HBV Screening, Testing, and Diagnosis

This is a PDF version of the following document:
Module 3: Screening and Diagnosis
Lesson 2: HBV Screening, Testing, and Diagnosis

You can always find the most up-to-date version of this document at https://www.hepatitisB.uw.edu/go/screening-diagnosis/diagnosis-hbv/core-concept/all.

HBV Screening Recommendations

recommendations for Hepatitis B Screening and Testing in the United States

Multiple organizations in the United States have recommended performing routine screening for hepatitis B virus (HBV) infection for persons who are at increased risk of acquiring HBV, including 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) [1,2,3,4] In March 2023, the CDC issued hepatitis B screening and testing guidance that recommends universal hepatitis B virus (HBV) screening for all adults, as well as risk-based and repeat testing for selected groups, utilizing a 3-test panel, which includes hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (anti-HBs), and total antibody to hepatitis B core antigen (anti-HBc).[5] In these recommendations, the term “screening” refers to conducting serologic testing of asymptomatic persons not known to be at increased risk for exposure to HBV; the term “testing” refers to conducting serologic testing of persons with HBV-related symptoms or who have increased risk for HBV.[5] The following list summarizes the new CDC draft recommendations.[5] Note that certain indications for screening depend on country-level HBV prevalence (Table 1).[3]

Universal Hepatitis B Screening

- Universal HBV screening in all adults 18 years of age or older at least once in a lifetime.
- The HBV testing should consist of HBsAg, anti-HBs, and anti-HBc.
- For persons undergoing universal hepatitis B screening, repeat testing does not need to occur if no subsequent risk for HBV acquisition occurs following screening with the 3-test panel.

Screening Pregnant People

- HBV screening for all pregnant persons during each pregnancy, preferably in the first trimester, regardless of vaccination status or prior screening history.
- The HBV testing should consist of HBsAg, anti-HBs, and anti-HBc.

Risk-based Testing

- HBV testing should be performed for all individuals at increased risk for HBV, regardless of age, provided they were susceptible to HBV at the time of increased risk.
- Periodic, repeat testing should be performed for susceptible persons with ongoing risk factors, regardless of age.

Definition for HBV Susceptible

- The CDC defines susceptible persons to be those who
  - Have never been infected with HBV (e.g., HBsAg negative and anti-HBc negative),

    AND
  - Have not received a hepatitis B vaccine that is licensed in the United States or are known to be vaccine nonresponders.

Definition of Increased Risk for HBV Infection

- The CDC identifies the following groups of people to be at increased risk for HBV:
  - Persons currently or formerly incarcerated in jail, prison, or another detention setting
  - Persons with current or past sexually transmitted infections (STIs) or multiple sex partners
  - Persons with current or past hepatitis C virus (HCV) infection
  - Persons born in regions with an HBV prevalence equal to or greater than 2%
  - United States-born persons who were not vaccinated as infants and whose parents were born in a region of high HBV prevalence (equal to or greater than 8%)
  - Persons with HIV infection
  - Persons with current or past injection drug use
  - Men who have sex with men
  - Infants born to people who are HBsAg-positive
  - Household contact with a person who has HBV infection
  - Needle-sharing or sexual contacts of persons with known HBV infection
  - Patients receiving predialysis, hemodialysis, peritoneal dialysis, or home dialysis
  - Persons with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels of unclear etiology
  - Persons who request HBV testing due to the potential reluctance to disclose stigmatizing risk factors

Additional Clinical Considerations for HBV Screening

The CDC does not provide guidance on the number of sex partners that confer increased risk for HBV acquisition.[5] Medical providers should consider the number of sex partners, type of sexual activity, and timing of prior HBV testing when deciding on repeat testing for people at risk for HBV acquisition.[5] Similarly, there is no clear guidance on the frequency in which HBV testing should be repeated for persons who remain at risk for infection. Decisions regarding the timing and frequency of repeat testing should be individualized based on risk factors, patient age, and immune status.[5]

Rationale for Universal HBV Screening in Adults

Chronic HBV is an indolent and often silent disease that over time can lead to serious health consequences, including cirrhosis, decompensated liver disease, hepatocellular carcinoma (HCC), and death.[6] Universal screening for HBV has the advantage of averting substantial morbidity and mortality and it has been shown to be cost-effective.[7] In addition, universal screening has a number of benefits at the individual and population levels, which are outlined below.[5]

- Chronic HBV infection can be easily detected before the onset of significant liver disease using reliable and inexpensive tests.[5]
- Multiple safe and effective antiviral options are available for persons who have an indication for treatment and can reduce the morbidity and mortality associated with chronic HBV.[4,8]
- Persons identified to have chronic HBV can undergo evaluation for cirrhosis, and if diagnosed with cirrhosis,& can receive further evaluation, management, and prevention of cirrhosis-related complications.[4,8,9]
- 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 the potential for cure.[10]
- Persons diagnosed with chronic HBV can receive hepatitis A immunization (if nonimmune) and receive counseling on how to minimize additional liver damage, such as avoiding alcohol intake or excessive acetaminophen ingestion.[3]
- Screening can identify persons who would benefit from hepatitis B vaccination or those who are at risk for HBV reactivation.[5]
- Identifying persons with chronic HBV can reduce the population spread of HBV through treatment of HBV and appropriate treatment and prevention measures.[4]
- Screening of pregnant persons can facilitate appropriate management to reduce the risk of perinatal infection.[5]

HBV Tests

A range of serologic tests is utilized to diagnose HBV infection and to determine whether a person lacks immunity to HBV. In addition, there are multiple serologic and non-serologic tests used to risk-stratify and monitor patients with chronic HBV. The following discusses the major tests used for hepatitis B diagnosis and monitoring. 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 below in the section on *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 at least 100 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 Surface Antigen (Anti-HBs): 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 mIU/mL or greater or 12 mIU/mL or greater (depending on the assay). 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: Total Antibody to Hepatitis B Core Antigen (Total anti-HBc): 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 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 major histocompatibility complex (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 therefore IgM anti-HBc is generally not detectable in persons with chronic HBV infection.
- **Hepatitis B e Antigen (HBeAg)**Play animation: Hepatitis B e Antigen (HBeAg): 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 blood 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 HBV 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 e Antigen (Anti-HBe): The appearance of anti-HBe generally is associated 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 these particles 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

Universal Screening

The CDC recommends universal HBV screening for all adults (18 years of age and older) using a 3-test panel, which includes:[5]

1. Hepatitis B surface antigen (HBsAg)
2. Antibody to hepatitis B surface antigen (anti-HBs)
3. Total antibody to hepatitis B core antigen (anti-HBc)

The benefits of using a 3-test panel are that it can identify individuals with current HBV infection, those with prior HBV infection, those with immunity due to prior vaccination, and those who are susceptible to HBV and would benefit from vaccination.[5]

Screening of Pregnant People

Pregnant people should be screened for HBV using the 3-test panel of HBsAg, anti-HBs, and anti-HBc. Pregnant people who have previously undergone HBV screening with a 3-test panel and do not have any subsequent risk for HBV can be screened using HBsAg alone.[5]

Risk-Based Testing

Susceptible persons at increased risk for HBV should be screened using the 3-test panel of HBsAg, anti-HBs, and anti-HBc.[5]

Incorporation of HBV Screening into Clinical Workflows

HBV Screening in Clinical Setting

In the clinic setting, when interacting with non-pregnant adults, the decision to screen for HBV should be based on an individual's prior screening status, vaccination status, and risk factors for HBV (Figure 1) .[5] All individuals who have not been previously screened for HBV should be offered HBV serologic screening, regardless of vaccination status.[5] Similarly, individuals who have previously been screened for HBV but remain susceptible due to lack of vaccination should undergo repeat HBV testing if they have experienced an activity or exposure associated with increased risk for HBV since their last screening. Vaccinated individuals who have previously been screened but experienced increased risk for HBV following their screening (but before vaccination) also warrant repeat testing.[5]

Initiating HBV Immunization Concurrent with Screening

There is no need to wait for serologic results to return prior to initiating hepatitis B vaccination, and individuals who have not completed the hepatitis B vaccine series should be offered vaccination concurrent with HBV screening. When HBV screening and vaccination are offered on the same day, it is important that vaccination occurs after the collection of blood, as hepatitis B vaccination can result in a transient HBsAg positivity for up to 18 days following vaccination.[5] In settings where persons refuse hepatitis B testing, or when serologic testing is not possible, vaccination should not be delayed, and serologic testing can be offered at a subsequent visit, as long as subsequent serologic screening occurs outside the 18 day window for transient HBsAg positivity.[5] Although results of HBV serologic testing need not delay the initiation of the hepatitis B vaccine series, results should guide the need for additional vaccine doses.[5]

Evolution of Serologic Tests after Infection and Vaccination

To 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.[3,11,12] Adults have resolution of 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.[11,12] 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 who recover from acute HBV infection 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 (mostly as IgG). During recovery and after the disappearance of HBsAg, persons who have immunologic control of acute infection will 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, 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.[13] 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 two 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 hepatitis B vaccination, seroprotection is defined by anti-HBs levels of at least 10 to 12 mIU/mL (depending on the assay used) 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.[14,15] Because the hepatitis 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 markers (Table 2).[16,17,18] 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 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 and 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 approximately 4 weeks following HBV acquisition (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 of 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 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 immunization, 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 are not performed, since these tests do not provide any additional diagnostic value over standard recommended tests.

- **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 in conjunction with negative HBsAg and negative anti-HBc 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]

For additional guidance on interpreting HBV serologies, please see the mini-lecture Interpreting Hepatitis B Serologies (included below).

Summary Points

- The CDC recommends universal HBV screening for all adults 18 years of age and older.
- Pregnant people should be screened for HBV during each pregnancy.
- Susceptible persons at increased risk for HBV should undergo periodic testing for HBV, regardless of age, while their risk for exposure persists.
- The CDC recommends using a 3-test panel to screen for HBV, which includes HBsAg, anti-HBs, and anti-HBc.
- 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 two 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 immunization, 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, serologic studies will show positive for anti-HBc and anti-HBs, but anti-HBs levels may wane over time.
- Persons 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.

Citations

1. 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] -

2. LeFevre ML. Screening for hepatitis B virus infection in nonpregnant adolescents and adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2014;161:58-66.
[PubMed Abstract] -

3. Weinbaum CM, Williams I, Mast EE, et al. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. MMWR Recomm Rep. 2008;57:1-20.
[PubMed Abstract] -

4. 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;67:1560-99.
[PubMed Abstract] -

5. 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;72:1-25.
[PubMed Abstract] -

6. Likhitsup A, Lok AS. Understanding the Natural History of Hepatitis B Virus Infection and the New Definitions of Cure and the Endpoints of Clinical Trials. Clin Liver Dis. 2019;23:401-16.
[PubMed Abstract] -

7. Toy M, Hutton D, Harris AM, Nelson N, Salomon JA, So S. Cost-Effectiveness of 1-Time Universal Screening for Chronic Hepatitis B Infection in Adults in the United States. Clin Infect Dis. 2022;74:210-17.
[PubMed Abstract] -

8. Tang LSY, Covert E, Wilson E, Kottilil S. Chronic Hepatitis B Infection: A Review. JAMA. 2018;319:1802-13.
[PubMed Abstract] -

9. Seto WK, Lo YR, Pawlotsky JM, Yuen MF. Chronic hepatitis B virus infection. Lancet. 2018;392:2313-24.
[PubMed Abstract] -

10. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2018;67:358-80.
[PubMed Abstract] -

11. Lee WM. Hepatitis B virus infection. N Engl J Med. 1997;337:1733-45.
[PubMed Abstract] -

12. Mahoney FJ. Update on diagnosis, management, and prevention of hepatitis B virus infection. Clin Microbiol Rev. 1999;12:351-66.
[PubMed Abstract] -

13. Hadziyannis SJ, Papatheodoridis GV. Hepatitis B e antigen-negative chronic hepatitis B: natural history and treatment. Semin Liver Dis. 2006;26:130-41.
[PubMed Abstract] -

14. McMahon BJ, Dentinger CM, Bruden D, et al. Antibody levels and protection after hepatitis B vaccine: results of a 22-year follow-up study and response to a booster dose. J Infect Dis. 2009;200:1390-6. [PubMed Abstract] -

15. Bruce MG, Bruden D, Hurlburt D, et al. Antibody Levels and Protection After Hepatitis B Vaccine: Results of a 30-Year Follow-up Study and Response to a Booster Dose. J Infect Dis. 2016;214:16-22. [PubMed Abstract] -

16. Mushahwar IK, Dienstag JL, Polesky HF, McGrath LC, Decker RH, Overby LR. Interpretation of various serological profiles of hepatitis B virus infection. Am J Clin Pathol. 1981;76:773-7. [PubMed Abstract] -

17. 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] -

18. Trépo C, Chan HL, Lok A. Hepatitis B virus infection. Lancet. 2014;384:2053-63. [PubMed Abstract] -

19. Lada O, Benhamou Y, Poynard T, Thibault V. Coexistence of hepatitis B surface antigen (HBs Ag) and anti-HBs antibodies in chronic hepatitis B virus carriers: influence of "a" determinant variants. J Virol. 2006;80:2968-75. [PubMed Abstract] -

20. Zhang JM, Xu Y, Wang XY, et al. Coexistence of hepatitis B surface antigen (HBsAg) and heterologous subtype-specific antibodies to HBsAg among patients with chronic hepatitis B virus infection. Clin Infect Dis. 2007;44:1161-9. [PubMed Abstract] -

21. Hadler SC, Francis DP, Maynard JE, et al. Long-term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. N Engl J Med. 1986;315:209-14. [PubMed Abstract] -

22. Jack AD, Hall AJ, Maine N, Mendy M, Whittle HC. What level of hepatitis B antibody is protective? J Infect Dis. 1999;179:489-92. [PubMed Abstract] -

References

- Aldershvile J, Frösner GG, Nielsen JO, Hardt F, Deinhardt F, Skinhøj P. Hepatitis B e antigen and antibody measured by radioimmunoassay in acute hepatitis B surface antigen-positive hepatitis. J Infect Dis. 1980;141:293-8. [PubMed Abstract] -

- Aldershvile J, Nielsen JO. HBeAg, anti-HBe and anti-HBc IgM in patients with hepatitis B. J Virol Methods. 1980;2:97-105. [PubMed Abstract] -

- Alhababi F, Sallam TA, Tong CY. The significance of 'anti-HBc only' in the clinical virology laboratory. J Clin Virol. 2003;27:162-9. [PubMed Abstract] -

- Almeida Neto C, Strauss E, Sabino EC, Sucupira MC, Chamone DA. Significance of isolated hepatitis B core antibody in blood donors from São Paulo. Rev Inst Med Trop Sao Paulo. 2001;43:203-8. [PubMed Abstract] -

- Cacciola I, Pollicino T, Squadrito G, Cerenzia G, Orlando ME, Raimondo G. Occult hepatitis B virus infection in patients with chronic hepatitis C liver disease. N Engl J Med. 1999;341:22-6. [PubMed Abstract] -

- Centers for Disease Control and Prevention (CDC). A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States. Recommendations of the Advisory Committee on Immunization Practices (ACIP) Part 1 Immunization of Infants, Children, and Adolescents. MMWR Morb Mortal Wkly Rep. 2005;54(RR-16):1-23. [CDC] -

- Chahal HS, Peters MG, Harris AM, McCabe D, Volberding P, Kahn JG. Cost-effectiveness of Hepatitis B Virus Infection Screening and Treatment or Vaccination in 6 High-risk Populations in the United States. Open Forum Infect Dis. 2019;6:ofy353. [PubMed Abstract] -

- Chou R, Dana T, Bougatsos C, Blazina I, Khangura J, Zakher B. Screening for hepatitis B virus infection in adolescents and adults: a systematic review to update the U.S. Preventive Services Task Force recommendation. Ann Intern Med. 2014;161:31-45. [PubMed Abstract] -

- De Feo TM, Grossi P, Poli F, et al. Kidney transplantation from anti-HBc+ donors: results from a retrospective Italian study. Transplantation. 2006;81:76-80. [PubMed Abstract] -

- Dickson RC, Everhart JE, Lake JR, et al. Transmission of hepatitis B by transplantation of livers from donors positive for antibody to hepatitis B core antigen. The National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database. Gastroenterology. 1997;113:1668-74. [PubMed Abstract] -

- Douglas DD, Taswell HF, Rakela J, Rabe D. Absence of hepatitis B virus DNA detected by polymerase chain reaction in blood donors who are hepatitis B surface antigen negative and antibody to hepatitis B core antigen positive from a United States population with a low prevalence of hepatitis B serologic markers. Transfusion. 1993;33:212-6. [PubMed Abstract] -

- Fong TL, Bunnapradist S, Jordan SC, Cho YW. Impact of hepatitis B core antibody status on outcomes of cadaveric renal transplantation: analysis of United network of organ sharing database between 1994 and 1999. Transplantation. 2002;73:85-9. [PubMed Abstract] -

- French AL, Operskalski E, Peters M, et al. Isolated hepatitis B core antibody is associated with HIV and ongoing but not resolved hepatitis C virus infection in a cohort of US women. J Infect Dis. 2007;195:1437-42. [PubMed Abstract] -

- Gandhi RT, Wurcel A, Lee H, et al. Isolated antibody to hepatitis B core antigen in human immunodeficiency virus type-1-infected individuals. Clin Infect Dis. 2003;36:1602-5. [PubMed Abstract] -

- Gandhi RT, Wurcel A, McGovern B, et al. Low prevalence of ongoing hepatitis B viremia in HIV-positive individuals with isolated antibody to hepatitis B core antigen. J Acquir Immune Defic Syndr. 2003;34:439-41.
[PubMed Abstract] -

- Ganem D, Prince AM. Hepatitis B virus infection--natural history and clinical consequences. N Engl J Med. 2004;350:1118-29.
[PubMed Abstract] -

- Gibney KB, Torresi J, Lemoh C, Biggs BA. Isolated core antibody hepatitis B in sub-Saharan African immigrants. J Med Virol. 2008;80:1565-9.
[PubMed Abstract] -

- Gow PJ, Mutimer DJ. De novo hepatitis B infection acquired during liver transplantation. QJM. 2001;94:271-5.
[PubMed Abstract] -

- Harris AM, Schoenbachler BT, Ramirez G, Vellozzi C, Beckett GA. Testing and Linking Foreign-Born People with Chronic Hepatitis B Virus Infection to Care at Nine U.S. Programs, 2012-2014. Public Health Rep. 2016;131 Suppl 2:20-8.
[PubMed Abstract] -

- Hennig H, Puchta I, Luhm J, Schlenke P, Goerg S, Kirchner H. Frequency and load of hepatitis B virus DNA in first-time blood donors with antibodies to hepatitis B core antigen. Blood. 2002;100:2637-41.
[PubMed Abstract] -

- Holt D, Thomas R, Van Thiel D, Brems JJ. Use of hepatitis B core antibody-positive donors in orthotopic liver transplantation. Arch Surg. 2002;137:572-5.
[PubMed Abstract] -

- Hoofnagle JH, Feinstone SM. Serological tests for non-A, non-B hepatitis: controversy. Liver. 1981;1:177-82.
[PubMed Abstract] -

- Hoofnagle JH, Seeff LB, Bales ZB, Zimmerman HJ. Type B hepatitis after transfusion with blood containing antibody to hepatitis B core antigen. N Engl J Med. 1978;298:1379-83.
[PubMed Abstract] -

- Hui CK, Cheung WW, Zhang HY, et al. Kinetics and risk of de novo hepatitis B infection in HBsAg-negative patients undergoing cytotoxic chemotherapy. Gastroenterology. 2006;131:59-68.
[PubMed Abstract] -

- Joller-Jemelka HI, Wicki AN, Grob PJ. Detection of HBs antigen in "anti-HBc alone" positive sera. J Hepatol. 1994;21:269-72.
[PubMed Abstract] -

- Kitchen AD, Harrison TJ, Meacock TJ, Zuckerman AJ, Harrison JF. Incidence and significance of hepatitis B core antibody in a healthy blood donor population. J Med Virol. 1988;25:69-75.
[PubMed Abstract] -

- Krajden M, McNabb G, Petric M. The laboratory diagnosis of hepatitis B virus. Can J Infect Dis Med Microbiol. 2005;16:65-72.
[PubMed Abstract] -

- Krogsgaard K, Aldershvile J, Kryger P, Andersson P, Nielsen JO, Hansson BG. Hepatitis B virus DNA, HBeAg and delta infection during the course from acute to chronic hepatitis B virus infection. Hepatology. 1985;5:778-82.
[PubMed Abstract] -

- Lee C, Gong Y, Brok J, Boxall EH, Gluud C. Hepatitis B immunisation for newborn infants of hepatitis B surface antigen-positive mothers. Cochrane Database Syst Rev. 2006;:CD004790.
[PubMed Abstract] -

- Lok AS, Everhart JE, Di Bisceglie AM, Kim HY, Hussain M, Morgan TR. Occult and previous hepatitis B virus infection are not associated with hepatocellular carcinoma in United States patients with chronic hepatitis C. Hepatology. 2011;54:434-42.
[PubMed Abstract] -

- Lok AS, Lai CL, Wu PC. Prevalence of isolated antibody to hepatitis B core antigen in an area endemic for hepatitis B virus infection: implications in hepatitis B vaccination programs. Hepatology. 1988;8:766-70.
[PubMed Abstract] -

- Mast EE, Weinbaum CM, Fiore AE, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) Part II: immunization of adults. MMWR Recomm Rep. 2006;55:1-33.
[PubMed Abstract] -

- Matsue K, Kimura S, Takanashi Y, et al. Reactivation of hepatitis B virus after rituximab-containing treatment in patients with CD20-positive B-cell lymphoma. Cancer. 2010;116:4769-76.
[PubMed Abstract] -

- Nelson NP, Easterbrook PJ, McMahon BJ. Epidemiology of Hepatitis B Virus Infection and Impact of Vaccination on Disease. Clin Liver Dis. 2016;20:607-28.
[PubMed Abstract] -

- Pawlotsky JM. The concept of hepatitis B virus mutant escape. J Clin Virol. 2005;34 Suppl 1:S125-9.
[PubMed Abstract] -

- Peeling RW, Boeras DI, Marinucci F, Easterbrook P. The future of viral hepatitis testing: innovations in testing technologies and approaches. BMC Infect Dis. 2017;17:699.
[PubMed Abstract] -

- Prieto M, Gómez MD, Berenguer M, et al. De novo hepatitis B after liver transplantation from hepatitis B core antibody-positive donors in an area with high prevalence of anti-HBc positivity in the donor population. Liver Transpl. 2001;7:51-8.
[PubMed Abstract] -

- Puoti M, Airoldi M, Bruno R, et al. Hepatitis B virus co-infection in human immunodeficiency virus-infected subjects. AIDS Rev. 2002;4:27-35.
[PubMed Abstract] -

- Quaglio G, Lugoboni F, Vento S, et al. Isolated presence of antibody to hepatitis B core antigen in injection drug users: do they need to be vaccinated? Clin Infect Dis. 2001;32:E143-4.
[PubMed Abstract] -

- Ramirez G, Cabral R, Patterson M, et al. Early Identification and Linkage to Care for People with

Chronic HBV and HCV Infection: The HepTLC Initiative. Public Health Rep. 2016;131 Suppl 2:5-11.
[PubMed Abstract] -

- Rehermann B, Ferrari C, Pasquinelli C, Chisari FV. The hepatitis B virus persists for decades after patients' recovery from acute viral hepatitis despite active maintenance of a cytotoxic T-lymphocyte response. Nat Med. 1996;2:1104-8.
[PubMed Abstract] -

- Schillie S, Murphy TV, Sawyer M, et al. CDC guidance for evaluating health-care personnel for hepatitis B virus protection and for administering postexposure management. MMWR Recomm Rep. 2013;62:1-19.
[PubMed Abstract] -

- Schmeltzer P, Sherman KE. Occult hepatitis B: clinical implications and treatment decisions. Dig Dis Sci. 2010;55:3328-35.
[PubMed Abstract] -

- Silva AE, McMahon BJ, Parkinson AJ, Sjogren MH, Hoofnagle JH, Di Bisceglie AM. Hepatitis B virus DNA in persons with isolated antibody to hepatitis B core antigen who subsequently received hepatitis B vaccine. Clin Infect Dis. 1998;26:895-7.
[PubMed Abstract] -

- Suehiro T, Shimada M, Kishikawa K, et al. Prevention of hepatitis B virus infection from hepatitis B core antibody-positive donor graft using hepatitis B immune globulin and lamivudine in living donor liver transplantation. Liver Int. 2005;25:1169-74.
[PubMed Abstract] -

- Tedder RS, Ijaz S, Gilbert N, et al. Evidence for a dynamic host-parasite relationship in e-negative hepatitis B carriers. J Med Virol. 2002;68:505-12.
[PubMed Abstract] -

- Tong S, Kim KH, Chante C, Wands J, Li J. Hepatitis B Virus e Antigen Variants. Int J Med Sci. 2005;2:2-7.
[PubMed Abstract] -

- Torbenson M, Thomas DL. Occult hepatitis B. Lancet Infect Dis. 2002;2:479-86.
[PubMed Abstract] -

- Tsang TK, Blei AT, O'Reilly DJ, Decker R. Clinical significance of concurrent hepatitis B surface antigen and antibody positivity. Dig Dis Sci. 1986;31:620-4.
[PubMed Abstract] -

- US Preventive Services Task Force, Owens DK, Davidson KW, et al. Screening for Hepatitis B Virus Infection in Pregnant Women: US Preventive Services Task Force Reaffirmation Recommendation Statement. JAMA. 2019;322:349-54.
[PubMed Abstract] -

- Weber B, Melchior W, Gehrke R, Doerr HW, Berger A, Rabenau H. Hepatitis B virus markers in anti-HBc only positive individuals. J Med Virol. 2001;64:312-9.
[PubMed Abstract] -

- Witt MD, Lewis RJ, Rieg G, Seaberg EC, Rinaldo CR, Thio CL. Predictors of the isolated hepatitis B core antibody pattern in HIV-infected and -uninfected men in the multicenter AIDS cohort study. Clin Infect Dis. 2012;56:606-12.
[PubMed Abstract] -

Figures

Figure 1 Incorporating HBV Screening and Testing into a Clinic Workflow: Nonpregnant Adults Aged ≥18 Years without a Known History of HBV Infection

Source: 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;72:1-25.

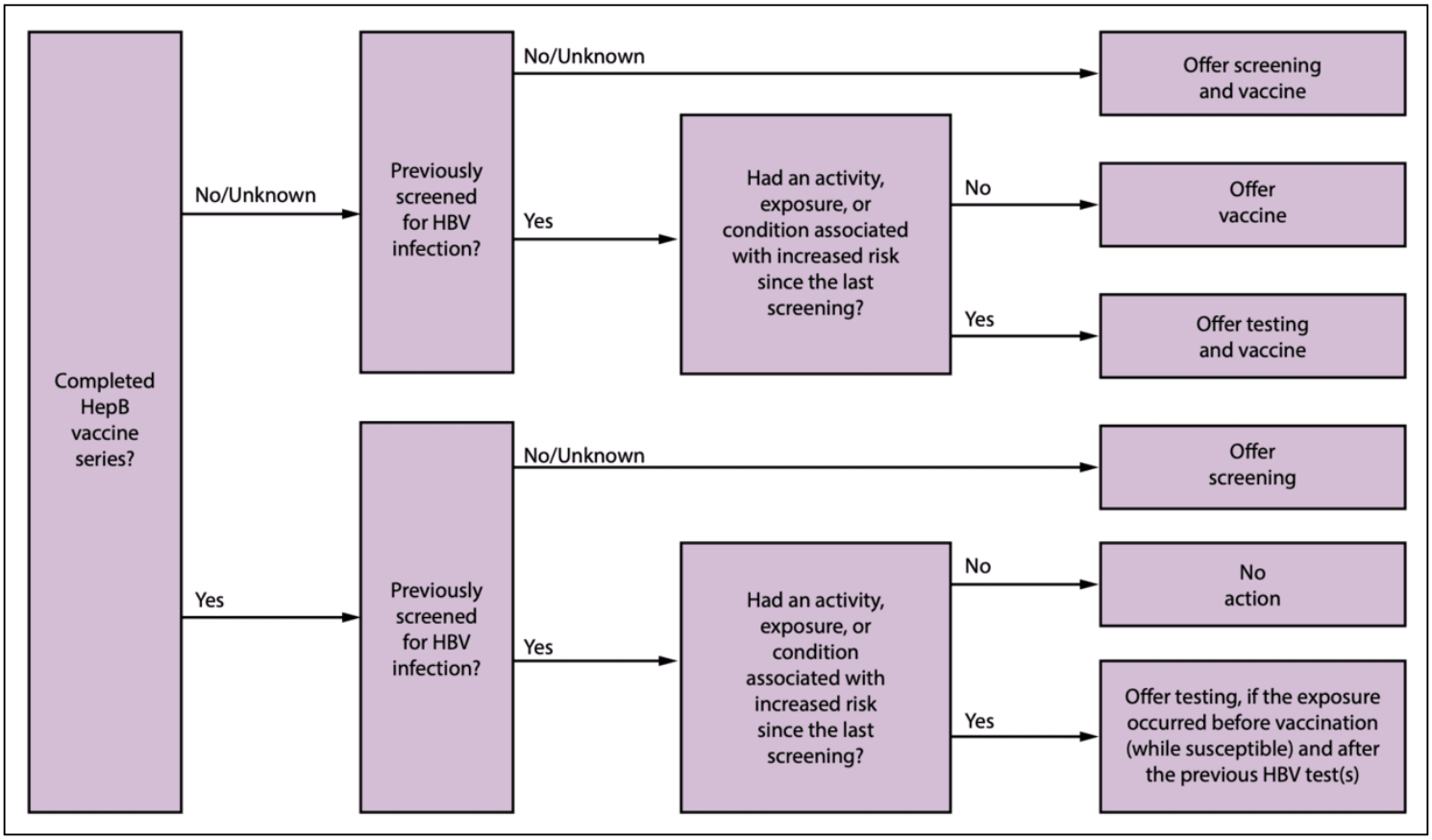

Table 1.

Global Prevalence of Chronic HBV Infection, by Country

Prevalence Category	Country
High (≥8%)	Angola, Cabo Verde, Central African Republic, Chad, Eswatini, Ghana, Guinea, Guinea-Bissau, Kiribati, Lesotho, Liberia, Mali, Mauritania, Niger, Nigeria, Philippines, Sao Tome and Principe, Sierra Leone, Solomon Islands, Taiwan, Timor-Leste, Togo, Tonga, Turkmenistan, Tuvalu, and Zimbabwe.
Intermediate (5.0-7.9%)	Albania, Benin, Burkina Faso, Cameroon, China, Côte d'Ivoire, Democratic People's Republic of Korea, Djibouti, Eritrea, Ethiopia, Federated States of Micronesia, Gabon, Indonesia, Kyrgyzstan, Moldova, Mongolia, Mozambique, Myanmar, Papua New Guinea, Senegal, Somalia, South Sudan, Syria, Tajikistan, Uzbekistan, Vanuatu, and Vietnam.
Low Intermediate (2.0-4.9%)	Afghanistan, Azerbaijan, Bangladesh, Belarus, Bosnia and Herzegovina, Bulgaria, Burundi, Cambodia, Comoros, Congo, Democratic Republic of Congo, Gambia, Georgia, Guyana, Haiti, Hong Kong, India, Iraq, Jamaica, Jordan, Kazakhstan, South Korea, Laos, Madagascar, Malawi, Malaysia, Marshall Islands, Oman, Pakistan, Romania, Rwanda, Samoa, Singapore, South Africa, Sri Lanka, Sudan, Tanzania, Thailand, Trinidad and Tobago, Tunisia, Turkey, Uganda, Yemen, and Zambia.
Low	Algeria, Argentina,

Prevalence Category	Country
(≤1.9%)	Armenia, Australia, Austria, Bahrain, Belgium, Belize, Bhutan, Bolivia, Brazil, Canada, Chile, Colombia, Costa Rica, Croatia, Cuba, Czechia, Denmark, Dominican Republic, Ecuador, Egypt, El Salvador, Estonia, Fiji, Finland, France, Germany, Greece, Guatemala, Honduras, Hungary, Iran, Ireland, Israel, Italy, Japan, Kenya, Kosovo, Kuwait, Lebanon, Libya, Mexico, Morocco, Nepal, Netherlands, New Zealand, Nicaragua, Norway, Palestine, Panama, Paraguay, Peru, Poland, Portugal, Qatar, Russia, Saudi Arabia, Slovakia, Slovenia, Spain, Suriname, Sweden, Switzerland, Ukraine, United Arab Emirates, United Kingdom, United States, and Venezuela.
Unknown prevalence (data not available)	American Samoa, Andorra, Anguilla, Antigua and Barbuda, Aruba, Bahamas, Barbados, Bermuda, Bonaire Sint Eustatius and Saba, Botswana, British Virgin Islands, Brunei, Cayman Islands, Cook Islands, Curaçao, Cyprus, Dominica, Equatorial Guinea, Falkland Islands, Faroe Islands, French Guiana, French Polynesia, Gibraltar, Greenland, Grenada, Guadeloupe, Guam, Holy See, Iceland, Isle of Man, Latvia, Liechtenstein, Lithuania, Luxembourg, Macao, Macedonia, Maldives, Malta, Martinique, Mauritius, Mayotte, Monaco, Montenegro, Montserrat, Namibia,

Prevalence Category	Country
	Nauru, New Caledonia, Niue, Northern Mariana Islands, Palau, Puerto Rico, Réunion, Saint Barthélemy, Saint Helena, Saint Kitts and Nevis, Saint Lucia, Saint Martin, Saint Pierre and Miquelon, Saint Vincent and the Grenadines, San Marino, Serbia, Seychelles, Sint Maarten, Tokelau, Turks and Caicos Islands, U.S. Virgin Islands, Uruguay, Wallis and Futuna, and Western Sahara.

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

- 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;72:1-25. [PubMed Abstract]

Table 2.

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

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]