Screening for Hepatitis B Virus Infection in Nonpregnant Adolescents and Adults: U.S. Preventive Services Task Force Recommendation Statement

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Description: Update of the 2004 U.S. Preventive Services Task Force (USPSTF) recommendation on screening for hepatitis B virus (HBV) infection.

Methods: The USPSTF reviewed the evidence on the benefits and harms of antiviral treatment, the benefits of education or behavior change counseling, and the association between improvements in intermediate and clinical outcomes after antiviral therapy.

Population: This recommendation applies to asymptomatic, nonpregnant adolescents and adults at high risk for HBV infection (including those at high risk who were vaccinated before being screened for HBV infection).

Recommendation: The USPSTF concludes that persons at high risk for infection should be screened for HBV infection. (B recommendation)

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* For a list of USPSTF members, see the **Appendix** (available at www.annals.org).

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The U.S. Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

Summary of Recommendation and Evidence

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

See also:

Related article 31
Editorial comment 76
Summary for Patients I-24

Web-Only
CME quiz
Consumer Fact Sheet

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

See **Figure 1** for a summary of the recommendation and suggestions for clinical practice.

Appendix Table 1 describes the USPSTF grades, and **Appendix Table 2** describes the USPSTF classification of levels of certainty about net benefit (both tables are available at www.annals.org).

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.

Figure 1. **Screening for hepatitis B virus infection in nonpregnant adolescents and adults: clinical summary of U.S. Preventive Services Task Force recommendation.**

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SCREENING FOR HEPATITIS B VIRUS INFECTION IN NONPREGNANT ADOLESCENTS AND ADULTS CLINICAL SUMMARY OF U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATION

Population	Asymptomatic, nonpregnant adolescents and adults at high risk for hepatitis B virus (HBV) infection (including those at high risk who were vaccinated before being screened for HBV infection)
Recommendation	**Screen persons at high risk for HBV infection.** **Grade: B**

Risk Assessment	Important risk groups for HBV infection with a prevalence of ≥2% that should be screened include: • Persons born in countries and regions with a high prevalence of HBV infection (≥2%) • U.S.-born persons not vaccinated as infants whose parents were born in regions with a very high prevalence of HBV infection (≥8%), such as sub-Saharan Africa and central and Southeast 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 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-α2a, entecavir, and tenofovir. Duration of treatment varies depending on the time required to suppress HBV DNA and normalize alanine aminotransferase levels; the presence of HBsAg, co-infection, 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 www.uspreventiveservicestaskforce.org.

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to www.uspreventiveservicestaskforce.org.

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 reg-

Table 1. **Geographic Regions With a Prevalence of Hepatitis B Surface Antigen ≥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
Carribean	Antigua and Barbuda, Dominica, Grenada, Haiti, Jamaica, St. Kitts and Nevis, St. Lucia, and Turks and Caicos Islands

* Adapted from reference 2. Estimates of prevalence of hepatitis B surface antigen, 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 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 **Figure 2**.
‡ A complete list of countries in each region is available at wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/hepatitis-b.
§ Asia includes 3 regions: Southeast, eastern, and northern Asia.

imens 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 were 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

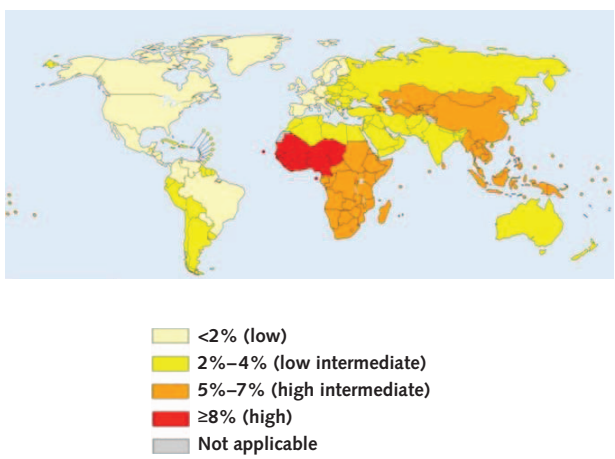
This recommendation applies to asymptomatic, nonpregnant adolescents and adults at high risk for HBV infection (including those at high risk who were vaccinated before being screened for HBV infection).

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 1**) (1). 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 (≥8%), such as sub-Saharan Africa, central and Southeast Asia, and China (**Figure 2**) (1–3, 5). Because the prevalence of HBV infection may gradually change over time, it is important to note that some countries and regions with prevalence rates between 5% and 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 esti-

Figure 2. **Prevalence of hepatitis B surface antigen in adults aged 19 to 49 years, 2005.**



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mated 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 or sexual partners of persons with HBV infection, and men who have sex with men (**Table 2**) (2, 7, 8).

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

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).

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.

Table 2. **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.
* Data from the United States and western Europe.

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 (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-α2b, pegylated interferon-α2a, lamivudine, adefovir, entecavir, telbivudine, and tenofovir. Approved first-line treatments are pegylated interferon-α2a, 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 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.

Other Considerations

Research Needs and Gaps

The development and validation of clinical decision support or other tools to help clinicians efficiently and accurately identify populations at high risk for HBV infection, including combinations of risk factors, are needed. Available clinical trials largely report intermediate or surrogate outcomes and are relatively short. Clinical trials of adequate duration and power to evaluate long-term health outcomes (for example, cirrhosis, end-stage liver disease, disease-specific mortality, quality of life, and all-cause mortality) are needed. In the absence of such randomized, controlled trials, registries to assess treatment efficacy are also needed.

Other Approaches to Prevention

For the USPSTF recommendation on screening for HBV infection in pregnancy, go to www.uspreventiveservicestaskforce.org/uspstf/uspshepbpg.htm. The USPSTF recommendation on screening for hepatitis C virus infection can be found at www.uspreventiveservicestaskforce.org/uspstf/uspshepc.htm.

Other Resources

The CDC provides information about HBV infection at www.cdc.gov/hepatitis/HBV/index.htm. For more information about adolescent vaccination, visit www.cdc.gov/mmwr/preview/mmwrhtml/rr5416a1.htm?s_cid=rr5416a1_e. For information on adult vaccination, visit www.cdc.gov/mmwr/preview/mmwrhtml/rr5516a1.htm?s_cid=rr5516a1_e. Further resources for clinicians can be found at www.cdc.gov/hepatitis/HBV/ProfResourcesB.htm.

Discussion

Burden of Disease

The epidemiology of HBV infection has been evolving in the United States, probably because of implementation of vaccination programs beginning in 1991. The number of reported acute symptomatic cases of HBV infection decreased from more than 20 000 annually in the mid-1980s to 2890 in 2011 (14). However, the actual estimated number of new cases in the United States (approximately 19 000) is approximately 6.5 times the number of reported cases because of underreporting (14). The populations more likely to have acute HBV infection are persons aged 30 to 39 years (2.33 cases per 100 000 in 2010), men, and black persons (1, 15).

The burden of HBV infection disproportionately affects foreign-born persons from countries with a high prevalence of infection and their unvaccinated offspring, HIV-positive persons, men who have sex with men, and injection drug users (**Table 2**). An estimated 700 000 to 2.2 million persons in the United States have chronic HBV infection (1, 3, 16). Persons born in regions with a prevalence of HBV infection of 2% or greater, such as countries in Africa and Asia, the Pacific Islands, and parts of South America, account for 47% to 95% of chronically infected persons in the United States (1).

The death rate for persons with HBV infection in the United States in 2010 was an estimated 0.5 per 100 000 (17). The highest death rates occurred in persons aged 55 to 64 years; men; and nonwhite, nonblack persons (17). Compared with non–HBV-related deaths, HBV-associated mortality is approximately 11 times higher among persons of non-Hispanic Asian or Pacific Islander descent (18).

Scope of Review

This is an update of the 2004 USPSTF recommendation on screening for chronic HBV infection in asymptomatic, nonpregnant persons in the general population (19). The USPSTF commissioned a systematic review with a focus on evidence gaps identified in the previous USPSTF recommendation and new studies published since 2004. New key questions focused on the benefits and harms of antiviral treatment, the benefits of education or behavior change counseling, and the association between improvements in intermediate and clinical outcomes after antiviral therapy. Key questions related to the immunization of children were excluded.

In 2009, the USPSTF published a reaffirmation of its 2004 recommendation on screening for HBV infection in pregnant women at their first prenatal visit (A recommendation) (10). The USPSTF will update its recommendation on prenatal screening in the future; therefore, it is not a focus of this recommendation.

Accuracy of Screening Tests

The USPSTF previously reviewed serologic testing for HBV and found it to be accurate (sensitivity and specificity >98%) (10).

Effectiveness of Early Detection and Treatment

No randomized, controlled trials compared screening with no screening to provide direct evidence of the benefit of screening. No trials examined the effectiveness of education or behavior change counseling in patients with

chronic HBV infection for reducing transmission or improving health outcomes.

Evidence on screening strategies for identifying persons with HBV infection is limited to 1 fair-quality, cross-sectional study ($n = 6194$) done in France in a clinic for sexually transmitted infections (20). It found that a screening strategy for HBV infection that focused on testing persons born in countries with a higher prevalence of infection missed approximately two thirds of those with HBV infection (sensitivity, 31%; number needed to screen, 16). An alternative screening strategy that tested men and unemployed persons identified 98% (48 of 49) of patients with HBV infection after screening approximately two thirds of the population (number needed to screen, 82) (20). Well-established risk factors, such as injection drug use and high-risk sexual behaviors, were not predictive. Applicability of this study to U.S. primary care settings may be limited (20).

Intermediate Outcomes

Twenty-two placebo-controlled trials ($n = 35$ to 515; duration, 8 weeks to 3 years) of antiviral therapy reported intermediate outcomes (for example, histologic improvement, HBeAg or HBsAg loss or seroconversion, or virologic response) (1). Two trials were rated as good quality; most of the remaining trials were rated as fair quality. Methodological issues in the other trials included unclear or inadequate methods of randomization, allocation concealment, and blinding.

Nine trials were done in the United States or Europe. Fifteen trials enrolled patients who were entirely or largely HBeAg-positive. Trials evaluated adefovir (4 trials), interferon-α2b (8 trials), lamivudine (9 trials), and tenofovir (1 trial). Trials reported baseline rates of prevalence of cirrhosis between 5% and 44% (1).

Pooled estimates showed that antiviral therapy was statistically significantly more effective than placebo or no treatment in achieving histologic improvement (7 trials; risk ratio [RR], 2.1 [95% CI, 1.8 to 2.6]; $I^2 = 0\%$), loss or seroconversion of HBeAg (10 trials; RR, 2.1 [CI, 1.6 to 2.9]; $I^2 = 4\%$) and HBsAg (11 trials; RR, 2.4 [CI, 1.2 to 4.9]; $I^2 = 0\%$), virologic response (9 trials; RR, 7.2 [CI, 3.2 to 16]; $I^2 = 58\%$), and normalization of ALT levels (12 trials; RR, 2.5 [CI, 2.1 to 3.0]; $I^2 = 27\%$) (1). Results remained consistent when stratified by individual drug and in sensitivity and subgroup analyses based on outcomes, study quality, duration of treatment, and HBeAg-positive status. Evidence on the first-line drugs pegylated interferon, entecavir, and tenofovir is limited (1).

Eight fair- to good-quality trials ($n = 42$ to 638; duration, 48 to 96 weeks) compared first-line antiviral drugs with lamivudine or adefovir. Entecavir (4 trials) and pegylated interferon (2 trials) were associated with an increased likelihood of favorable intermediate outcomes (virologic and histologic improvement) compared with lamivudine (1). Analyses were limited by small numbers of trials. Entecavir was associated with an increased likelihood of virologic (4 trials; RR, 1.6 [CI, 1.1 to 2.5]; $I^2 = 94\%$) and histologic (2 trials; RR, 1.2 [CI, 1.1 to 1.3]; $I^2 = 0\%$) improvements compared with lamivudine. Compared with lamivudine, pegylated interferon-α2b was associated with an increased likelihood of loss or seroconversion of HBeAg (1 trial; RR, 1.6 [CI, 1.2 to 2.1]) and HBsAg (2 trials; RR, 16 [CI, 2.2 to 121]; $I^2 = 0\%$), normalization of ALT levels (2 trials; RR, 1.4 [CI, 1.2 to 1.6]; $I^2 = 0$), and virologic (2 trials; RR, 2.8 [CI, 1.9 to 4.4]; $I^2 = 0\%$) and histologic (2 trials; RR, 1.2 [CI, 1.0 to 1.4]; $I^2 = 0\%$) improvements.

Head-to-head trials of entecavir versus lamivudine were heterogeneous for virologic response (4 trials; RR, 1.6 [CI, 1.1 to 2.5]; $I^2 = 94\%$) (1). Estimates from all trials favored entecavir over lamivudine (RR, 1.3 to 2.1), including the 2 largest good-quality trials (RR, 2.1 [CI, 1.8 to 2.4] and 1.3 [CI, 1.2 to 1.4]). Studies comparing tenofovir with adefovir (2 trials) showed no clear differences in effect on intermediate outcomes (1).

Clinical Outcomes

Eleven randomized trials ($n = 40$ to 651; duration, 10 months to 7.5 years) of antiviral therapy versus placebo or no treatment reported clinical outcomes (for example, cirrhosis, hepatocellular carcinoma, and mortality). One trial was rated as good quality, and the remaining trials were rated as fair quality (1). Methodological issues included inadequate details about method of randomization, allocation concealment, and blinding.

Five trials were done in the United States or Europe. Two trials enrolled mostly HBeAg-negative patients. Trials evaluated adefovir (2 trials), interferon-α2a (2 trials), and lamivudine (4 trials). Trials reported baseline rates of prevalence of cirrhosis between 5% and 40% (1). Pooled estimates for incident cirrhosis (3 trials; RR, 0.70 [CI, 0.33 to 1.46]; $I^2 = 0\%$), hepatocellular carcinoma (5 trials; RR, 0.57 [CI, 0.32 to 1.04]; $I^2 = 2\%$), and mortality (5 trials; RR, 0.55 [CI, 0.18 to 1.71]; $I^2 = 43\%$) had trends that favored antiviral therapy over placebo but were probably underpowered for these outcomes (1).

The largest trial, the CALM (Cirrhosis Asian Lamivudine Multicentre) study, had a large effect on the pooled estimate for hepatocellular carcinoma (1, 17). Forty-one sites across Australia, China, Hong Kong, Malaysia, New Zealand, the Philippines, Singapore, Taiwan, and Thailand participated in the trial. Eighty-five percent of patients were men, and 98% were Asian (21). This fair-quality study enrolled 651 patients with advanced liver disease who were randomly assigned to lamivudine or placebo.

The trial was discontinued early after a median duration of 32.4 months because it reached a prespecified stopping threshold for a composite outcome (hepatic decompensation, hepatocellular carcinoma, spontaneous bacterial

peritonitis, bleeding gastroesophageal varices, or liver-related death) (1, 21). Results were adjusted for country, sex, baseline ALT levels, Child–Pugh score, and Ishak fibrosis score. Lamivudine was associated with decreased risk for hepatocellular carcinoma (adjusted hazard ratio [HR], 0.49 [CI, 0.25 to 0.99]), disease progression (adjusted HR, 0.45 [CI, 0.28 to 0.73]), and worsening of liver disease (adjusted HR, 0.45 [CI, 0.22 to 0.90]) than placebo (21).

Too few clinical events were reported in head-to-head trials of entecavir or pegylated interferon-α2a versus pegylated and nonpegylated interferon to determine effects on clinical outcomes (1).

Association Between Intermediate and Clinical Outcomes

Seven fair-quality and 3 poor-quality observational studies evaluated the link between intermediate and clinical health outcomes after antiviral therapy (1). These 10 observational studies (n = 22 to 818; follow-up, 4.0 to 9.9 years) assessed various intermediate (virologic or biochemical remission, histologic improvement, HBeAg loss, or composite intermediate outcomes) and clinical (death, hepatocellular carcinoma, or a composite clinical outcome) outcomes (1). The patient populations (determined by such factors as HBeAg status and prevalence of cirrhosis at baseline) and antiviral therapy administered (lamivudine vs. interferon) also varied. Methodological issues included unclear blinding status of outcome assessors and failure to report loss to follow-up and address key confounders (age, sex, fibrosis stage, HBV viral load, and HBeAg status) (1).

Observational studies found that improvements in various intermediate outcomes were associated with improved clinical outcomes (1). One fair-quality study in HBeAg-negative patients found that maintenance of virologic remission (no virologic breakthrough) was associated with a reduced risk for hepatocellular carcinoma (adjusted HR, 0.10 [CI, 0.01 to 0.77]) (22). One fair-quality study evaluated achieving virologic remission with lamivudine therapy in HBeAg-negative patients and found no significant benefit (adjusted HR, 0.77 [CI, 0.35 to 1.69]) in the reduction of hepatocellular carcinoma (23).

HBV Vaccination

Vaccination was associated with decreased risk for HBV acquisition in health care workers (4 trials; RR, 0.5 [CI, 0.4 to 0.7]; I^2 = 18%) on the basis of the presence of serologic markers (HBsAg or anti-HBc) (24). Pooled analyses from 3 fair- to good-quality trials showed that vaccination was also associated with a decreased risk for HBV acquisition than placebo in men who have sex with men on the basis of HBsAg seroconversion (RR, 0.2 [CI, 0.1 to 0.4]; I^2 = 45%) or elevated ALT levels (RR, 0.2 [CI, 0.2 to 0.3]; I^2 = 2%) (4, 25–27). Studies did not evaluate the effects of HBV vaccination on long-term clinical outcomes.

Harms of Screening and Treatment

Pooled estimates showed no statistically significant difference between antiviral therapy and placebo or no treatment in risk for serious adverse events (12 trials; RR, 0.8 [CI, 0.6 to 1.1]; I^2 = 0%) or any adverse event (7 trials; RR, 0.96 [CI, 0.9 to 1.0]; I^2 = 0%) (1). Studies did show an increased risk for withdrawal due to adverse events (9 trials; RR, 4.0 [CI, 1.4 to 11]; I^2 = 0%). Results for harms were largely consistent when stratified according to individual drugs (1).

Two head-to-head trials showed that pegylated interferon-α2a was associated with greater risk for serious adverse events (RR, 2.1 [CI, 1.0 to 4.5]; I^2 = 0%), withdrawals due to adverse events (RR, 7.6 [CI, 1.1 to 52.0]; I^2 = 38%), and any adverse event (RR, 1.7 [CI, 1.5 to 2.0]; I^2 = 55%) than lamivudine. There were no statistically significant differences between entecavir and lamivudine or tenofovir and adefovir (1).

No placebo-controlled trials of pegylated interferon-α2a or entecavir reported harms, and only 1 trial each of telbivudine and tenofovir reported harms (1).

Estimate of Magnitude of Net Benefit

The USPSTF found adequate evidence that HBV vaccination is effective at decreasing disease acquisition. The USPSTF also found convincing evidence that antiviral treatment in patients with chronic HBV infection is effective at improving intermediate outcomes (virologic or histologic improvement or clearance of HBeAg).

The USPSTF concludes with moderate certainty that antiviral treatment results in an important improved clinical outcome (reduced incidence of hepatocellular carcinoma) and that antiviral therapy regimens have small harms. As a result, the USPSTF concludes that the net benefit of screening for HBV infection in high-risk populations is moderate.

How Does Evidence Fit With Biological Understanding?

Acute HBV infections are usually self-limited. Risk for chronic infection is inversely proportional to the age at acquisition. Hepatitis B virus infection becomes chronic in more than 90% of infants and approximately 25% to 50% of children aged 1 to 5 years but fewer than 5% of older children and adults. Chronic infection spontaneously resolves in 0.5% of persons annually (2, 3). Hepatitis B virus infection that persists for at least 6 months is considered chronic.

Potential long-term sequelae include cirrhosis, hepatic decompensation, and hepatocellular carcinoma. Increased viral load is associated with greater risk for cirrhosis, hepatocellular carcinoma, liver-related death, and disease transmission. Approximately 15% to 25% of persons with chronic HBV infection die of cirrhosis or hepatocellular carcinoma (3).

Response to Public Comments

A draft version of this recommendation statement was posted for public comment on the USPSTF Web site from

11 February to 10 March 2014. Some comments requested clarification about risk factors, screening tests, vaccinations, and screening frequency. Others asked for a definition of "immunosuppressed."

In response to these comments, the USPSTF added language about populations that are at risk in the Clinical Considerations section. The USPSTF also added language to clarify about screening tests and vaccination. Language was added to the section on research gaps. Text was added to address screening frequency and to clarify the definition of "immunosuppressed."

Update of the Previous USPSTF Recommendation

In 2004, the USPSTF recommended against screening for chronic HBV infection in asymptomatic persons in the general population (D recommendation) (19). The USPSTF found that screening for HBV infection in the general population did not improve long-term health outcomes, such as cirrhosis, hepatocellular carcinoma, or mortality; the prevalence of HBV infection was low in the general population; and most infected persons did not develop chronic infection, cirrhosis, or HBV-related liver disease. The USPSTF noted limited evidence on the effectiveness of treatment interventions and on potential harms related to screening (for example, labeling and anxiety) (1, 15). As a result, the USPSTF concluded that the potential harms of screening for HBV infection in the general population probably exceeded the potential benefits (19).

In the 2004 recommendation, the USPSTF focused only on the general population. In the current recommendation, the USPSTF focused on high-risk populations as it considered new evidence on the benefits and harms of antiviral treatment, the benefits of education or behavior change counseling, and the association between improvements in intermediate and clinical outcomes after antiviral therapy. The USPSTF found new evidence that antiviral regimens improve health outcomes (reduced incidence of hepatocellular carcinoma) and that HBV vaccination is effective at decreasing disease acquisition in high-risk populations.

Recommendations of Others

The CDC and the American Association for the Study of Liver Diseases recommend screening for HBV infection in high-risk persons, including all foreign-born persons from regions with an HBsAg prevalence of 2% or greater, regardless of vaccination history; U.S.-born persons not vaccinated as infants whose parents were born in regions with an HBsAg prevalence of 8% or greater; injection drug users; men who have sex with men; household contacts and sexual partners of HBsAg-positive persons; patients receiving hemodialysis; and immunosuppressed and HIV-positive persons (2, 11). The CDC also recommends screening for HBV infection in blood, organ, or tissue donors; persons with occupational or other exposures to infectious blood or body fluids; and those who received HBV vaccination as adolescents or adults with high-risk behaviors (2). In addition, the American Association for the Study of Liver Diseases recommends that persons with multiple sexual partners or a history of sexually transmitted infections, inmates of correctional facilities, and persons with hepatitis C virus infection be screened (11).

The Institute of Medicine endorses screening for HBV infection in high-risk groups similar to those recommended by the CDC (28). The American Academy of Family Physicians recommends screening for HBV infection in persons at high risk for infection and recommends against routinely screening the general asymptomatic population (29).

From the U.S. Preventive Services Task Force, Rockville, Maryland.

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Requests for Single Reprints: Reprints are available from the USPSTF Web site (www.uspreventiveservicestaskforce.org).

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Appendix: U.S. Preventive Services Task Force

Members of the U.S. Preventive Services Task Force at the time this recommendation was finalized† are Michael L. LeFevre, MD, MSPH, *Chair* (University of Missouri School of Medicine, Columbia, Missouri); Albert L. Siu, MD, MSPH, *Co-Vice Chair* (Mount Sinai School of Medicine, New York, and James J. Peters Veterans Affairs Medical Center, Bronx, New York); Kirsten Bibbins-Domingo, MD, PhD, *Co-Vice Chair* (University of California, San Francisco, and San Francisco General Hospital, San Francisco, California); Linda Ciofu Baumann, PhD, RN (University of Wisconsin, Madison, Wisconsin); Susan J. Curry, PhD (University of Iowa College of Public Health, Iowa City, Iowa); Karina W. Davidson, PhD, MASc (Columbia University Medical Center, New York, New York); Mark Ebell, MD, MS (University of Georgia, Athens, Georgia); Francisco A.R. García, MD, MPH (Pima County Department of Health, Tucson, Arizona); Matthew W. Gillman, MD, SM (Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts); Jessica Herzstein, MD, MPH (Air Products, Allentown, Pennsylvania); Alex R. Kemper, MD, MPH, MS (Duke University, Durham, North Carolina); Ann E. Kurth, PhD, RN, MSN, MPH (Global Institute of Public Health, New York, New York); Douglas K. Owens, MD, MS (Freeman Spogli Institute for International Studies, Stanford University, Stanford, California); William R. Phillips, MD, MPH (University of Washington, Seattle, Washington); Maureen G. Phipps, MD, MPH (Warren Alpert Medical School, Brown University, Providence, Rhode Island); and Michael P. Pignone, MD, MPH (University of North Carolina, Chapel Hill, North Carolina).

† For a list of current Task Force members, go to www.uspreventiveservicestaskforce.org/members.htm.

Appendix Table 1. **What the USPSTF Grades Mean and Suggestions for Practice**

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer/provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.	Offer/provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer/provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

Appendix Table 2. **USPSTF Levels of Certainty Regarding Net Benefit**

Level of Certainty*	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as: the number, size, or quality of individual studies; inconsistency of findings across individual studies; limited generalizability of findings to routine primary care practice; and lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: the limited number or size of studies; important flaws in study design or methods; inconsistency of findings across individual studies; gaps in the chain of evidence; findings that are not generalizable to routine primary care practice; and a lack of information on important health outcomes. More information may allow an estimation of effects on health outcomes.

* The USPSTF defines *certainty* as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general primary care population. The USPSTF assigns a certainty level on the basis of the nature of the overall evidence available to assess the net benefit of a preventive service.