Draft for Public Comment

CDC Recommendations for Hepatitis B Screening and Testing — United States, 2022

Introduction

Persons with chronic hepatitis B (HBV) infection are at increased risk for liver cancer and cirrhosis and are 70%–85% more likely to die prematurely than the general population (1-4). Between 880,000 to 1.89 million persons are living with HBV infection in the United States (5, 6); two-thirds of whom may be unaware of their infection (7). Chronic hepatitis B disproportionately affects persons born outside the United States; while accounting for only 14% of the U.S. general population, non–U.S.-born persons account for 69% of the U.S. population living with chronic HBV infection (5, 6, 8).

Hepatitis B is transmitted through contact with infected blood or body fluids, such as through sex, injection-drug use, or from birth to an infected mother. Hepatitis B vaccination is highly effective in preventing infection with HBV and subsequent liver disease; however, 70% of adults in the United States self-reported they were unvaccinated as of 2018 (9). While current treatment is not considered curative, recommended treatment and monitoring can reduce morbidity and mortality (10, 11).

Providing a framework to reach the World Health Organization (WHO) viral hepatitis elimination goals, the *Viral Hepatitis National Strategic Plan for the United States* calls for an increase in the proportion of persons with HBV infection who are aware of their infection from 32% (2013–2016) to 90% by 2030 (12). In support of this goal, this report uses current evidence to update previous 2008 CDC recommendations for risk-based testing and management of persons with chronic hepatitis B in the United States (13). This report is a resource for health care professionals, public health officials, and organizations supporting awareness, prevention, and linkage to care.

Hepatitis B Screening and Testing Recommendations

The following recommendations for hepatitis B screening augment those issued by CDC in 2008 (13). CDC recommends (Box 1):

- Universal hepatitis B screening

  - Hepatitis B screening at least once in a lifetime for adults aged ≥18 years (new recommendation).
  - During screening, test for hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (anti-HBs), and total antibody to hepatitis B core antigen (anti-HBc) (new recommendation). Screening with the three tests ("3-test panel") can help identify persons who have a current HBV infection, have resolved infection and who may be susceptible to reactivation, are susceptible and need vaccination, or are vaccinated[1] (Table 1).

- Screening pregnant persons
  - Hepatitis B screening for all pregnant persons during each pregnancy, preferably in the first trimester, regardless of vaccination status or history of testing (14).
  - Pregnant adults aged ≥18 years should be screened with the 3-test panel unless they have received screening with the 3-test panel in the past (new recommendation). Adults with a history of 3-test panel screening and without subsequent risk can be tested for only HBsAg during pregnancy.
- Risk-based testing
  - Testing for all individuals with a history of increased risk for HBV infection (Box 2), regardless of age, if they were susceptible during the period of increased risk (Figure 1). Susceptible persons include those who have never been infected with HBV and either did not receive a U.S. licensed hepatitis B vaccine series completed according to the recommended schedule or who are known vaccine nonresponders (14). Persons with a history of appropriately timed 3-test panel screening and without subsequent risk do not need to be retested.

[1] Anti-HBs ≥10 mIU/mL is a known correlate of protection only when testing follows a complete hepatitis B (HepB) vaccine series

- Periodic testing for susceptible persons, regardless of age, with ongoing risk for exposure(s), while risk for exposures(s) persist. Offer testing if the risk for exposure occurred after previous HBV tests and while the person was susceptible (Figure 1).

- The following persons have an increased risk for HBV infection:
  - persons currently or formerly incarcerated in a jail, prison, or other detention setting (new recommendation);
  - persons with current or past sexually transmitted infections (STIs) or multiple sex partners (new recommendation);
  - persons with current or past hepatitis C virus infection (new recommendation);
  - persons born in regions with HBV prevalence ≥2% (Box 3);
  - U.S.-born persons not vaccinated as infants whose parents were born in regions with HBV prevalence ≥8% (Box 3);
  - persons with HIV infection;
  - persons with current or past injection-drug use (IDU);
  - men who have sex with men (MSM);
  - infants born to HBsAg-positive persons (refer to *Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices* (14) for additional information on postvaccination serologic testing);
  - household, needle-sharing, or sexual contacts of persons with known HBV infection;
  - patients receiving predialysis, hemodialysis, peritoneal dialysis, or home dialysis (refer to *Recommendations for preventing transmission of infections among chronic hemodialysis patients*(15) for recommendations for hemodialysis patients); and
  - persons with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels of unknown origin.

- Anyone who requests hepatitis B testing may receive it, regardless of disclosure of risk, because many may be reluctant to disclose stigmatizing risks (new recommendation).

Screening for HBV infection is justified by the following: 1) HBV infection has substantial morbidity and mortality; 2) chronic infection can be detected before the onset of symptoms of liver disease using reliable and inexpensive screening tests; 3) treatment for chronic HBV infection can reduce morbidity and mortality; 4) universal screening of adults is cost-effective; and 5) screening can identify persons who are at risk for reactivation or who would benefit from vaccination.

Recommendations for screening blood donors, newly arrived refugees, persons initiating cytotoxic or immunosuppressive therapy, and for testing hemodialysis patients and persons involved in exposure events that may warrant postexposure prophylaxis and postvaccination serologic testing, are described elsewhere (13-18).

Clinical considerations

Screening among adults aged >80 years should consider the clinical benefits of screening for individual patients. Frequency of periodic testing should be a shared decision between the patient and provider based on individual risk factors and immune status. Having multiple sex partners can increase the risk for exposure to HBV and other STIs, but there is currently insufficient evidence to specify the number of sex partners and the time frame for screening to identify cases of chronic infection. Consider the number of partners, type of sex, and timing of last test when recommending testing for persons with multiple sex partners.

BOX 1. Hepatitis B screening and testing recommendations

Universal hepatitis B screening

- Hepatitis B screening at least once in a lifetime for adults aged ≥18 years (new recommendation)

Screening pregnant persons

- Hepatitis B screening for all pregnant persons during each pregnancy, preferably in the first trimester, regardless of vaccination status or history of testing* (14)

Risk-based testing

- Testing for all individuals with a history of increased risk for hepatitis B virus (HBV) infection (Box 2), regardless of age, if they were susceptible during the period of increased risk† (Figure 1)
- Periodic testing for susceptible persons, regardless of age, with ongoing risk for exposure(s), while risk for exposures(s) persist
- During screening, test for HBsAg, anti-HBs, and total anti-HBc (new recommendation)

* Pregnant adults should be screened with the 3-test panel, unless they have received screening with the 3-test panel in the past. Adults with a history of 3-test panel screening and without subsequent risk can be tested for only HBsAg during pregnancy.

† Susceptible persons include those who have never been infected with HBV and either did not receive a U.S. licensed hepatitis B vaccine series completed according to the recommended schedule or who are known vaccine nonresponders.

BOX 2. Activities, exposures, or conditions associated with an increased risk for HBV infection

- Incarceration in a jail, prison, or other detention setting (New recommendation)
- STIs or multiple sex partners (new recommendation)
- Hepatitis C virus infection (new recommendation)
- Persons who request hepatitis B testing (new recommendation)
- Persons born in regions with HBV prevalence ≥2%*
- U.S.-born persons not vaccinated as infants whose parents were born in regions with HBV prevalence ≥8%*
- HIV infection
- Injection-drug use
- Men who have sex with men
- Infants born to HBsAg-positive persons†
- Household, needle-sharing, or sexual contacts of persons with known HBV infection
- Predialysis, hemodialysis, peritoneal dialysis, or home dialysis patients §
- Elevated alanine aminotransferase or aspartate aminotransferase levels of unknown origin

Abbreviations: HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; STIs = sexually transmitted infections.
*Recommended for one-time, but not periodic testing.
† For additional information on postvaccination serologic testing, refer to: 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.
§ For more information on recommendations for hemodialysis patients, refer to: Alter MJ, Arduino MJ, Lyerla HC, Miller ER, Tokars JI. Recommendations for preventing transmission of infections among chronic hemodialysis patients. MMWR Recomm Rep 2001;50:1–43.

Virus Description and Transmission

HBV is a partially double-stranded DNA virus in the *Hepadnaviridae* family. HBV DNA is enclosed in a nucleocapsid protein, called the hepatitis B core antigen (HBcAg), which is further surrounded by surface antigen (HBsAg) envelope protein (19, 20). HBV replicates by reverse transcription of an RNA intermediate

(21). During viral replication, a circulating peptide, hepatitis B e antigen (HBeAg), can also be produced (20). The liver is the primary site of HBV replication, and the virus can integrate into the host hepatocyte genome. HBV can also form closed covalent circular DNA, which can persist in the nuclei of host hepatocytes (19). There are 10 HBV genotypes (A through J), which are associated with different geographic areas, disease severity, and responses to antiviral therapy (22).

Persons who test positive for HBsAg, HBV DNA, or both are considered infectious. HBV is concentrated most highly in blood, but semen and vaginal secretions are also considered infectious (23, 24). Although HBV has been detected in other body fluids, including urine, saliva, tears, cerebrospinal fluid, and feces, the lower concentration of virus or lower epidemiologic plausibility make them less likely vehicles of transmission (25, 26). HBV has also been found in breastmilk, but breastfeeding by persons with HBV infection does not appear to increase risk for infection among infants who received recommended immunoprophylaxis (27).

HBV is transmitted by direct contact through percutaneous, mucosal, or nonintact skin exposure to infectious blood or body fluids. Transmission can occur during sex with an infected partner; birth to an infected person; sharing needles, syringes, or drug-preparation equipment; contact with blood from or open sores on an infected person; exposure to needle sticks or sharp instruments; and sharing certain items with an infected person that can break the skin or mucous membranes, potentially resulting in exposure to blood (e.g., razors, toothbrushes, glucose monitoring equipment). HBV is not spread by kissing, hugging, coughing, ingesting food or water, sharing eating utensils or drinking glasses, or casual touching (24, 25, 28).

Outside the body, HBV can survive and remain infectious in the environment for at least seven days and can be transmitted through contact with nonintact skin (29-31).

Interpretation of Screening Tests

Table 1. Interpretation of screening test results for HBV infection and recommended action

Clinical State	HBsAg	Anti-HBs	Total Anti-HBc*	IgM anti-HBc	Action
Acute infection	Positive	Negative	Positive	Positive	Link to hepatitis B care
Chronic infection	Positive	Negative	Positive	Negative	Link to hepatitis B care
Resolved infection	Negative	Positive	Positive	Negative	Counsel about reactivation risk
Immune from vaccination	Negative	Positive†	Negative	Negative	Reassure if history of HepB vaccine series completion
Susceptible, never infected	Negative	Negative§	Negative	Negative	Offer hepatitis B vaccine
Isolated core antibody positive¶	Negative	Negative	Positive	Negative	Depends on the cause of the positive result (see Follow-up After Hepatitis B Testing)

Abbreviations: Anti-HBs = antibody to hepatitis B surface antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IgM anti-HBc = immunoglobulin class M antibodies to hepatitis B core antigen; Total anti-HBc = total antibody to hepatitis B surface antigen.

*Total anti-HBc is a measure of both immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies to HBcAg.

†Immune if anti-HBs concentration is ≥10 mIU/mL after vaccine series completion.

§Anti-HBs concentrations may wane over time among vaccine responders. Refer to: 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.

¶Can be the result of a past infection where anti-HBs levels have waned, occult infection, passive transfer of anti-HBc to an infant born to an HBsAg-positive gestational parent, a false positive, or mutant HBsAg strain that is not detectable by laboratory assay.

The three main serological markers used to determine HBV infection status are HBsAg, anti-HBsAg, and anti-HBc (Table 1). HBV DNA is a measure of viral load. HBeAg is a marker for viral replication and high infectivity; antibody to HBeAg (anti-HBe) correlates with the current loss of replicating virus. Figure 2 shows the timing of serological markers over a typical course of infection.

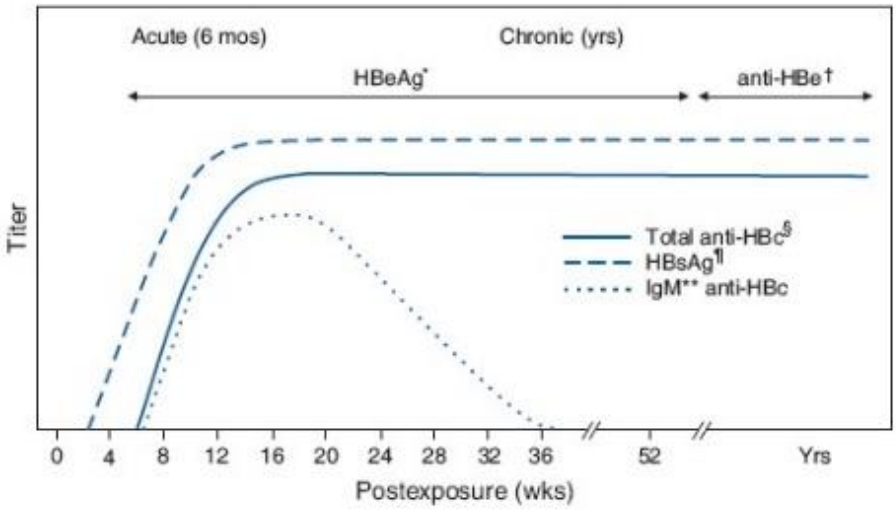
The presence of HBsAg indicates current HBV infection, either acute or chronic, while presence of anti-HBs at concentrations ≥10 mIU/mL indicates immunity or resolved infection after completion of vaccine series. Among vaccine responders, anti-HBs can decline over time to levels below 10 mIU/mL, but the majority are still immune and will mount an immune response to a vaccine challenge at least 30 years after vaccination (32-

35); CDC, unpublished analysis, 2021). Hepatitis B immune globulin (HBIG) can provide anti-HBs for 4–6 months after administration; therefore, testing for anti-HBs within 6 months of HBIG administration is not an accurate measure of a person's immune status (36).

Anti-HBc develops in all HBV infections and generally persists for life. Persons whose immunity to HBV is from a vaccine do not develop anti-HBc; therefore, testing for total anti-HBc can be used to identify persons with a past or ongoing infection. Assays for total anti-HBc detect both IgM and IgG antibodies to HBcAg; there is currently no commercially available test for IgG anti-HBc alone. In conjunction with other HBV serological markers, testing for anti-HBc can further differentiate between acute and chronic infection; IgM anti-HBc is positive during acute infection and negative during chronic infection. Testing for IgM anti-HBc alone is not sufficient to assess chronic HBV infection.

After identifying a person with HBV infection, testing for HBeAg, anti-HBe, and HBV DNA can provide information on the level of infectiousness (i.e., viral load, replication) and help inform clinical management.

Figure 2. Typical serologic course of acute hepatitis B virus (HBV) infection with progression to chronic HBV infection



* Hepatitis B e antigen.
† Antibody to HBeAg.
§ Antibody to hepatitis B core antigen.
¶ Hepatitis B surface antigen.
** Immunoglobulin M.

Clinical Features and Natural History

The incubation period from exposure to a positive HBsAg test has been shown to be as short as 6 days (37). Serial serum specimens from 4 patients prospectively followed showed abnormal serum ALT levels occurred on average 2 months after exposure, with a range of 41–77 days (37).

Infants, children aged <5 years, and immunosuppressed adults with acute HBV infection are typically asymptomatic, and persons aged <30 years are less likely to be symptomatic compared with persons aged ≥30 years (38). Signs and symptoms of acute HBV disease are like those of other types of acute viral hepatitis and can include fever, fatigue, loss of appetite, nausea, vomiting, abdominal pain, dark urine, clay-colored stool, joint pain, and jaundice. Fulminant hepatitis occurs in approximately 1% of persons who are acutely infected with jaundice and may result in death or liver failure necessitating liver transplantation (39, 40).

HBV infection is considered chronic if HBsAg persists longer than 6 months. Risk for progression to chronic infection is inversely related to age at time of infection; approximately 90% of neonates develop chronic infection compared to approximately 5% of immunocompetent adults (38, 41-43). Adults who are immunosuppressed are at higher risk for developing chronic infection (41). Approximately 0.5%–2% of chronic infections spontaneously resolve per year of infection without treatment (marked by loss of HBsAg), although not at a steady rate over time (44-46).

The American Association for the Study of Liver Diseases (AASLD) categorizes chronic HBV infection into four phases: immune tolerant, immune active, immune inactive, and reactivation (11). Phases are based on test results, primarily HBeAg and HBV DNA levels, as well as liver function tests, and are characterized by varying levels of liver inflammation and fibrosis. Disease progression is often dynamic, rather than a linear progression in severity. Symptoms during the chronic infection period are not an accurate predictor of disease severity; patients with chronic HBV infection may be asymptomatic until they present with progressed liver injury (47).

Patients with chronic HBV infection are at increased risk for cirrhosis and liver cancer and are 70%–85% more likely to die prematurely than the general population (1-4). Therefore, routine monitoring of patients with HBV infection is necessary to identify those at higher risk for progression to hepatocellular carcinoma (HCC), cirrhosis, or liver failure (11, 48).

Reactivation, the rapid increase or reappearance of HBV activity[2], is associated with transplants, use of immunosuppressive therapy, and direct-acting antiviral therapy for treatment of hepatitis C (11, 49-51). Reactivation is more likely to occur among persons who are HBsAg- or HBV DNA-positive, but also can occur in persons with a history of HBV infection (anti-HBc-positive) who are HBsAg-negative. If the person becomes symptomatic, the clinical presentation of reactivation can range from mild disease to severe hepatitis resulting in death.

Hepatitis D virus (HDV) is a satellite virus that only infects persons who are also infected with HBV. Coinfection with HDV can impact the clinical course and management of HBV infection and can lead to more rapid progression of HBV infection (52). Lack of systematic surveillance makes it difficult to estimate the true prevalence of HDV infection in the United States.

Epidemiology and Risk Factors

Acute HBV

Based on the 3,192 acute hepatitis B cases reported to CDC in 2019, there were an estimated 20,700 new infections (95% confidence interval [CI] = 11,800–50,800) after adjusting for under-ascertainment and underreporting. During 2012–2019, the number of reported acute hepatitis B cases in the United States remained relatively stable (53, 54).

[2] HBV reactivation is the loss of HBV immune control in HBsAg-positive, anti-HBc-positive or HBsAg-negative, anti-HBc-positive patients receiving immunosuppressive therapy for a concomitant medical condition; a rise in HBV DNA compared to baseline (or an absolute level of HBV DNA when a baseline is unavailable); and reverse seroconversion (seroreversion) from HBsAg-negative to HBsAg-positive for HBsAg-negative, anti-HBc-positive patients.[11]

Geographical differences exist, with the highest rate of cases (≥2.5 per 100,000) reported by Maine, West Virginia, Kentucky, Tennessee, Florida, Ohio, and Indiana (*54*). During 2011–2017, the rate of acute HBV infections among women of childbearing age was stable nationally but increased in Kentucky (0.1% to 0.2%), Alabama (0% to 0.3%), and Indiana (0% to 0.1%) (55).

The overall rate of acute infections in the United States is 1.0 per 100,000 population. The rate of reported acute HBV infections among persons aged 0–19 years has remained ≤0.1 case per 100,000 population since 2006, in large part due to routine childhood vaccination (54). However, transmission of HBV infection persists in adults, especially among older adults where vaccine uptake is suboptimal.

Rates of acute HBV infection are higher among males (1.3) than females (0.7) and are highest among non-Hispanic White (1.0), non-Hispanic Black persons (0.9) (all rates per 100,000 population). Among the 1,780 reported cases that included risk information for IDU, 35% reported IDU (54). Among the 1,042 cases that included partner data, 23% reported multiple sex partners. Of the 2,009 case reports that included any risk information, 47% had no risk identified.

Chronic HBV

Based on National Health and Nutrition Examination Survey (NHANES) data, an estimated 880,000 persons were living with chronic HBV infection during 2013–2018 (95% CI = 580,000–1,170,000) (5). The prevalence of resolved or current HBV infection was 11.7 million (range = 10.2–13.5 million). NHANES does not include institutionalized populations and, also, may underestimate the prevalence among ethnic minority groups that are not well represented in the survey.

In a 2018 meta-analysis of prevalence, of the estimated 1.89 million persons (range = 1.49–2.40 million) chronically infected with hepatitis B living in the United States, 0.42 million (range = 0.28–0.67 million) were U.S.-born and 1.47 million (95% CI = 1.21–1.73 million) were non–U.S.-born (6, 56). By region, the highest

proportion of persons with chronic HBV infection in the United States were born in Eastern Asia, South Eastern Asia, the Caribbean, South Central Asia, and Western Africa (6).

During 2011–2017, the rate of chronic HBV infection among women of childbearing age tested for HBV increased in Mississippi (0.2% to 0.4%), Kentucky (0.2% to 0.4%), and West Virginia (0.3% to 0.4%) (*55*). In 2019, the rate of newly reported cases of chronic HBV infection among adults varied by age, with the highest rate of 11.3 per 100,000 persons reported among persons aged 30–39 years, and the lowest rate of 0.5 per 100,000 persons reported among persons aged 0–19 years (54).

In 2019, there were 1,662 deaths due to HBV infection in the United States reported to CDC, resulting in an age-adjusted rate of 0.42 per 100,000 persons (95% CI = 0.40–0.44) (54). The highest death rates occurred among Asian and Pacific Islander persons (2.10 per 100,000), males (0.66 per 100,000), and persons aged 65–74 years (1.54 per 100,000). However, deaths attributable to HBV infection have been found to be underreported on death certificates (1).

Hepatitis B vaccination coverage

Vaccination is highly effective in preventing the transmission of HBV. The 2-dose hepatitis B (HepB) vaccine series, prepared with a novel adjuvant, produces a protective antibody response in 90%–100% of adults and the 3-dose series produces a response in 70%–90% of adults (57). Among healthy infants receiving the 3-dose HepB vaccine series, approximately 95% are protected (57, 58). HepB vaccination (≥3 doses) coverage by age 24 months among children born in 2017 and 2018 was 91.9% (59). Coverage with ≥3 doses of HepB vaccine among children aged 13–17 years (born during 2002–2008) was 92.6% (60). Vaccine coverage (≥3 doses) is lower among adults: 30% among adults aged ≥19 years, 40.3% for adults aged 19–49 years, and 19.1% for adults aged ≥50 years in 2018 (9). Coverage data are not available for the 2-dose HepB vaccine recommended by ACIP in 2018.

Methods

This report updates CDC recommendations for hepatitis B screening of adults previously published in 2008 (*13*). CDC evaluated the addition of a universal screening recommendation among adults as well as testing persons expected to be at increased risk for HBV infection that were not included in the 2008 testing guidelines.

Members of the CDC Guidelines Work Group followed CDC guideline development and reporting standards to develop research questions needed to assess the proposed updates; conduct systematic reviews; assess the quality of the evidence; and review existing systematic reviews, meta-analyses, and cost-effectiveness analyses when available (Supplementary Appendix 1 and Tables). Comprehensive systematic reviews of the literature were conducted for recommendations on 1) expanding screening to all adults (i.e., universal screening) and periodic testing for HBV infection among persons with 2) HCV infection or 3) a history of incarceration.

For all three systematic reviews, literature searches were conducted by CDC librarians with direction from subject matter experts. Searches were conducted for English-language literature published worldwide in Medline (OVID), Embase (OVID), CINAHL (Ebsco), and Cohrane Library. Duplicates were identified and removed using Endnote (version 20; Clarivate Analytics) and DistillerSR systematic review software (version 2.35; Evidence Partners) automated "find duplicates" functions.

The CDC's Viral Hepatitis Steering Committee considered multiple tools (e.g., GRADE) to assess the quality of the evidence. The mixed methods appraisal tool (MMAT) was selected because it is a validated tool for assessing nonrandomized analytic and descriptive studies, which make up most of the hepatitis B prevalence literature (61). Users rate each study on methodological quality criteria, indicating whether criteria were met with "Yes," "No," or "Can't Tell."

CDC determined that the new recommendations constituted scientific information that will have a clear and substantial impact on important public policies and private sector decisions. Therefore, the Information Quality Act required peer review by specialists in the field who were not involved in the development of these

recommendations. CDC solicited nominations for reviewers from the AASLD, Infectious Disease Society of America, and American College of Physicians (ACP). Five clinicians with expertise in hepatology, gastroenterology, internal medicine, or infectious diseases provided structured peer reviews. In addition, feedback from the public was solicited through a Federal Register notice announcing the availability of the draft recommendations for public comment from [dates TBD]. CDC received [TBD, peer review in progress] public comments on the draft document from [TBD, e.g., academia, professional organizations, industry, and the public].

The Work Group also presented these guidelines to the CDC/HRSA Advisory Committee on HIV, Viral Hepatitis and STD Prevention and Treatment.

The Steering Committee considered results of the systematic reviews in conjunction with cost-effectiveness analyses, supplemental literature, practicality of implementing guidelines, public health benefits, subject matter expertise, and reviewer feedback.

Systematic Review Methods: Universal Screening

The search period was January 1, 2008 (the year of the last CDC screening guidelines) through February 8, 2021 (Supplementary Tables). Search results were supplemented by relevant studies identified through reference lists in review articles and by newly published studies. DistillerSR was used to organize the review process. Each article was reviewed for inclusion by two of the authors (EC and LP). Differences in inclusion were discussed until consensus was reached. Articles were included if they contained the prevalence or incidence of HBV infection among adults aged ≥18 years or linkage-to-care data. Articles were excluded if they were outside the United States and U.S. territories; only reported data from a study not conducted in humans, environmental studies, or technology assessments; lacked original data (e.g., editorials, reviews, modeled data); were case reports; or only included self-reported (i.e., unconfirmed) HBV infection prevalence (Supplementary Table 3). Once a reviewer identified an article as meeting any exclusion criterion, additional exclusion criteria

were not assessed or recorded. When multiple articles reported data on the same cohort, the article with the most complete data was included. Data were independently abstracted by two reviewers (EC and LP) and discrepancies were discussed until consensus was reached or a third reviewer (NN) resolved. Finally, two independent assessors (LP, JB, or NN) used the MMAT to assess the quality of articles used to calculate the prevalence of HBV infection in the general population.

Systematic Review Methods: Persons with HCV Infection

The search period was January 1, 2005 through September 22, 2020 (Supplementary Table 5). DistillerSR and Endnote were used to organize the review process. Titles were reviewed by one reviewer (PS or EC) and those that were clearly irrelevant to the research question were excluded. Each potentially relevant article was reviewed for inclusion by two of the authors (MH, PS). Differences in inclusion were discussed until consensus was reached (Supplementary Table 6). Data from the included full text articles were independently abstracted by two reviewers (MH, PS, or EC). The quality of the articles was assessed using the MMAT.

Systematic Review Methods: Persons Ever Incarcerated

The CDC Guidelines Work Group used an existing literature search of articles on hepatitis B and hepatitis C in correctional and detention facilities. The search period was January 1, 2000 through March 3, 2021 (Supplementary Table 8). Abstracts were reviewed by two reviewers (AH, LH, JB, OR, or EC) for relevance, and discrepancies in inclusion were resolved by the first author (EC) or by consensus discussion. Only articles containing incidence or prevalence of HBV infection among persons with a history of incarceration or incarceration as a risk factor for HBV infection were included in this review (Supplementary Table 9). Data from the included full text articles were independently abstracted by two reviewers (LP, EC) and differences were resolved by consensus discussion. The quality of the articles was assessed using the MMAT.

Summary of the Universal Screening Systematic Review and Review of Evidence

After deduplication, there were 2,580 records available for initial title screen; 1,374 articles were excluded during title screen. An additional 1,028 articles were excluded during abstract review. Among the 178 full text articles, 136 did not meet inclusion criteria after review, leaving 42 articles included in the final review. An additional article that met inclusion criteria, but was published after the search period, was abstracted to supplement evidence from the systematic search.

There were 17 articles considered to have HBV testing data from the general population (i.e., screening persons not known to be at increased risk for HBV infection) (Supplementary Table 10). Current testing recommendations are risk-based, therefore studies with convenience samples of persons already tested for HBV infection were considered biased toward overestimating the prevalence of hepatitis B, even if the study did not explicitly state that there was risk-based testing. The remainder of the articles (n = 25) were on populations whose risk of HBV infection was not considered representative of the general U.S. population (i.e., persons at increased risk for HBV infection).

Key Research Questions

Q1: How would adult universal screening for hepatitis B affect the number (and composition) of persons who screen positive for HBV infection?

Q1a. What is the prevalence of chronic HBV infection in the United States? In the general population, by age groups?

The CDC Guidelines Work Group defined chronic hepatitis B as persons who were HBsAg-positive and included one study where authors classified the patients as chronic hepatitis B without providing a definition. Studies among first-time blood donors, organ donors, pregnant persons (among whom universal screening is already recommended), NHANES enrollees, and patients seeking care for a condition other than HBV infection

were included. A quality assessment summary score is not recommended for the MMAT tool; therefore, the individual ratings are in Supplementary Table 13.

Based on 17 studies, conducted both in the United States and Guam, the median prevalence of chronic HBV infection in the general population was 0.4% (range: 0.0%–2.0%). Based on studies conducted in the United States alone, the prevalence was 0.38% (range: 0.0%–0.74%).

There were eight studies that reported prevalence of a history of infection (i.e., anti-HBc-positive, HBsAg-negative) ─ the median was 6.2% (range: 4.8%–14.0%) (62-69).

The age of patients with chronic HBV infection (if available) is provided in Supplementary Table 10. There were no clear trends in the burden of chronic HBV infection by age across studies. Therefore, the Work Group considered the economic analysis, vaccination rates and efficacy, the epidemiology of acute and chronic infections from surveillance data, ease of implementation, and harms of missed identification of chronic infections in determining the age thresholds for universal adult screening.

Q1b. What is the yield (number of new diagnoses per tests performed) and sensitivity of alternative HBV screening strategies (e.g., universal versus targeted screening or screening strategies based on alternative risk factors)?

As part of their HBV screening recommendations systematic review, the U.S. Preventive Services Task Force (USPSTF) assessed the yield (number of new diagnoses per tests performed) and sensitivity of alternative HBV infection screening strategies (70). They identified three fair quality studies, none of which were in the United States, which may limit the applicability (71-73). Based on these studies, the number needed to screen to identify one HBV infection using risk-based strategies ranged from 32 to 148. In comparison, fewer than 20 persons need to be screened to identify a case of HCV using risk-based screening (74).

Only one of the studies, conducted in France, assessed CDC's risk-based testing criteria (72). Authors found that using risk-based testing had 100% sensitivity (i.e., 100% of infected individuals were identified) and that 70% of persons reported at least one risk factor; however, the study population specifically overrepresented people at increased risk for infection. No studies directly assessed universal screening.

The CDC Work Group also considered a prospective study of patients with cancer at one U.S. health center that found applying CDC risk criteria to screening had 97% sensitivity (75). The proportion of patients who met at least one risk criterion was 91%. Therefore, in terms of provider time, universal screening may be more efficient than risk-based testing.

Q2: How many additional persons would be linked to care?

2a. What is the diagnostic accuracy of HBV testing?

The diagnostic accuracy of HBV testing has previously been well described and was not included as part of the systematic review.

2b. What are the harms of hepatitis B screening?

Data on harms in the systematic review were limited. Abara et al. found that women with public insurance and who self-paid for health care services were less likely to be screened, even though HBsAg screening costs should have been covered (76). The authors hypothesized that out-of-pocket payments might be a barrier to screening. Sears et al. assessed acceptability of hepatitis screening by patients during colonoscopies and found 78% acceptance (77).

It is expected that harms of screening for hepatitis B would be similar to those for hepatitis C. A prior review found possible harms of screening for hepatitis C to be physical pain, anxiety, cost, interpersonal problems related to learning infection status, stigma, time, fear, and reluctance to disclose risk behaviors (78). Other

plausible harms include distress from false-positive results, insurability and employment issues, and treatment adverse effects.

The CDC Work Group concluded that potential harms of screening did not outweigh the benefits. Additionally, universal screening might reduce harms compared with risk-based screening by not requiring individuals to disclose potentially stigmatizing risk conditions (e.g., immigration status, IDU) to get tested.

2c. What proportion of persons who screen positive for HBV infection are linked to care? 2d. What proportion of persons who screen positive for HBV infection are treatment eligible? 2e. What proportion of eligible persons who screen positive for HBV infection are treated?

Only two studies from the review reported on linkage-to-care. In a study among people attending free clinics, 69% enrolled in follow-up care (79). In a free screening clinic, 78% of patients with HBV infection elected to undergo follow-up monitoring (i.e., ALT, HBV DNA) and 24% (11 of 45) of those monitored were eligible for treatment (i.e., viral load >20,000 copies per ml) (80).

Data on treatment were only available in two studies of antiviral treatment during chemotherapy. In Haider et al., 23% of patients at risk for reactivation were prescribed a preventive nucleoside analogue (81). In another study, 12% (18 of 152) of patients with a previous HBV infection received antiviral drugs, and 73% (11 of 15) of patients with chronic HBV infection received antiviral drugs (67).

To answer these key questions, the CDC Work Group also assessed evidence from three additional studies that were not part of the systematic review. In a 2008–2016 study of adults with chronic HBV infection and commercial insurance, 36% (6,004 of 16,644) of patients were linked to care (defined as having had an ALT test and HBV DNA or HBeAg test) (82). Of the patients with chronic HBV infection with prescription claims, 18% (2,926 of 16,572) were treated. Among 2,338 patients with chronic HBV infection followed in a prospective cohort study, 78% had one or more ALT tests annually, 37% had one or more HBV DNA tests

annually, and 32% were treated (83). Not all patients with chronic HBV infection require treatment; estimates of patients with HBV infection meeting AASLD criteria for treatment range from 24%–48% (84, 85).

Overall, the CDC Work Group found linkage-to-care rates ranged from 36% to 78%, and that 18% to 32% of patients with chronic HBV infection are prescribed treatment.

Q3: How many new infections of HBV would be prevented?

3a. What proportion of close contacts are at risk for infection?

The CDC Work Group did not identify evidence directly assessing the proportion of close contacts at risk for infection and cannot estimate the proportion of new infections that would be prevented by screening. There was evidence of the proportion of close contacts of people with HBV infection who themselves have HBV.

From the systematic review, Ramsey et al. found that in a cohort of patients with cancer and previous HBV infection, 8.1% reported having a household contact with HBV infection (who was not a sex partner), and 15.2% reported sexual contact with a person with HBV infection. Of the patients with chronic HBV infection, 0.5% reported a nonsexual household contact with HBV infection, and 1.5% reported sexual contact with an HBV-infected person (67).

In a study of programs testing and linking hepatitis B patients to care in the United States, 14% of household contacts of persons who were HBsAg-positive were themselves HBsAg-positive, and 30% had a history of infection (anti-HBc-positive) (86). In 2019, surveillance data indicated 10% (92 of 899) of acute cases had a sexual contact and 2% (17 of 899) had a nonsexual household contact (*54*). However, relying on self-reports of close contacts with hepatitis B likely underestimates the risk. Global studies from 1974–2007 found that 14%–60% of persons living in households with persons with chronic HBV infection have serologic evidence of resolved HBV infection and 3%–30% have chronic infection (13).

While screening can prevent further spread of HBV infection, the CDC Work Group was unable to estimate the size of that impact.

Q4: Do desirable management and treatment effects outweigh undesirable effects?

This question was not assessed by the systematic review because it has been reported elsewhere. The USPSTF reviewed effectiveness of treatment on reducing viral load, HBeAg, HBsAg, cirrhosis, HCC, and death (70). They found that antiviral therapy is associated with viral suppression, HBsAg loss, normalization of ALT levels, and HBeAg loss. Antiviral therapy was associated with decreased risk for HCC and mortality compared with placebo or no therapy, but data were sparse and estimates imprecise. Therapy was not associated with an increased risk for serious adverse events. The AASLD's systematic review used to inform its treatment guidelines concluded that recommended treatment reduces cirrhosis, decompensated cirrhosis, HCC, and death in adults with active chronic HBV infection and was strongly recommended (10).

Cost-Effectiveness of Universal Screening

A 2021 economic analysis on the cost-effectiveness of one-time universal hepatitis B screening of adults aged 18–69 years informed these guidelines (87). With an estimated prevalence of undiagnosed chronic HBV infection of 0.24%, universal HBsAg screening in adults aged 18–69 years is cost-saving compared with current practice, assuming antiviral treatment drug costs remain below $894 per year. Undiagnosed prevalence was based on the NHANES estimate of 0.36% and the finding that 67% of people were unaware of their infection (*88*).

Compared with current practice, universal screening is expected to avert an additional 7.4 cases of compensated cirrhosis, 3.3 cases of decompensated cirrhosis, 5.5 cases of HCC, 1.9 liver transplants, and 10.3 HBV-related deaths per 100,000 screened. Universal HBsAg screening of adults aged 18–69 years would save $262,857 per quality-adjusted life year (QALY) and would result in a gain of 135 QALYs per 100,000 adults screened. A probabilistic sensitivity analysis that varied all parameters in the model simultaneously showed a >99%

likelihood that universal screening would be cost-effective compared with current practice at a willingness-to-pay threshold of $50,000 per QALY.

A sensitivity analysis found that using the 3-test panel (HBsAg, anti-HBc, anti-HBs) and assuming the current Medicare reimbursement of $28.27, universal screening with the 3-test panel would be cost-effective with an incremental cost-effectiveness ratio (ICER) of $11,207 per QALY.

An unpublished analysis using the same methods as those in the economic analysis described above, but raising the upper age limit to 80 years, found that one-time universal screening of adults aged 18–80 years with HBsAg test would save $200,334 and result in a gain of 128 QALYs per 100,000 adults screened.

Persons at Higher Risk for HBV Infection Recommended for Testing

Persons at increased risk for HBV infection are those with exposure to contaminated blood or infectious body fluids.

New Recommendations

Persons with current or past HCV infection. The systematic review found 8,295 articles for review; after title review, 1,233 potentially relevant articles remained. After review of articles meeting inclusion and exclusion criteria, 17 articles were included. In 10 U.S. studies, the prevalence of current HBV infection (based on HBsAg positivity, HBV DNA positivity, or ICD-10 codes) among people with HCV infection ranged from 0.2% to 5.8% (median = 1.2%) (89-98). Among people with HCV infection, the prevalence of ever being exposed to HBV ranged from 24.7% to 62.6% (median = 43.0%); this was based on anti-HBc positivity, regardless of other HBV test results (91-94, 97, 99). Isolated anti-HBc positivity ranged from 36.9% to 53.8% (median = 39.5%) among HCV patients who were anti-HBc-positive (91, 94, 97).

HBV Reactivation during direct-acting antiviral (DAA) therapy

FDA requires a Boxed Warning about the risk for HBV reactivation be added to the drug labels of DAA medicine for HCV infection, directing health care professionals to screen and monitor for HBV infection in all patients receiving DAA treatment (100).

A published systematic review of HBV reactivation during DAA therapy among patients with hepatitis C found the overall risk of HBV reactivation was 24% (95% CI: 19%–30%) in patients with untreated chronic HBV infection and 1.4% (95% CI: 0.8%–2.4%) in patients with resolved HBV infection (49). The risk for HBV reactivation-related hepatitis was 9% (95% CI: 5%–16%) in patients with chronic HBV infection and did not occur in patients with resolved infection. There were three (out of 1,621) patients with chronic HBV infection who had a major clinical event related to the reactivation (liver decompensation or failure), but there were no deaths.

Four studies were published after the 2018 Mücke systematic review. In two national cohort studies of U.S. veterans with chronic hepatitis C prescribed DAA therapy, HBV reactivation was rare (<0.1%) and more frequent among HBsAg-positive patients (91, 101). Similarly, two additional U.S.-based cohort studies of hepatitis C patients coinfected with HBV did not detect any cases of DAA-associated HBV reactivation (97, 102).

Outcomes

In a study comparing hepatitis C patients achieving sustained virologic response (SVR) to HCV treatment, anti-HBc positivity was identified as an independent risk factor for the development of HCC (hazard ratio [HR] = 5.57; 95% CI: 1.45–21.39) (103). Conversely, a nested case-control study of HBsAg-negative patients with hepatitis C showed that neither previous nor occult HBV infection was associated with the development of HCC (104). Clinically significant hepatic events, including HBV reactivation, were more common among cirrhotic than noncirrhotic anti-HBc-positive patients with chronic hepatitis C undergoing DAA therapy (101). Among a cohort of HCV-infected veterans who initiated DAA treatment, those who were HBV/HCV coinfected (odds

ratio [OR] = 2.25; 95% CI: 1.17–4.31) and those with resolved hepatitis B (OR = 1.09; 95% CI: 1.03–1.15) were more likely to achieve SVR compared with HCV-monoinfected patients (93).

Patients with hepatitis C and documented HBV viremia [HBV DNA+] were at a significantly higher risk for cirrhosis (adjusted hazard ratio [aHR] = 1.89, 95% CI: 1.46–2.45), HCC (aHR = 2.12; 95% CI: 1.26–3.60), and death (aHR = 1.62; 95% CI: 1.33–1.99) than HCV-monoinfected patients, after controlling for demographic, clinical, and antiviral treatment-related factors in a national cohort of U.S. veterans (96). In this cohort, absence of HBV replication was associated with a clinical course similar to that of HCV-monoinfected patients. Compared with HCV-monoinfected patients, HBV/HCV coinfected patients had more advanced fibrosis, a faster fibrosis progression rate, and more severe steatosis (92). In a matched case-control study, HBsAg-negative hepatitis C patients with HCC were more likely to be anti-HBc-positive, both isolated anti-HBc-positive (OR = 2.98; 95% CI: 2.12–5.08) and with anti-HBs-positivity (OR = 1.84; 95% CI: 1.22–3.08), than HCV-infected controls without HCC (105).

Many studies were limited by incomplete test data and use of descriptive tests of significance rather than models that controlled for other variables. The results from the MMAT quality assessment are in Supplementary Table 13.

Persons currently or formerly incarcerated in a jail, prison, or other detention setting. The systematic review of hepatitis B in correctional settings used for these testing guidelines was part of a larger review that also contained articles on hepatitis C in correctional settings ("review 1"). The initial search of hepatitis B and hepatitis C corrections literature yielded 2,395 unique articles for review; of these 1,961 were deemed irrelevant by title and abstract screening, resulting in 434 potential hepatitis B and hepatitis C articles for review 1. A secondary abstract review ("review 2"), that applied the inclusion and exclusion criteria for these guidelines, resulted in 57 articles that met the inclusion criteria for full-text review; three of these articles were also

included as part of the hepatitis B universal screening systematic review. After full-text review, 10 articles were included.

Among eight studies, the prevalence of chronic HBV infection in persons with a history of incarceration ranged from 0.6% to 8.7% (median: 1.0%)(106-113). Two studies of currently incarcerated men assessed incidence, which ranged from 2,700 to 3,579 infections per 100,000 people per year (108, 111). One study reported 41 acute HBV infections acquired in prison, but there was no report of the total number tested and therefore a prevalence or incidence rate could not be calculated (113). Another study reported an infection rate of 1.2% during an outbreak of HBV in a high-security correctional facility (106).

Three studies found an increased risk for HBV infection associated with incarceration. A study of blood donors found that persons detained ≥3 nights in a jail or detention facility had 3 times higher odds of having serologic evidence of HBV infection, but the comparison group was not provided ($p \leq 0.001$)(114). Another study showed that persons incarcerated >14 years had 1.68 (95% CI: 1.08–2.59) higher odds of ever acquiring HBV infection compared with those incarcerated ≤7 years (111). Finally, a third study showed that persons with any self-reported history of incarceration had increased odds (OR = 1.84; 95% CI: 1.02–3.31) of ever having HBV infection compared with persons with no history of incarceration (115).

The reasons for increased risk for HBV infection among persons who have been incarcerated might include behaviors that occur prior to or during incarceration, including drug use, higher-risk sex, percutaneous exposures (e.g., tattooing), and structural factors that affect the level of risk for these behaviors (e.g., availability of condoms, clean syringes, engagement in health care). To ensure all incarcerated persons receive recommended HBV testing, correctional and detention facilities should consider offering HBV screening at intake in addition to periodic testing for susceptible persons serving long-term sentences.

Persons with current or past STI or multiple sex partners. The CDC Work Group used a published systematic review and meta-analysis to assess risk among persons with a history of a non-HIV STI (116). This

analysis of studies worldwide found positive and statistically significant associations between the prevalence of HBV infection and other STIs. There were three U.S. studies, published during 2008–2009, with four estimates of HBsAg prevalence among persons with current syphilis or any STI; the median prevalence was 1.6% (range: 0.9%–33.2%). Among the four estimates, two were among groups with other risk factors for HBV infection (people being processed into jail and MSM). There were seven U.S. studies, published during 1998–2000, with nine estimates of prevalence of current or past HBV infection (HBsAg or anti-HBc-positive) among persons with current or past STIs; the median prevalence was 22.4% (range: 8.6%–83.5%). Among the nine estimates of past infection, four were among groups with other risk factors for HBV infection (e.g., persons who use drugs, persons with HIV infection, MSM).

A study of national surveillance reports and survey data from 2013 to 2018 found that after excluding cases with a report of IDU, there were 1,324 (38.2%) cases of sexually transmitted acute HBV infection; 5.3% of persons reported sexual contact with a person with HBV infection, 3.1% reported being male and having sex with another male partner, 27.8% reported having multiple sex partners, and 2% reported a prior history of STI treatment 6 weeks to 6 months before their hepatitis B diagnosis (117). Cases were classified into mutually exclusive categories in the order listed. Testing persons who report having multiple sex partners aligns with AASLD recommendations to screen persons who are not in a long-term mutually monogamous relationship (i.e., >1 sex partner during the previous 6 months) (11).

Other persons at higher risk for infection

Persons born in regions with prevalence of HBV infection ≥2%. A 2021 systematic review and meta-analysis estimated the prevalence of non–U.S.-born persons with chronic HBV infection in the United States is 3.1% (95% CI: 2.5%–3.6%); Africa has the highest regional prevalence (8.6%), followed by Asia (5.9%), and

Oceania (4.5%) (6). Box 3 lists the estimated prevalence of hepatitis B (low, low–intermediate, intermediate, and high) for countries with available data.

Persons born in the United States not vaccinated as infants whose parents were born in regions with prevalence of HBV infection ≥8%. This population is at increased risk for infection because the higher underlying prevalence in the population increases the likelihood of perinatal or close contact exposures. Box 3 lists the estimated prevalence of HBV infections (low, low–intermediate, intermediate, and high) for countries with available data.

Persons with HIV infection. Several studies with varying inclusion criteria and time periods during 1986–2012 used prospective cohort data from the U.S. Military HIV Natural History Study (NHS) to calculate the prevalence of hepatitis B among persons with HIV infection. Among patients in the NHS, coinfection ranged from 3.0% to 6.0% (118-120). In a large prospective cohort study of adults with HIV infection, annual chronic hepatitis B prevalence during 1996–2007 ranged from 7.8% to 8.6% (121).

Persons with current or past IDU. A systematic review estimated the prevalence of current HBV infection among persons who inject drugs (PWID) to be 11.8% (range: 3.5%–20%) and ever-infection to be 22.6% (122). Transmission of HBV among PWID may be increasing. A study of prevalence of anti-HBc in national survey data found an increase among PWID from 35% during 2001–2006 to 58.4% during 2013–2018 (123).

MSM. A sample of Los Angeles County residents from the National HIV Behavioral Surveillance system found 19% (95% CI: 15%–24%) of MSM had current or past HBV infection; 35% of the sample was coinfected with HIV (124). A survey of MSM from six U.S. metropolitan areas from 1998 to 2000 found the prevalence of ever-infection to be 20.6%, and 2.3% of participants had current HBV infection; HBV infection was independently associated with a history of another STI, having more lifetime partners, ever engaging in anal intercourse, and ever using injection drugs (125).

Infants born to HBsAg-positive persons. Without preventive steps, 90% of infants born to HBsAg- and HBeAg-positive persons and 5%–20% of infants born to HBsAg-positive HBeAg-negative persons will become infected (42, 126, 127). Refer to the *Advisory Committee on Immunization Practices guidance on managing infants born to people who are HBsAg-positive* (14).

Household, needle-sharing, or sexual contacts of persons with known HBV infection. HBV is highly infectious and can survive in the environment for prolonged periods, putting close contacts of people with known HBV infection at greater risk (see Summary of the Universal Screening Systematic Review and Review of Evidence section above).

Predialysis, hemodialysis, peritoneal dialysis, or home dialysis patients. A study during 1997–2001 of adult hemodialysis patients found an adjusted prevalence of HBV infection of 2.4% (95% CI: 2.1–2.7) (128). While dialysis was only reported in 3% (34 of 1,292) of 2019 acute HBV cases, the risk for developing chronic infection is higher among immunosuppressed persons undergoing dialysis than immunocompetent persons (54, 129, 130). For testing recommendations for hemodialysis patients refer to: *Recommendations for preventing transmission of infections among chronic hemodialysis patients* (15).

Persons with elevated ALT or AST levels of unknown origin. Persons with known chronic liver disease (e.g., cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis) are not at increased risk for HBV infection unless they have additional exposures or risk factors. However, persons with persistently elevated ALT or AST without a known cause should be tested for HBV infection as part of a medical evaluation of these abnormal laboratory values.

BOX 3. Prevalence of chronic HBV infection, by country or territory*

High (≥8% prevalence): 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, Zimbabwe.

Intermediate (5%–7.9% prevalence): 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, Vietnam.

Low–intermediate (2%–4.9% prevalence): 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, Zambia.

Low (≤1.9% prevalence): Algeria, Argentina, 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, Venezuela.

No data: 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, 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, United States Virgin Islands, Uruguay, Wallis and Futuna, Western Sahara.

* Source: CDA Foundation's Polaris Observatory; 2021. Available from https://cdafound.org/polaris/ (Accessed July 6, 2021).

Rationale for Screening

The goal of hepatitis B screening is to identify persons who are currently infected with HBV. FDA-approved tests should be used according to the manufacturer's instructions for screening. Testing for the three main serological markers used to determine HBV infection, HBsAg, anti-HBs, and total anti-HBc, allows clinicians to determine whether the patient has a current or previous infection and might distinguish whether they are vaccinated or susceptible. Identifying patients who previously were infected with hepatitis B allows for counseling on the risk of reactivation and any necessary monitoring. Counseling can also include a recommendation to have close contacts tested. While screening can identify persons who are unvaccinated and susceptible, screening is not a requirement for HepB vaccination (cite 2022 ACIP when available).

Follow-up After Hepatitis B Virus Testing

Persons with current HBV infection. Patients with acute infection should be counseled about their risk for developing chronic HBV infection and the risk for reactivation. There is no specific treatment for acute infections.

Persons diagnosed with chronic HBV infection can benefit from monitoring and counseling, including mental health support. The AASLD has developed guidance for the monitoring and treatment of chronic HBV infection

(11). Simplified guidance for primary care medical providers or other nonspecialists are available from the Hepatitis B Primary Care Workgroup (131).

To prevent liver damage, patients should be vaccinated against hepatitis A (if not already vaccinated), screened for hepatitis C and hepatitis D (per AASLD guidelines), and receive the Alcohol Screening and Brief Intervention (11, 78, 132). Depending on the likely route of transmission, the patient might benefit from STI screening and drug treatment or harm reduction counseling. A full list of recommended steps for examination, education, laboratory, serology, and imaging are provided in Table 2.

All patients who test positive should be provided information on how to prevent transmission to others (Box 4). It is recommended that household, sexual, and needle-sharing contacts of patients with either a current or past HBV infection be notified, tested, and vaccinated, as appropriate. As resources allow, viral hepatitis or STI programs within local or state health departments might be available to support providers with contact tracing and notification.

People should not be excluded from practicing in the health care field, school, play, child care, work, or other settings because they are infected with HBV (133, 134).

Table 2. Initial medical evaluation of people who are HBsAg-positive*

History/examination	Patient education	Routine laboratory tests	Serology/virology	Imaging/staging studies
□ Symptoms/signs of cirrhosis □ Alcohol Screening and Brief Intervention □ Metabolic risk factors □ Family history of hepatocellular carcinoma □ Hepatitis A vaccination status; offer vaccine if unvaccinated	□ Educate patients on how to prevent transmission to others (Box 4) □ Identify sex partners, household contacts, or needle-sharing contacts for screening and vaccination □ Recommend abstinence or limited use of alcohol □ Recommend steps to reduce risk of metabolic syndrome and fatty liver □ Refer to harm reduction counseling or drug treatment services, as needed	□ CBC □ Comprehensive metabolic panel including: □ AST/ALT □ Total bilirubin □ Alkaline phosphatase □ Albumin □ Creatinine □ INR	□ HBeAg/anti-HBe □ HBV DNA □ Anti-HAV (total or IgG) to determine need for vaccination if none documented □ Anti-HCV □ Anti-HDV[†] □ Anti-HIV □ Other STIs (as indicated)	□ Abdominal ultrasound[§] □ Elastography (e.g., FibroScan) *or* Serum fibrosis assessment (e.g., APRI, FibroSure, FIB-4)

Abbreviations: AST/ALT = alanine aminotransferase/aspartate aminotransferase; Anti-HAV = antibody to hepatitis A virus; Anti-HBe = antibody to hepatitis B e antigen; Anti-HCV = antibody to hepatitis C virus; Anti-HDV = antibody to hepatitis D virus; CBC = complete blood count; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV DNA = hepatitis B virus deoxyribonucleic acid; STI = sexually transmitted infection.

*Table adapted from *Hepatitis B Primary Care Workgroup. Hepatitis B Management: Guidance for the Primary Care Provider 2020* (131)

[†] Refer to *Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance* (11)

[§] Ultrasound for hepatocellular carcinoma surveillance has higher diagnostic accuracy than alpha fetoprotein (AFP), therefore AFP alone is not recommended except where ultrasound is unavailable or unaffordable (11).

Persons with resolved (past) HBV infection. Patients should be counseled about their history of HBV infection and risk for reactivation. It is recommended that household, sex, and needle-sharing contacts of patients with either a current or past HBV infection be notified, tested, and vaccinated, as appropriate.

Persons who are susceptible to HBV infection. Patients should be informed that they have never been infected with HBV and are not currently protected from future infection. All persons who are susceptible to infection should be offered the hepatitis B vaccine per current ACIP recommendations (cite 2022 ACIP when available). Anti-HBs concentrations can wane over time among vaccine responders. For persons with a clearly documented vaccination series who test negative for anti-HBs, refer to ACIP HepB vaccination guidelines (14).

Persons who are susceptible and at increased risk for HBV infection should be periodically tested. Frequency of periodic testing should be a shared decision between the patient and provider based on individual risk factors and immune status.

Persons who are fully vaccinated against HBV infection. Patients are considered fully vaccinated if they have completed a HepB vaccine series, and can be reassured. Vaccination status should be clearly documented in the medical record. Anti-HBs concentrations can wane over time among vaccine responders. For persons with a clearly documented vaccination series who test negative for anti-HBs, refer to ACIP HepB vaccination guidelines (14). Revaccination and postvaccination testing after series completion are not routinely recommended; for more information, refer to ACIP recommendations (cite 2022 ACIP when available).

Persons with isolated core antibody. Patients with isolated core antibody should have their immune status and risk history considered before deciding next steps. Newer total anti-HBc tests have improved specificity, with manufacturers reporting specificity above 96% (135). If a person does not have risk factors, the result may be a false-positive, and repeat testing with the same assay is warranted to confirm the results (136). A false-positive result means the person is susceptible and should be offered the hepatitis B vaccine per current ACIP recommendations (cite 2022 ACIP when available).

A national survey from 2001–2018 found the prevalence of isolated positive anti-HBc to be 0.8% (approximately 2.1 million persons) (137). Among patients exposed to HBV, an isolated positive anti-HBc result may be the result of loss of anti-HBs after past resolved infection; occult infection (where HBsAg is negative, but HBV DNA

is positive); being in the window period before appearance of anti-HBs; or an HBsAg mutant infection (that is not picked up by an HBsAg test unable to detect mutants). Patients who are immunocompromised should be considered as being at risk for HBV reactivation, and HBV DNA testing is recommended to assess for occult infection (11). In infants, an isolated anti-HBc result may be the result of passive placental transfer from an HBsAg-positive person, which is why testing for anti-HBc is not indicated before aged 24 months (14).

Patient Education

Patient education should be conducted in a culturally sensitive, nonstigmatizing manner in the patient's primary language (both written and oral whenever possible). Bilingual, bicultural, medically trained interpreters should be used when indicated.

Reporting

Acute and chronic cases of hepatitis B should be reported to the appropriate state or local health jurisdiction in accordance with requirements. The Council of State and Territorial Epidemiologists publishes case definitions for the classification of reportable cases of HBV infection (138, 139). CDC has updated guidance for health departments on viral hepatitis surveillance and case management (140).

BOX 4. Prevention messages for patients diagnosed with HBV infection

- To prevent or reduce risk for transmission to others, HBsAg-positive persons should
  - notify their household, sexual, and needle-sharing contacts that they should be tested for markers of HBV infection; if susceptible, contacts should complete the HepB vaccine series;
  - use condoms to protect susceptible sex partners from acquiring HBV infection from sexual activity until the sex partners can be vaccinated and their immunity documented (condoms and other prevention methods can also reduce risks for other STIs);
  - cover cuts and skin lesions to prevent spread of infectious secretions or blood;
  - clean blood spills with bleach solution (141);
  - refrain from donating blood, plasma, tissue, or semen;
  - refrain from sharing household articles (e.g., toothbrushes, razors) that could become contaminated with blood;
  - refrain from sharing needles, syringes, and other injection equipment; and
  - dispose of blood, body fluids, and medical waste properly.
- Newborns of HBsAg-positive pregnant persons should receive the HepB vaccine and hepatitis B immune globulin at birth and complete the HepB vaccine series according to the recommended immunization schedule (14).
- When seeking medical or dental care, HBsAg-positive persons should inform those responsible for their care of their HBsAg status so they can be evaluated and have their care managed appropriately.

Recommendations and Guidance of Other Organizations

CDC assessed systematic review literature, new cost-effective analyses, and indirect evidence of the effects of screening to develop the hepatitis B screening recommendations in this report. Practicality of implementing guidelines, public health benefits, and subject matter expertise were also considered.

USPSTF, AASLD, and ACP also make hepatitis B screening recommendations. The 2021 USPSTF systematic review found that no study directly evaluated the effects of screening for HBV infection on clinical outcomes and that risk-based screening strategies identify nearly all patients with HBV infection (142). USPSTF recommends screening adolescents and adults at increased risk for hepatitis B with HBsAg tests.

AASLD also recommends screening people at increased risk for infection; however, this guidance is primarily based on previous CDC recommendations. Notably, AASLD differs from CDC by recommending screening of unvaccinated people with diabetes aged 19–49 years, travelers to countries with intermediate or high prevalence of HBV infection, and residents and staff of facilities for developmentally disabled people (11). CDC's universal adult screening recommendation recommends screening, but not periodic testing, for these groups. AASLD also only recommends anti-HBc testing in certain groups (11).

In their best practice advice, ACP and CDC recommend testing people at increased risk for HBV infection with tests for HBsAg, total anti-HBc, and anti-HBs (136). The best practice risk groups align with current testing recommendations (Box 2) except that the former omits people with a history of STIs or multiple sex partners.

Future Directions

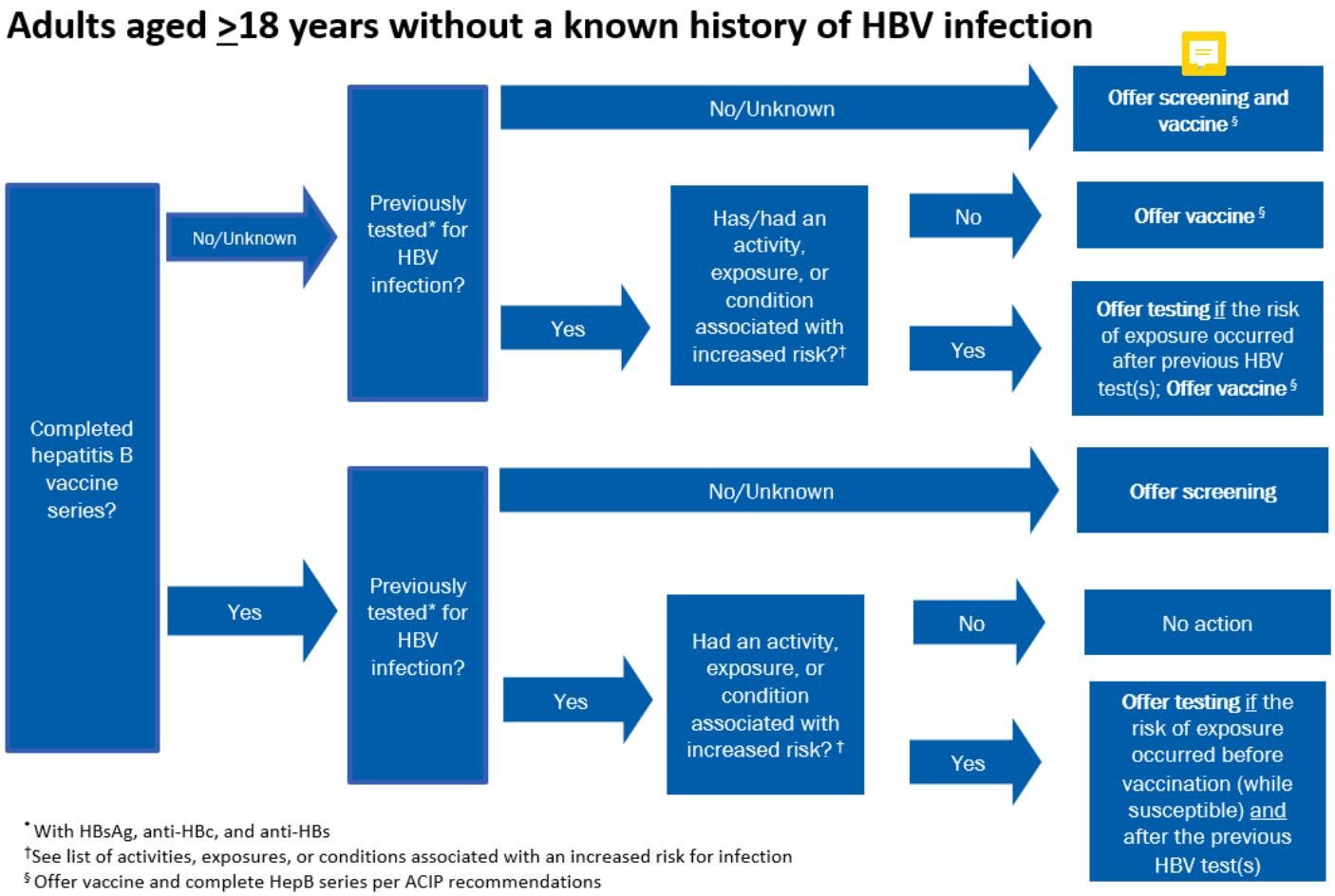
CDC will review these recommendations as new treatments, tests, epidemiology, HepB vaccination rates, and experience gained from implementation of these recommendations become available; recommendations will be revised as needed. The CDC Guidelines Work Group did not do a systematic review to reassess any of the groups at increased risk for HBV infection from the 2008 guidelines; future recommendations might modify the groups recommended for periodic testing. Additional data on the ideal frequency of periodic testing is needed.

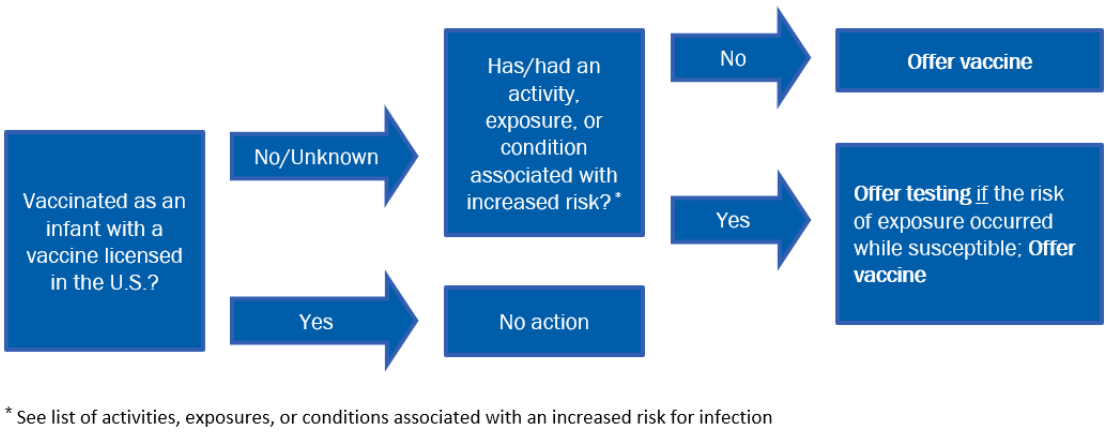
Conclusion

Universal screening of adults is cost-effective compared with current practice and averts liver disease and death (143). Although a curative treatment is not yet available, early diagnosis and treatment of chronic HBV infections reduces the risk for cirrhosis, liver cancer, and death (10, 11). Risk-based testing alone has not

identified most people living with chronic hepatitis B and is inefficient for providers to implement. Along with vaccination strategies, universal screening of adults and appropriate testing of people at increased risk for HBV infection will improve health outcomes, reduce the burden of hepatitis B in the Unites States, and advance viral hepatitis elimination goals.

Figure 1. Incorporating hepatitis B screening and testing into a clinic workflow, by age





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