)](#): Structurally, HBsAg is the main outer surface (envelope) protein of intact HBV. In addition, excess HBsAg proteins that are produced can form free subviral spherical and tubular particles that do not contain other viral elements. These subviral particles outnumber the intact hepatitis B virions by about 1,000 to 1. The HBsAg is detected by enzyme immunoassay (EIA). After initial infection, HBsAg becomes detectable in blood on average at about 4 weeks. The presence of HBsAg indicates active infection, except in the situation whereby HBsAg is transiently present after receipt of a dose of hepatitis B vaccine.
- Hepatitis B Surface Antibody (anti-HBs)**[Play animation: Antibody to Hepatitis B e Antigen \(Anti-HBe\)](#): The appearance of anti-HBs follows declining HBsAg titers and indicates recovery from HBV infection. The anti-HBs binds to the HBsAg that is present on the surface of the intact virions and on the HBsAg subviral lipoprotein particles (spheres and filaments). Early in the course of infection most of the anti-HBs is bound to HBsAg and thus not detectable in blood. If a vigorous T-cell immune response clears most of the intact virions and subviral particles from the circulation, free (unbound) anti-HBs becomes detectable at high titers. The presence of anti-HBs indicates either recovery from natural infection and immunity to HBV or a response to HBV vaccination with the development of immunity. For those with prior infection or prior vaccination, immunity is defined by anti-HBs levels of 10 to 12 mIU/mL or greater. In addition, with a treatment-related cure of HBV, which is uncommon, anti-HBs will appear.
- Total Antibody to Hepatitis B Core Antigen (Total anti-HBc)**[Play animation: Hepatitis B e Antigen \(HBeAg\)](#): The HBV core (or nucleocapsid) is the shell-like inner region of the virus that encloses HBV DNA and the HBV polymerase enzyme. The total anti-HBc includes IgM anti-HBc and IgG anti-HBc. The anti-HBc forms in response to hepatitis B core antigen (HBcAg) peptides, which are small fragments of the HBcAg. The HBcAg peptides are formed when intact virions are degraded inside of macrophages (antigen presenting cells) or when HBcAg is newly synthesized and processed within hepatocytes. The HBcAg peptides do not circulate in significant quantity in the blood, and there is no existing assay for HBcAg. The immune system is triggered to form anti-HBc when the HBcAg peptides are shuttled to the surface of cells by MHC class 1 or 2 molecules. Anti-HBc does not bind to intact virions since the core is completely surrounded by the viral envelope. The formation of anti-HBc indicates past exposure to the virus and it is not seen following HBV immunization. The role, if any, of anti-HBc in controlling or preventing HBV infection is not known. Anti-HBc remains persistently detectable in most individuals following HBV infection, with the persistent anti-HBc predominantly consisting of IgG anti-HBc.
- IgM Antibody to Hepatitis B Core Antigen (IgM anti-HBc)**[Play animation: IgM Antibody to Hepatitis B Core Antigen \(IgM Anti-HBc\)](#): Anti-HBc is the first antibody to appear following acute HBV infection and it typically becomes detectable within 6 to 8 weeks after infection. Most of the early anti-HBc consists of IgM anti-HBc. The detection of IgM anti-HBc indicates infection within the prior 6 months. The IgM anti-HBc is the most reliable test for distinguishing acute from chronic HBV infection, although rarely, some patients with chronic HBV can demonstrate recurrent anti-HB core IgM during acute flares of their disease. By about 6 months after acute HBV infection most of the IgM anti-HBc is replaced by IgG anti-HBc and thus IgM anti-HBc is generally not detectable in persons with chronic HBV infection.
- Hepatitis B e Antigen (HBeAg)**[Play animation: Total Antibody to Hepatitis B Core Antigen \(Total anti-HBc\)](#): Within hepatocytes, HBeAg and HBcAg are generated from the same region of the HBV DNA. The newly formed HBeAg is then secreted from the hepatocyte into the circulation. In contrast,

the HBcAg is assembled into the HBV core and incorporated into the intact virion. Although abundant HBeAg is produced, it is not a component of the intact hepatitis B virion or subviral particles and it is not required for viral infection, assembly, or replication. The function of HBeAg is unclear, but it may play an immunomodulatory role in natural infection by suppressing cytotoxic T-lymphocyte responses. The presence of HBeAg is typically associated with elevated HBV DNA levels and high infectivity, but it is variably present in persons with chronic infection. Certain precore and basal core promoter mutations are associated with reduced or abolished HBeAg protein production.

- **Antibody to Hepatitis B e Antigen (anti-HBe)**[Play animation: Antibody to Hepatitis B Surface Antigen \(Anti-HBs\)](#): The appearance of anti-HBe generally coincides with declining HBeAg titers and indicates a favorable immune response to HBV infection. In some instances, initial detection of anti-HBe may occur weeks after HBeAg disappears from blood. For reasons that are not clear, anti-HBe usually appears in blood only after the immune system has controlled most of the initial HBV infection and cleared most of the HBeAg from the systemic circulation. The anti-HBeAg that appears following HBeAg clearance will generally persist, but unlike anti-HBs, it does not have a known role in controlling or neutralizing HBV infection, nor does it have any known role in preventing HBV infection.
- **HBV DNA**[Play animation: HBV DNA](#): The HBV DNA is found in the intact virion, but not in the spherical or filamentous particles, since they contain only HBsAg. The presence of HBV DNA indicates active infection (acute or chronic). Detection of HBV DNA is not usually used for diagnostic purposes, but it does play a major role in risk stratification and monitoring response to antiviral therapy.

Recommended Screening Tests

The CDC, AASLD, USPSTF, and ACP have all published guidelines outlining who and how to screen for HBV infection with slight variations in the recommended screening tests exists between these guidance documents.[1,2,3,4,8,9] The following section aims to summarize recommended HBV screening tests for at-risk groups and highlight key differences between published guidelines (Table 2).

Persons Born in Countries with a 2% or Higher Chronic HBV Prevalence

The CDC, AASLD, USPSTF, and ACP all recommend routine screening for HBV infection in all persons born in countries with a 2% or greater prevalence of chronic HBV infection. This similarly includes certain indigenous populations with high chronic HBV endemicity, regardless of their country of origin.

- CDC: Screening for HBsAg is recommended regardless of prior vaccination status. In persons at ongoing risk for HBV infection, anti-HBs or anti-HBc is recommended to determine ongoing susceptibility.
- AASLD: Screening is recommended using HBsAg and anti-HBs.
- USPSTF: Screening is recommended using HBsAg, anti-HBs, and anti-HBc.
- ACP: Screening is recommended using HBsAg, anti-HBs, and anti-HBc.

Not Vaccinated Against HBV as Infant and Parents Born in Regions with High HBV Endemicity

The following recommendations apply to persons born in the United States who were not vaccinated as an infant and whose parents were born in countries of high chronic HBV endemicity (defined as an HBsAg prevalence 8% or greater). Due to the high risk for HBV exposure prior to vaccination, persons who received catch-up vaccination series as children or adolescents should not necessarily be considered immune but rather undergo the following screening.

- CDC: Screening for HBsAg is recommended for those not vaccinated as infants, regardless of maternal HBsAg status. In persons at ongoing risk for HBV infection, anti-HBs or anti-HBc is recommended to determine ongoing susceptibility.
- AASLD: Screening is recommended using HBsAg and anti-HBs.
- USPSTF: Screening is recommended using HBsAg, anti-HBs, and anti-HBc.
- ACP: No specific guidance provided.

Men who Have Sex with Men

In the absence of vaccination, men who have sex with men represent a population at ongoing risk for HBV acquisition. In this setting, serologic testing should routinely be performed to identify susceptible persons where hepatitis B vaccination is indicated.

- CDC: Screening is recommended using HBsAg and either anti-HBs or anti-HBc.
- AASLD: Screening is recommended using HBsAg and anti-HBs.
- USPSTF: Screening is recommended using HBsAg, anti-HBs, and anti-HBc.
- ACP: Screening is recommended using HBsAg, anti-HBs, and anti-HBc.

Persons who Inject Drugs

In the absence of vaccination, persons who inject drugs (PWID) represent a population at ongoing risk for HBV acquisition. In this setting serologic testing can identify (1) persons who may have chronic HBV and require treatment and (2) susceptible persons who should receive hepatitis B vaccination.

- CDC: Screening is recommended using HBsAg and either anti-HBs or anti-HBc.

- AASLD: Screening is recommended using HBsAg and anti-HBs.
- USPSTF: Screening is recommended using HBsAg, anti-HBs, and anti-HBc.
- ACP: Screening is recommended using HBsAg, anti-HBs, and anti-HBc.

Persons with HIV Infection

Due to shared risk factors, persons living with HIV have a higher prevalence of HBV infection than the general population. All major guidelines recommend persons with HIV should be screened for HBV and vaccinated for HBV if susceptible.

- CDC: Screening is recommended using HBsAg and either anti-HBs or anti-HBc.
- AASLD: Screening is recommended using HBsAg, anti-HBs, and anti-HBc.
- USPSTF: Screening is recommended using HBsAg, anti-HBs, and anti-HBc.
- ACP: Screening is recommended using HBsAg, anti-HBs, and anti-HBc.

Household, Needle-Sharing, or Sexual Contacts of Persons with HBV Infection

Given the prevalence of HBV infection amongst family members if perinatal or early childhood transmission is a concern, all household members should be screened for HBV. In addition, needle-sharing and sexual contacts of persons with chronic HBV infection should be screened for HBV due to potential exposure to HBV.

- CDC: Screening is recommended using HBsAg and either anti-HBs or anti-HBc.
- AASLD: Screening is recommended using HBsAg and anti-HBs.
- USPSTF: Screening is recommended using HBsAg, anti-HBs, and anti-HBc.
- ACP: Screening is recommended using HBsAg, anti-HBs, and anti-HBc.

Persons Needing Immunosuppressive Therapy

Persons receiving immunosuppressant therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatologic or gastroenterologic disorder or those with impending immunosuppression, should undergo full serologic screening for HBV to evaluate for the need for vaccination, as well as for the presence of chronic HBV infection that might warrant prophylactic antiviral therapy or close monitoring for HBV reactivation. This is ideally done prior to the initiation of immunosuppressive agents.

- CDC: Screening is recommended using HBsAg, anti-HBs, and anti-HBc.
- AASLD: Screening is recommended using HBsAg, anti-HBs, and anti-HBc.
- USPSTF: USPSTF references CDC guidelines but does not make specific recommendations regarding this population.
- ACP: Screening is recommended using HBsAg, anti-HBs, and anti-HBc.

Persons with End-Stage Renal Disease, including Persons Receiving Hemodialysis

In the United States, the prevalence of HBV infection in persons receiving hemodialysis is approximately twice the national average.[8] In patients on dialysis, there is a unique role for repeat testing given the propensity for waning HBV immunity in this population and the presence of an ongoing risk for exposure.[4]

- CDC: Initial screening is recommended using HBsAg, anti-HBs, and anti-HBc. Vaccine non-responders should be monitored for acquisition of HBV infection using HBsAg testing.
- AASLD: Screening is recommended using HBsAg, anti-HBs, and anti-HBc.
- USPSTF: The USPSTF guidance references the CDC guidelines but does not make specific recommendations regarding this population.
- ACP: Screening is recommended using HBsAg, anti-HBs, and anti-HBc.

Donors of Blood, Plasma, Organs, Tissues, or Semen

Due to the risk of HBV transmission to others, prospective donors of blood, plasma, organs, tissues, or semen should undergo testing for HBV prior to blood, tissue, semen or organ donation.

- CDC: Screening is recommended using HBsAg, anti-HBs, and anti-HBc.
- AASLD: Screening is recommended using HBsAg, anti-HBs, and anti-HBc.
- USPSTF: The USPSTF references CDC guidelines but does not make specific recommendations regarding this population.
- ACP: Screening is recommended using HBsAg, anti-HBs, and anti-HBc.

Persons with Elevated Alanine Aminotransferase Levels

Persons with elevated alanine aminotransferase (ALT) levels of unclear etiology should undergo screening for HBV infection to rule out HBV as a cause of hepatitis. Cutoffs for ALT vary by sex and by lab.

- CDC: Screening is recommended using HBsAg. In persons at risk for HBV infection, testing for anti-HBs or anti-HBc is also recommended to determine susceptibility and need for HBV immunization.
- AASLD: Screening is recommended using HBsAg and anti-HBs.
- USPSTF: No guidance provided.
- ACP: Screening is recommended for women with an ALT 19 IU/L or greater and man with an ALT 30 IU/L of greater using HBsAg, anti-HBs, and anti-HBc.

Pregnant Persons

Universal screening for HBV should be performed in all pregnant persons, ideally at the first perinatal visit to identify women who are chronically infected and ensure appropriate linkage to care and measures to prevent perinatal HBV transmission. Pregnant persons with ongoing risk factors for HBV acquisition, those with new clinical or laboratory signs of hepatitis, and those who were not screened earlier in pregnancy should also undergo screening at the time of labor and delivery. For additional information on HBV screening and management during pregnancy, please see the lesson on “Preventing HBV Perinatal Transmission.”

- CDC: Screening during each pregnancy is recommended using HBsAg. Screening should ideally occur during the first perinatal visit. Women who were not screened earlier in their pregnancy, those for whom the HBsAg results are not available (or unknown), and those with ongoing risk factors for HBV should be screened using HBsAg at the time of labor and delivery.
- AASLD: Screening is recommended for all pregnant women using HBsAg and anti-HBs.
- USPSTF: Screening during each pregnancy is recommended using HBsAg. Screening should ideally occur during the first perinatal visit. Women with an unknown HBsAg status and those with ongoing risk factors for HBV should be screened using HBsAg at the time of labor and delivery.
- ACP: Screening is recommended for all pregnant women using HBsAg.

Infants Born to Mothers with HBV Infection

Perinatal transmission remains the most common mode of HBV transmission worldwide.^[10] Although the routine use of hepatitis B immune globulin (HBIG) and birth-dose vaccination dramatically decreases the risk of perinatal transmission, ^[11] there can still be breakthrough transmissions so routine screening for HBV infection should be performed in all infants born to HBsAg-positive mothers.

- CDC: Screening is recommended using HBsAg and anti-HBs 1 to 2 months following completion of a 3-shot HBV immunization series. Due to passive transfer of maternal antibodies to the fetus, screening of the newborn should be performed after the age of 9 months or after at least 1 month following the of completing a full vaccination series.
- AASLD: Screening is recommended using HBsAg and anti-HBs at 9 to 15 months of age for infants

born to HBs-Ag positive mothers.

- USPSTF: USPSTF guidelines on HBV screening in pregnant women reference existing CDC guidelines for screening infants born to HBsAg-positive mothers but do not make their own recommendation.[9]
- ACP: Screening is recommended using HBsAg, anti-HBs, and anti-HBc.

Persons who are the Sources of Blood or body Fluids Resulting in an Exposure

Following an exposure to blood or bodily fluids (e.g. needlestick, sexual assault) that might require postexposure prophylaxis), management of the exposed individual depends on their own HBV immune status and the HBsAg status of the source patient.[12] When the exposed patient is not known to be immune to HBV, timely screening of persons who are the source of blood or bodily fluid exposures should be performed to determine the next best step in management (see lesson on “Occupational HBV Postexposure Prophylaxis” for further details).

- CDC: Screening is recommended using HBsAg. In the case of occupational exposure, screening the source patient is unnecessary when the healthcare worker has completed the hepatitis B vaccine series and has a documented anti-HBs level of 10 mIU/mL or greater.
- AASLD: Screening is recommended using HBsAg, anti-HBs, and anti-HBc.
- USPSTF: No guidance provided.
- ACP: No guidance provided.

Unvaccinated Persons Traveling to Countries with a HBV Chronic Infection Prevalence of 2% or Greater

Although not included in CDC, USPSTF, or ACP guidelines, the AASLD recommends routine screening of all travelers to countries with intermediate or high prevalence of HBV infection, defined as a HBsAg prevalence of 2% or higher; travelers who screen seronegative for HBV should subsequently receive the hepatitis B vaccine.[4]

- CDC: No guidance provided.
- AASLD: Screening is recommended using HBsAg and anti-HBs.
- USPSTF: No guidance provided.
- ACP: No guidance provided.

Evolution of Serologic Tests after Infection and Vaccination

To optimally understand and interpret HBV serologic diagnostic tests, it is important to understand how serologic markers evolve over time after initial infection and after receiving hepatitis B vaccine. Following acute HBV infection, the evolution of the pattern of serologic markers depends on the outcome of the host immune response, which typically correlates with the patient's age.[3,13,14] Adults have resolution of the HBV infection resolved their HBV infection approximately 90% of the time, whereas 30 to 90% of young children will fail to resolve the infection and thus develop chronic HBV infection.[13,14] The following discussion will summarize the evolution of key serologic markers during acute HBV infection with recovery, chronic HBV, and post-immunization, with each topic accompanied by corresponding animations from the Centers for Disease Control and Prevention Hepatitis B Serology Training as audio-visual guides to aid in understanding.

Acute HBV Infection with Recovery

Following acquisition of HBV, the first detectable serologic marker in blood is HBsAg. Detection of HBsAg typically occurs at 4 weeks following infection, with a range of 1 to 9 weeks following infection. Typically, when HBsAg is detectable during acute infection, HBV DNA can also be detected in blood. During early infection persons may also test positive for HBeAg, which is a marker of infectivity and higher HBV DNA levels. Nearly all persons will test negative for HBsAg and HBV DNA by 15 weeks after the onset of symptoms. With acute HBV infection IgM anti-HBc is typically detectable at the onset of symptoms and persists for 6 to 9 months following infection. Total anti-HBc, which consists of IgM anti-HBc and IgG anti-HBc, can similarly be detected at the onset of symptoms, but persists indefinitely as a marker of prior infection. During recovery, and after the disappearance of HBsAg, persons who resolve their acute infection develop antibodies to HBs (anti-HBs), which may persist indefinitely or wane over time. It is important to note that following the disappearance of HBsAg and prior to the appearance of anti-HBs, there is a period of time when IgM anti-HBc and total anti-HBc may be the only detectable serologic markers. This period of time is known as the window period.

Chronic HBV Infection

Persons who do not resolve their acute infection will progress to have chronic hepatitis B. In these cases, HBsAg and total anti-HBc will remain positive for the duration of infection. HBV DNA is also typically detectable in serum. HBeAg, a marker of infectivity and higher viral load, is also generally present in chronic infection. Over time, HBeAg-positive patients can lose their ability to produce e antigen through the selection of replicating HBV with spontaneous mutations in the precore or basal core promoter region of the HBV genome.[15] In addition to HBeAg loss, they can eventually develop anti-HBe, a change that can be associated with lower HBV DNA levels if they become an inactive carrier. A diagnosis of chronic HBV can be made in the following 2 ways:

1. Detection of HBsAg, HBeAg, or HBV DNA on 2 separate samples 6 months apart, or
2. Detection of HBsAg, HBeAg, or HBV DNA on a single sample with a concurrent negative IgM anti-HBc

Vaccination

Vaccination against hepatitis B results in the development of anti-HBs. Following Hep B vaccination, seroprotection is defined by anti-HBs levels of at least 10 to 12 mIU/mL 1 to 2 months after completion of the vaccine series. In the absence of repeated exposure, anti-HBs levels may wane over time; although in immunocompetent hosts immunity is likely maintained, even when anti-HBs levels fall below 10 mIU/mL.[16] Because the Hep B vaccine contains HBsAg, hepatitis B vaccination may cause a transient false-positive HBsAg for 2 to 3 weeks following vaccination. This result is clinically insignificant and does not represent infection.

Interpretation of HBV Serologic Tests

The three major tests used for hepatitis B screening are HBsAg, anti-HBs, and anti-HBc. The following summarizes the interpretation of test results with these three serologic tests ([Table 3](#)).[\[8,17,18\]](#) The anti-HBc test may consist of a total anti-HBc or an IgM anti-HBc. The IgM anti-HBc has value primarily when considering acute hepatitis B infection. For diagnostic purposes, testing for HBeAg and anti-HBe is usually not performed, since they typically do not provide additional diagnostic information. For persons who are diagnosed with HBV infection, evaluation of HBeAg, anti-HBe, and HBV DNA are all usually performed and monitoring of these labs can be important in persons on treatment for chronic HBV.

- **Never Infected and Susceptible:** Persons who have never been infected with HBV or vaccinated with HBV vaccine are susceptible to HBV will have a negative HBsAg, negative total anti-HBc, negative IgM anti-HBc, and negative anti-HBs. In addition, prior HBV vaccine nonresponders who have never been infected with HBV can also have this same serologic profile.
- **Acute HBV Infection:** Following exposure to the hepatitis B virus, HBsAg is the first detectable serologic marker in blood. Detection of HBsAg typically occurs at 4 weeks following infection (range 1 to 9 weeks). In early acute infection, HBsAg may be the only detectable serologic marker, unless HBV DNA is tested, which would also be positive. In addition, most patients with acute HBV also test positive for HBeAg, which is a marker of infectivity and higher HBV DNA levels. During this early period, it can be challenging to make the diagnosis if acute HBV infection, especially in the absence of symptoms and IgM anti-HBc, but typically the serum aminotransferases (ALT or AST) are quite elevated in this setting and additional history of exposure risk can also provide additional information.
- **Recovered from Past Infection and Immune:** Following acute HBV infection most adults will spontaneously clear their infection and subsequently test negative for HBsAg and HBV. In this situation, persons who have cleared the HBV infection have positive tests for anti-HBc and anti-HBs. In contrast, persons who receive HBV vaccine, which consists of pure HBsAg, will develop anti-HBs, but not anti-HBc.
- **Chronic HBV Infection:** Persons who do not resolve their acute infection will progress to have chronic hepatitis B. With chronic HBV, HBsAg and total anti-HBc will remain positive for the duration of infection. In addition, most persons with chronic HBV have persistently positive serum HBV DNA levels. Although persons with chronic HBV almost always have a negative anti-HBs test, there are a few reports of the simultaneous presence of HBsAg and anti-HBs in persons with chronic HBV.[\[19,20\]](#) For diagnostic purposes, testing for HBeAg and anti-HBe is usually not performed, since the results are in persons with chronic HBV, the results are variable as a subset of persons with chronic HBV will clear HBeAg and develop anti-HBe.
- **Immune from Vaccination:** All modern HBV vaccines utilize recombinant HBsAg as the primary immunogen. The host serologic response to the vaccine is the development of anti-HBs. The hepatitis B vaccines do not generate an anti-HBc immune response. A positive anti-HBs with all other HBV serologic markers negative indicates immunity as a result of vaccination, whereas a positive titer for both anti-HBs and anti-HBc indicates immunity from past infection with HBV. An anti-HBs titer greater than 10 to 12 mIU/mL correlates with protective immunity.[\[21,22\]](#)

Summary Points

- The CDC, AASLD, USPSTF and ACP have all issued recommendations for routine HBV screening in persons at increased risk for HBV infection.
- In addition to identifying chronically infected individuals who would benefit from HBV treatment, fibrosis staging, and HCC screening, routine HBV screening in at-risk groups allow healthcare providers to counsel HBV positive patient on interventions to support liver health (e.g. alcohol cessation) and reduce HBV transmission.
- A range of serologic tests are utilized to diagnose HBV infection, including HBsAg, anti-HBs, total anti-HBc, IgM anti-HBc, HBeAg, anti-HBe, and HBV DNA.
- Recommended screening tests for HBV differ slightly by recommending body (e.g. CDC, AASLD, USPSTF, ACP) and based on the patient's risk factor(s) for HBV infection.
- The serologic hallmark of acute HBV infection is the detection of IgM anti-HBc, which is typically detectable at the onset of symptoms and persists for 6 to 9 months following infection.
- Because HBsAg is detected first following infection with HBV, in early acute infection, HBsAg may be the only detectable serologic marker.
- Chronic HBV can be diagnosed by detection of HBsAg, HBeAg, or HBV DNA on 2 separate samples 6 months apart, or by detection of HBsAg, HBeAg, or HBV DNA on a single sample with a concurrent negative IgM anti-HBc.
- Following hepatitis B vaccination, seroprotection is defined by anti-HBs level of 10 to 12 mIU/mL or greater 1 to 2 months after completion of the vaccine series.
- Following resolution of HBV infection, patients will be serologically positive for total anti-HBc and anti-HBs; although anti-HBs levels may waning over time.
- Person who have never been infected with HBV and are susceptible to HBV will have a negative HBsAg, negative total anti-HBc, negative IgM anti-HBc, and negative anti-HBs.

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Table 1.

Global Prevalence of Chronic HBV Infection, by Country

Prevalence Category	Country
High (≥8%)	Angola, Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Congo, Côte d'Ivoire, Djibouti, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Haiti, Kiribati, Kyrgyzstan, Laos, Liberia, Malawi, Mali, Mauritania, Mongolia, Mozambique, Namibia, Nauru, Niger, Nigeria, Niue, Papua New Guinea, Senegal, Sierra Leone, Solomon Islands, Somalia, South Sudan, Sudan, Swaziland, Togo, Tonga, Uganda, Vanuatu, Vietnam, Yemen, and Zimbabwe.
Intermediate (5.0-7.9%)	Albania, Bhutan, Cape Verde, China, Democratic Republic of the Congo, Ethiopia, Kazakhstan, Kenya, Marshall Islands, Moldova, Oman, Romania, Rwanda, Samoa, South Africa, Tajikistan, Tanzania, Thailand, Tunisia, Tuvalu, Uzbekistan, and Zambia.
Low Intermediate (2.0-4.9%)	Algeria, Azerbaijan, Bangladesh, Belarus, Belize, Brunei Darussalam, Bulgaria, Cambodia, Colombia, Cyprus, Dominican Republic, Ecuador, Eritrea, Federated States of Micronesia, Fiji, Georgia, Italy, Jamaica, Kosovo, Libya, Madagascar, Myanmar, New Zealand, Pakistan, Palau, Philippines, Peru, Russia, Saudi Arabia, Singapore, South Korea, Sri Lanka, Suriname, Syria, Tahiti, and Turkey.
Low (≤1.9%)	Afghanistan, Argentina, Australia, Austria, Bahrain, Barbados, Belgium, Bolivia,

Prevalence Category Country

Bosnia and Herzegovina, Brazil, Canada, Chile, Costa Rica, Croatia, Cuba, Czech Republic, Denmark, Egypt, France, Germany, Greece, Guatemala, Hungary, Iceland, India, Indonesia, Iran, Iraq, Ireland, Israel, Japan, Jordan, Kuwait, Lebanon, Lithuania, Malaysia, Mexico, Morocco, Nepal, Netherlands, Nicaragua, Norway, Palestine, Panama, Poland, Portugal, Qatar, Serbia, Seychelles, Slovakia, Slovenia, Spain, Sweden, Switzerland, Ukraine, United Kingdom, United Arab Emirates, United States of America, and Venezuela.

No data

Andorra, Antigua and Barbuda, Armenia, The Bahamas, Botswana, Chad, Comoros, Cook Islands, Dominica, El Salvador, Finland, Grenada, Guinea-Bissau, Guyana, Honduras, Latvia, Lesotho, Lithuania, Luxembourg, Macedonia, Maldives, Malta, Mauritius, Monaco, Montenegro, North Korea, Paraguay, Saint Kitts and Nevis, Saint Lucia, Saint Vincent and the Grenadines, San Marino, Sao Tome and Principe, Timor-Leste, Trinidad and Tobago, Turkmenistan, and Uruguay.

NOTE: This table is based on data from the Centers for Disease Control and Prevention (CDC)
Source:

- 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;67:1-31. [[PubMed Abstract](#)]

Table 2.

Hepatitis B Screening Recommendations

Risk Group	CDC	AASLD	USPST
Persons born in countries with a 2% or higher HBV prevalence	HBsAg [^]	HBsAg anti-HBs	HBsAg anti-HBs anti-HBc
Persons born in the United States who were not vaccinated against HBV as an infant and whose parents were born in regions with high HBV endemicity (defined as an HBsAg prevalence 8% or greater)	HBsAg [^]	HBsAg anti-HBs	HBsAg anti-HBs anti-HBc
Men who have sex with men	HBsAg anti-HBs OR anti-HBc	HBsAg anti-HBs	HBsAg anti-HBs anti-HBc
Persons who inject drugs	HBsAg anti-HBs OR anti-HBc	HBsAg anti-HBs	HBsAg anti-HBs anti-HBc
Persons with HIV infection	HBsAg anti-HBs OR anti-HBc	HBsAg anti-HBs anti-HBc	HBsAg anti-HBs anti-HBc
Household, needle-sharing, or sexual contacts of persons with HBV infection	HBsAg anti-HBs OR anti-HBc	HBsAg anti-HBs	HBsAg anti-HBs anti-HBc
Persons needing immunosuppressive therapy, including chemotherapy, immunosuppression related to organ transplantation, and immunosuppression for rheumatologic or gastroenterologic disorders	HBsAg anti-HBs anti-HBc	HBsAg anti-HBs anti-HBc	No organization recommendation
Persons with end-stage renal disease, including persons receiving hemodialysis	HBsAg anti-HBs anti-HBc	HBsAg anti-HBs anti-HBc	No organization recommendation
Donors of blood, plasma, organs, tissues, or semen	HBsAg anti-HBs anti-HBc	HBsAg anti-HBs anti-HBc	No organization recommendation
Persons with elevated alanine aminotransferase levels	HBsAg [^]	HBsAg anti-HBs	No organization recommendation
Pregnant women	HBsAg at the first perinatal visit; repeat HBsAg at the time of labor and delivery for women who have ongoing risk factors or an unknown HBsAg status	HBsAg anti-HBs	HBsAg at the perinatal visit HBsAg at the time of labor and delivery for women who have ongoing risk factors or an unknown HBsAg status
Infants born to HBsAg-positive mothers	HBsAg anti-HBs (obtain both 1-2 months after completing a 3-shot series for HBV).*	HBsAg anti-HBc (obtain both at 9-15 months of age)	No organization recommendation

Risk Group	CDC	AASLD	USPST
Unvaccinated persons traveling to countries with a HBV chronic infection prevalence of 2% or greater	No organizational recommendation	HBsAg anti-HBs	No organizational recommendation
^ Consider anti-HBc OR anti-HBs in persons with ongoing risk *Testing should not be performed before 9 months of age or within 1 month of completing the vaccine series #Screening source patients for HBsAg is not necessary in the case of occupational exposure, when the healthcare provider is wearing appropriate PPE			

Source:

- Abara WE, Qaseem A, Schillie S, McMahon BJ, Harris AM. 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;167:794-804. [[PubMed Abstract](#)]
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Table 3.

Interpretation of Test Results for Hepatitis B Virus Infection

HbsAg	Total anti-HBc	IgM anti-HBc	Anti-HBs	HBV DNA	Interpretation
-	-	-	-	-	Never infected; susceptible
+	-	-	-	+ or -	Early acute infection (positive or negative HBV DNA), or Transient (up to 18 days) after vaccination with negative HBV DNA
+	+	+	-	+	Acute infection
-	+	+	+ or -	+ or -	Acute resolving infection
-	+	-	+	-	Recovered from past infection and immune
+	+	-	-	+	Chronic infection
-	+	-	-	+ or -	Isolated core antibody False-positive (susceptible), or Past infection (resolved), or "low-level" chronic infection (unlikely to be infectious), or Passive transfer of anti-HBc to infant born to HBsAg-positive mother
-	-	-	-	+	Immune if anti-HBs concentration is ≥ 10 mIU/mL after completing vaccine series, or Passive transfer after hepatitis B immune globulin administration (for 3-6 months)

Abbreviations: anti-HBc = antibody to hepatitis B core antigen; anti-HBs = antibody to hepatitis B surface antigen; HBsAg = hepatitis B surface antigen; HBV DNA = hepatitis B virus deoxyribonucleic acid; IgM =

HbsAg	Total anti-HBc	IgM anti-HBc	Anti-HBs	HBV DNA	Interpretation
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immunoglobulin class M.

Source:

- 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;67:1-31. [[PubMed Abstract](#)]

