

Screening for Hepatitis B Virus Infection in Nonpregnant Adolescents and Adults: Recommendation Statement

As published by the U.S. Preventive Services Task Force.

This summary is one in a series excerpted from the Recommendation Statements released by the USPSTF. These statements address preventive health services for use in primary care clinical settings, including screening tests, counseling, and preventive medications.

The complete version of this statement, including supporting scientific evidence, evidence tables, grading system, members of the USPSTF at the time this recommendation was finalized, and references, is available on the USPSTF website at <http://www.uspreventiveservicestaskforce.org/>.

This series is coordinated by Sumi Sexton, MD, Associate Medical Editor.

A collection of USPSTF recommendation statements published in *AFP* is available at <http://www.aafp.org/afp/uspstf>.

Summary of Recommendation and Evidence

The USPSTF recommends screening for hepatitis B virus (HBV) infection in persons at high risk for infection (*Table 1*). **B recommendation.**

See the Clinical Considerations section for more information about risk factors for HBV infection.

Rationale

IMPORTANCE

Approximately 700,000 to 2.2 million persons in the United States have chronic HBV infection.¹⁻³ In the United States, persons considered at high risk for HBV infection include those from countries with a high prevalence of HBV infection, HIV-positive persons, injection drug users, household contacts of persons with HBV infection, and men who have sex with men.²

The natural history of chronic HBV infection varies but can include the potential long-term sequelae of cirrhosis, hepatic decompensation, and hepatocellular carcinoma. An estimated 15% to 25% of persons with chronic HBV infection die of cirrhosis or hepatocellular carcinoma.^{2,4} Those with chronic infection also serve as a reservoir for person-to-person transmission of HBV infection. Screening for HBV infection could identify chronically infected persons who may benefit from treatment or other interventions, such as surveillance for hepatocellular carcinoma.

DETECTION

Identification of chronic HBV infection based on serologic markers is considered accurate. Immunoassays for detecting hepatitis B surface antigen (HBsAg) have a reported sensitivity and specificity of greater than 98%.

BENEFITS OF DETECTION AND EARLY INTERVENTION

The USPSTF found no randomized, controlled trials that provide direct evidence of the health benefits (that is, reduction in morbidity, mortality, and disease transmission) of screening for HBV infection in asymptomatic, nonpregnant adolescents and adults.

The USPSTF found adequate evidence that HBV vaccination is effective at decreasing disease acquisition.

The USPSTF found convincing evidence that antiviral treatment in patients with chronic HBV infection is effective at improving intermediate outcomes (that is, virologic or histologic improvement or clearance of hepatitis B e antigen [HBeAg]) and adequate evidence that antiviral regimens improve health outcomes (such as reduced risk for hepatocellular carcinoma). The evidence showed an association between improvement in intermediate outcomes after antiviral therapy and improvement in clinical outcomes, but outcomes were heterogeneous and the studies had methodological limitations.

The USPSTF found inadequate evidence that education or behavior change counseling reduces disease transmission.

The prevalence of HBV infection differs among various populations. As a result, the magnitude of benefit of screening varies according to risk group.

The USPSTF concludes that screening is of moderate benefit for populations at high risk for HBV infection, given the accuracy of the screening test and the effectiveness of antiviral treatment.

HARMS OF DETECTION AND EARLY INTERVENTION

The USPSTF found inadequate evidence on the harms of screening for HBV infection.

Although evidence to determine the magnitude of harms of screening is limited, the USPSTF considers these harms to be small to none.

The USPSTF found adequate evidence that antiviral therapy regimens are associated with a higher risk for withdrawal due to adverse events than placebo. However, trials found no difference in the risk for serious adverse events or the number of participants who had any adverse event. In addition, most antiviral adverse events are self-limited with discontinuation of therapy. The USPSTF

found adequate evidence that the magnitude of harms of treatment is small to none.

USPSTF ASSESSMENT

The USPSTF concludes with moderate certainty that screening for HBV infection in persons at high risk for infection has moderate net benefit.

Clinical Considerations

PATIENT POPULATION UNDER CONSIDERATION

This recommendation applies to asymptomatic, nonpregnant adolescents and adults

Table 1. Screening for Hepatitis B Virus Infection in Nonpregnant Adolescents and Adults: Clinical Summary of the USPSTF Recommendation

Population	Asymptomatic, nonpregnant adolescents and adults who have not been vaccinated for hepatitis B virus (HBV) infection and other high-risk individuals (including persons who were vaccinated prior to being screened for HBV)
Recommendation	Screen persons at high risk for HBV infection. Grade: B
Risk assessment	Important risk groups for HBV infection with a prevalence of $\geq 2\%$ that should be screened include: Persons born in countries and regions with a high prevalence of HBV infection ($\geq 2\%$) U.S.-born persons not vaccinated as infants whose parents were born in regions with a very high prevalence of HBV infection ($\geq 8\%$), such as sub-Saharan Africa and southeast and central Asia HIV-positive persons Injection drug users Men who have sex with men Household contacts or sexual partners of persons with HBV infection For more information on countries and regions with a high prevalence of HBV infection, visit: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5708a1.htm .
Screening tests	A U.S. Food and Drug Administration–approved hepatitis B surface antigen (HBsAg) test followed by a licensed, neutralizing confirmatory test for initially reactive results should be used to screen for HBV infection. Testing for antibodies to HBsAg (anti-HBs) and hepatitis B core antigen (anti-HBc) is also done as part of a screening panel to help distinguish between infection and immunity. Diagnosis of chronic HBV infection is characterized by persistence of HBsAg for at least 6 mo.
Treatment	HBV treatment consists of antiviral regimens. Approved first-line treatments are pegylated interferon α 2a, entecavir, and tenofovir. Duration of treatment varies depending on time required to achieve HBV DNA suppression and normalize alanine aminotransferase levels; the presence of HBeAg, coinfection, and cirrhosis; and the choice of drug.
Balance of benefits and harms	There is moderate certainty that screening for HBV infection in persons at high risk for infection has moderate net benefit.
Other relevant USPSTF recommendations	The USPSTF has made recommendations on screening for HBV infection in pregnant women and screening for hepatitis C virus infection in adults. These recommendations are available at http://www.uspreventiveservicestaskforce.org .

NOTE: For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, go to <http://www.uspreventiveservicestaskforce.org>.

HIV = human immunodeficiency virus; USPSTF = U.S. Preventive Services Task Force.

who have not been vaccinated and other persons at high risk for HBV infection (including those at high risk who were vaccinated before being screened for HBV infection).

ASSESSMENT OF RISK

A major risk factor for HBV infection is country of origin. The risk for HBV infection varies substantially by country of origin in foreign-born persons in the United States. Persons born in countries with a prevalence of HBV infection of 2% or greater account for 47% to 95% of those with chronic HBV infection in the United States (*Table 2*).² Another important risk factor for HBV infection is lack of vaccination in infancy in U.S.-born persons with parents from a country or region with high prevalence ($\geq 8\%$), such as sub-Saharan Africa, central and southeast Asia, and China^{1-3,5} (see figure at <http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/hepatitis-b-virus-infection-screening-2014#figure-prevalence-of-hbv-adults-ages-19-to-49-years-2005>). Because HBV infection prevalence may gradually change over time, it is important to note that some countries and regions with prevalence rates between 5-7% are considered to be highly endemic areas.

The Centers for Disease Control and Prevention (CDC) uses a prevalence threshold of 2% or greater to define countries with high risk for HBV infection.² Because this threshold is substantially higher than the estimated prevalence of HBV infection in the general U.S. population (0.3% to 0.5%),^{2,4,6} it is a reasonable threshold for deciding to screen a patient population or risk group. Additional risk groups for HBV infection with a prevalence of 2% or greater that should be screened include HIV-positive persons, injection drug users, household contacts of persons with HBV infection, and men who have sex with men^{2,7,8} (*Table 3*^{2,6,7}).

The CDC also recommends screening in persons receiving hemodialysis or cytotoxic or immunosuppressive therapy (for example, chemotherapy for malignant diseases and immunosuppression related to organ transplantation and for rheumatologic and gastroenterologic disorders).²

Table 2. Geographic Regions with an HBsAg Prevalence $\geq 2\%$ *

Region†	Countries‡
Africa	All
Asia§	All
Australia and South Pacific	All except Australia and New Zealand
Middle East	All except Cyprus and Israel
Eastern Europe	All except Hungary
Western Europe	Malta, Spain, and indigenous populations in Greenland
North America	Alaska natives and indigenous populations in northern Canada
Mexico and Central America	Guatemala and Honduras
South America	Ecuador; Guyana; Suriname; Venezuela; and Amazonian areas of Bolivia, Brazil, Colombia, and Peru
Caribbean	Antigua and Barbuda, Dominica, Grenada, Haiti, Jamaica, St. Kitts and Nevis, St. Lucia, and Turks and Caicos Islands

HBsAg = hepatitis B surface antigen.

*—Adapted from reference 2. Estimates of prevalence of HBsAg, a marker of chronic hepatitis B virus infection, are based on limited data and may not reflect current prevalence in countries that have implemented childhood hepatitis B virus vaccination. In addition, the prevalence of HBsAg may vary within countries by subpopulation and locality.

†—The regions with the highest prevalence ($> 5\%$) are sub-Saharan Africa and central and southeast Asia. See <http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/hepatitis-b-virus-infection-screening-2014#figure-prevalence-of-hbv-adults-ages-19-to-49-years-2005>.

‡—A complete list of countries in each region is available at <http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/hepatitis-b>.

§—Asia includes 3 regions: southeast, east, and north Asia.

Some persons with combinations of risk factors who are not members of one of these risk factor groups may also be at increased risk for HBV infection. However, reliable information about combinations of risk factors is not available. Clinicians should exercise their judgment in deciding whether these persons are at sufficiently high risk to warrant screening. For example, screening is probably appropriate in settings that treat a large proportion of persons at increased risk, such as clinics for sexually transmitted infections; HIV testing and treatment centers; health care settings that provide services for injection drug users or men who have sex with men; correctional facilities; and institutions that serve populations from countries with a high prevalence of infection, including community health centers.²

Table 3. Prevalence of HBV Infection, by Risk Group

Risk group	Persons with HBV infection, %	Reference
HIV-positive persons*	4.0–17.0	2, 6
Injection drug users	2.7–11.0	2, 7
Household contacts or sexual partners of persons with HBV infection	3.0–20.0	2
Men who have sex with men	1.1–2.3	2

HBV = hepatitis B virus; HIV = human immunodeficiency virus.

*—Data from the United States and Western Europe.

Information from references 2, 6, and 7.

The prevalence of HBV infection is low in the general U.S. population, and most infected persons do not develop complications. Therefore, screening is not recommended in those who are not at increased risk. The USPSTF notes that high rates of HBV infection have been found in cities and other areas with high numbers of immigrants or migrant persons from Asia or the Pacific Islands or their adult children.⁹ Providers should consider the population they serve when making screening decisions.

SCREENING TESTS

The CDC recommends screening for HBsAg with tests approved by the U.S. Food and Drug Administration, followed by a licensed, neutralizing confirmatory test for initially reactive results.² Immunoassays for detecting HBsAg have a reported sensitivity and specificity greater than 98%.¹⁰ A positive HBsAg result indicates acute or chronic infection.

Testing for antibodies to HBsAg (anti-HBs) and hepatitis B core antigen (anti-HBc) is also done as part of a screening panel to help distinguish between infection and immunity. Acute HBV infection (acquired within 6 months after infection) is characterized by the appearance of HBsAg and followed by the appearance of IgM anti-HBc. The disappearance of HBsAg and the presence of anti-HBs and anti-HBc indicate the resolution of HBV infection and natural immunity. Anti-HBc, which persist for life, are present only after HBV infection and do not develop in persons whose immunity to HBV is due to vaccination.

Persons who have received HBV vaccination have only anti-HBs. Diagnosis of chronic HBV infection is characterized by persistence of HBsAg for at least 6 months. Levels of HBV DNA can fluctuate and are not a reliable marker of chronic infection.^{1,2,11}

TREATMENT

Antiviral Regimens. The goals of antiviral treatment are to achieve sustained suppression of HBV replication and remission of liver disease to prevent cirrhosis, hepatic failure, and hepatocellular carcinoma. Interferons or nucleoside or nucleotide analogues are used to treat HBV infection. The U.S. Food and Drug Administration has approved 7 antiviral drugs for treatment of chronic HBV infection: interferon- α 2b, pegylated interferon- α 2a, lamivudine, adefovir, entecavir, telbivudine, and tenofovir. Approved first-line treatments are pegylated interferon- α 2a, entecavir, and tenofovir. Combination therapies have been evaluated but are not approved by the U.S. Food and Drug Administration and are generally not used as first-line treatment because tolerability, efficacy, and rates of resistance are low.¹

Several factors affect the choice of antiviral drug, including patient characteristics, HBV DNA and serum aminotransferase levels, and HBeAg status. Biopsy is sometimes done to determine the extent of liver inflammation and fibrosis.¹ Surrogate end points of antiviral treatment include loss of HBeAg and HBsAg, HBeAg seroconversion in HBeAg-positive patients, and suppression of HBV DNA to undetectable levels by polymerase chain reaction in patients who are HBeAg-negative and anti-HBe-positive.^{2,11} Duration of treatment varies depending on the time required to suppress HBV DNA levels and normalize alanine aminotransferase (ALT) levels; HBeAg status; the presence of cirrhosis; and the choice of drug.¹

Vaccination. The current U.S. strategy to eliminate HBV transmission includes universal vaccination of all infants at birth and vaccination of adolescents and high-risk adults, such as injection drug users and household contacts of patients with HBV infection.^{1,12} Three doses of HBV vaccine result in a protective antibody response of greater than 90% in adults and greater than

95% in adolescents.¹ The CDC recommends that susceptible persons who are screened for HBV infection may, if indicated, receive the first dose of the HBV vaccine at the same medical visit.^{2,13}

SCREENING INTERVAL

Periodic screening may be useful in patients with ongoing risk for HBV transmission (for example, active injection drug users, men who have sex with men, and patients receiving hemodialysis) who do not receive vaccination. Clinical judgment should determine screening frequency, because the USPSTF found inadequate evidence to determine specific screening intervals.

This recommendation statement was first published in *Ann Intern Med.* 2014;161(1):58-66.

The "Other Considerations," "Discussion," "Update of the Previous USPSTF Recommendation," and "Recommendations of Others" sections of this recommendation statement are available at <http://www.uspreventiveservicestaskforce.org/Page/Topic/recommendation-summary/hepatitis-b-virus-infection-screening-2014>.

The USPSTF recommendations are independent of the U.S. government. They do not represent the views of the Agency for Healthcare Research and Quality, the U.S. Department of Health and Human Services, or the U.S. Public Health Service.

REFERENCES

1. Chou R, Dana T, Bougatsos C, Blazina I, Khangura J, Zakher B. Screening for hepatitis B virus infection in nonpregnant adolescents and adults: a systematic review to update the U.S. Preventive Services Task Force recommendation. *Ann Intern Med.* [in press]
2. Weinbaum CM, Williams I, Mast EE, Wang SA, Finelli L, Wasley A, et al; Centers for Disease Control and Prevention. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep.* 2008;57(RR-8):1-20.
3. Kowdley KV, Wang CC, Welch S, Roberts H, Brosgart CL. Prevalence of chronic hepatitis B among foreign-born persons living in the United States by country of origin. *Hepatology.* 2012;56:422-33.
4. Chou R, Dana T, Bougatsos C, Blazina I, Zakher B, Khangura J. Screening for Hepatitis B Virus Infection in Non-pregnant Adolescents and Adults: Systematic Review to Update the 2004 U.S. Preventive Services Task Force Recommendation. Evidence Synthesis No. 110. AHRQ Publication No. 12-05172-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2014.
5. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity. *Vaccine.* 2012;30:2212-9.
6. Wilkins T, Zimmerman D, Schade RR. Hepatitis B: diagnosis and treatment. *Am Fam Physician.* 2010;81:965-72.
7. Alter MJ. Epidemiology of viral hepatitis and HIV co-infection. *J Hepatol.* 2006;44:S6-9.
8. Torbenson M, Kannangai R, Astemborski J, Strathdee SA, Vlahov D, Thomas DL. High prevalence of occult hepatitis B in Baltimore injection drug users. *Hepatology.* 2004;39:51-7.
9. Lin SY, Chang ET, So SK. Why we should routinely screen Asian American adults for hepatitis B: a cross-sectional study of Asians in California. *Hepatology.* 2007;46:1034-40.
10. U.S. Preventive Services Task Force. Screening for hepatitis B virus infection in pregnancy: U.S. Preventive Services Task Force reaffirmation recommendation statement. *Ann Intern Med.* 2009;150:869-73.
11. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology.* 2009;50:661-2.
12. Mast EE, Margolis HS, Fiore AE, Brink EW, Goldstein ST, Wang SA, et al; Advisory Committee on Immunization Practices. 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 Recomm Rep.* 2005;54(RR-16):1-31.
13. Mast EE, Weinbaum CM, Fiore AE, Alter MJ, Bell BP, Finelli L, et al; Advisory Committee on Immunization Practices Centers for Disease Control and Prevention. 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(RR-16):1-33.■