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Hepatitis C Virus Testing of Persons Born During 1945 to 1965: Recommendations From the Centers for Disease Control and Prevention

Bryce D. Smith, PhD; Rebecca L. Morgan, MPH; Geoff A. Beckett, PA-C, MPH; Yngve Falck-Ytter, MD; Deborah Holtzman, PhD; and John W. Ward, MD

Description: The Centers for Disease Control and Prevention (CDC) developed these evidence-based recommendations to increase the proportion of hepatitis C virus (HCV)–infected persons who know their status and are linked to appropriate care and treatment. The recommendations also address brief alcohol screening, as alcohol accelerates progression of liver disease in these persons. They augment CDC's 1998 and 1999 recommendations based on risk and medical indication and are not meant to replace those recommendations.

Methods: These recommendations are based on systematic reviews of evidence published between 1995 and February 2012 in MEDLINE, EMBASE, CINAHL, the Cochrane Central Register of Controlled Trials, Sociological Abstracts, and the Database of Abstracts of Reviews of Effects. Selected studies included cross-sectional and cohort studies that addressed either prevalence of HCV in the United States or clinical outcomes (for example, hepatocellular carcinoma and serious adverse events) in treated patients and systematic reviews of trials that assessed effectiveness of brief screening interventions for alcohol consumption. The Grading of Recommendations Assessment, Development, and Evaluation framework was used to assess the quality of the evidence.

Recommendation 1: Adults born during 1945 to 1965 should receive 1-time testing for HCV without prior ascertainment of HCV risk. (Grade: strong recommendation; moderate-quality evidence).

Recommendation 2: All persons identified with HCV infection should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment services for HCV infection and related conditions as indicated (Grade: strong recommendation; moderate-quality evidence).

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For author affiliations, see end of text.

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An estimated 2.7 to 3.9 million persons are living with hepatitis C virus (HCV) infection in the United States (1). Incidence of HCV increased markedly during the 1970s and 1980s, reaching an average of 230 000 new infections each year throughout the 1980s (2). Incidence declined rapidly in the 1990s because of effective screening of blood donors starting in 1992 and reduced numbers of new infections among persons who inject drugs. Incidence declined until 2006 and has since remained stable, with 17 000 new infections in 2010 (2). Those who were infected in the remote past have been living with HCV infection for 20 to 40 years and are at increased risk for HCV-related morbidity and mortality.

Hepatitis C virus infection accounts for more than 50% of incident hepatocellular carcinoma (HCC) (3), which is the fastest-growing cause of cancer-related death (4) and the leading indication for liver transplantation in the United States (5–8). Annual HCV-associated mortality in the United States increased more than 50% between 1999 and 2007. Data from death certificates show that HCV-related deaths now outpace deaths due to HIV (9). Modeling studies forecast substantial increases in morbidity and mortality among HCV-infected persons as they enter into their third, fourth, and fifth decades of living with HCV infection (10, 11). The CDC estimates that without care or treatment 1.76 million persons with HCV infection will develop cirrhosis, more than 400 000 will develop HCC, and more than 1 million will die of HCV-related disease (12).

In 1998, the CDC issued recommendations for identifying HCV-infected persons (1). Testing for HCV was recommended for persons most likely to be infected, including those who had ever injected drugs, received clotting factor concentrates produced before 1987, ever received long-term hemodialysis, had laboratory evidence of liver disease (persistently elevated alanine aminotransferase levels), and received blood transfusions or organ transplants before July 1992. Other populations recommended for testing included persons who received blood or blood components before July 1992. Screening also was recommended for persons who had a recognized blood exposure (health care, emergency medical, and public safety workers after sticks from needles or sharps or mucosal exposure, and children born to HCV-infected mothers). In 1999, HCV testing was recommended for persons with HIV (13).

The success of risk-based testing strategies has been limited. Depending on the level of risk in the population and site-specific testing practices, an estimated 45% to 85% of U.S. adults are chronically infected with HCV yet

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unaware of their condition (14–17). Testing for HCV seromarkers is suboptimal even among high-risk populations for whom routine testing is recommended (14, 15): A sizeable percentage of these persons remain unaware of their infection status (18).

Hepatitis C virus infection is typically asymptomatic until substantial liver disease occurs, so a primary care clinician would have few reasons to order diagnostic tests on the basis of patient presentation. If all persons with a single elevated alanine aminotransferase level were tested for HCV, 50% of chronic cases would remain unidentified (19) and 20% to 30% of persons with persistently normal alanine aminotransferase levels develop serious liver disease (20). In addition, many health care providers lack knowledge about the prevalence, natural history, diagnostic tests, testing algorithms, and management of HCV infection (21–24). Fewer than one half of all U.S. physicians ask their patients sensitive questions related to high-risk behaviors (22), and accuracy of patient recall of risk behaviors, including drug use, decreases over time (25).

Because of the limited effectiveness of the current HCV testing recommendations in identifying undiagnosed infections, the CDC considered a prevalence-based HCV testing strategy to increase the proportion of infected persons who know their HCV infection status: 1-time HCV testing of persons born between 1945 and 1965. These persons account for 76.5% of all prevalence of HCV antibodies or anti-HCV (that is, all persons ever infected with HCV have HCV antibodies, and 75% of these persons develop chronic infection) in the United States (26). Because alcohol accelerates progression of liver disease in HCV-infected persons (27), the CDC also addressed brief alcohol screening for HCV-infected persons.

Target Population and Recommendation Focus

The target population was adults born or living in the United States. Efforts were focused on identifying testing strategies that would increase the proportion of HCV-infected persons who know their status. In particular, we examined whether a testing strategy based on year of birth would identify persons living with HCV infection who have not been identified by risk-based testing. We also considered 1) associations between achieving a sustained virologic response (SVR) with treatment and clinical outcomes and 2) potential effectiveness and benefits of offering brief alcohol interventions to HCV-infected persons.

Recommendation Development Process

A 35-member workgroup comprising persons within the Division of Viral Hepatitis; members of other federal agencies; representatives from local and state health departments and from advocacy, community, and professional groups; clinicians; and methodologists guided the development of the recommendations. **Table 1** shows the questions that we asked.

Table 1. **Questions to Guide the Development of Recommendations**

What is the effect of a testing strategy based on birth year vs. the standard of care (i.e., risk-based testing) for identification of HCV infection?
Should HCV testing (vs. no testing) be conducted among adults at average risk for infection who were born between 1945 and 1965?
Among persons tested for and identified with HCV infection, is treatment-related SVR (vs. treatment failure) associated with reduced liver-related morbidity and all-cause mortality?
Should HCV testing followed by brief alcohol intervention (vs. no intervention) be carried out to reduce or stop drinking among HCV-infected persons?

HCV = hepatitis C virus; SVR = sustained virologic response.

Two independent reviewers searched multiple databases to identify English-language studies pertinent to the questions. For prevalence data, we selected cross-sectional and cohort studies with data relevant to the United States that we had identified through searches of the following databases between 1995 and May 2011: MEDLINE, EMBASE, CINAHL, the Cochrane Central Register of Controlled Trials, Sociological Abstracts, and the Database of Abstracts of Reviews of Effects. We searched the same databases through February 2012 to identify studies that examined the association of HCC with HCV treatment among persons who achieved an SVR compared with those who did not. To identify observational studies and controlled trials with data related to mortality, serious adverse events, and quality of life (QOL) among treated HCV-infected persons, we conducted a series of MEDLINE searches from database inception through July 2011. For evidence related to effective alcohol screening and counseling interventions, we selected systematic reviews or meta-analyses of trials that were identified in MEDLINE searches through July 2011.

The Grading of Recommendations Assessment, Development, and Evaluation framework was used to develop these recommendations (28). Two investigators with experience using this framework independently produced evidence tables and profiles for each question. The criteria considered when determining the quality of the evidence were risk of bias, imprecision, indirectness (for example, addressing a different population than the one under consideration), inconsistency of results, publication bias, dose–response effect, magnitude of the effect, and plausible confounders. The final quality of evidence for the outcomes was categorized into 1 of 4 levels: very low, low, moderate, and high.

To determine the strength of the recommendation, the 9 workgroup members from the Division of Viral Hepatitis and the external workgroup assessed the quality of evidence, benefits and harms, values and preferences (of persons being targeted for testing), and resource implications before arriving at a consensus on the recommendations. These work group members have expertise in HCV prevention, epidemiology, education and training, and re-

search and evaluation, as well as in the Grading of Recommendations Assessment, Development, and Evaluation framework. Recommendations can be categorized into strongly for or against the recommendation or conditionally for or against the recommendation.

Comments and Modification

The draft recommendations went through a peer-review and public-comment process. For peer review, 3 experts in the field of viral hepatitis, who had not been previously involved with the recommendation development process, commented on the draft recommendation. The draft recommendations were externally posted on the Federal Register Management System (www.regulations.gov) for public comment from 22 May to 8 June 2012. Modifications were made to the document on the basis of the comments received. Most comments requested additional information on the mode of transmission and methodological framework used to grade the evidence.

Guidelines and Rationale

Recommendation 1: The CDC recommends that adults born during 1945 to 1965 should receive 1-time testing for HCV without prior ascertainment of HCV risk. (Grade: strong recommendation; moderate-quality evidence).

Of 31 studies that addressed the prevalence of HCV infection in the United States, 3 involved nationally representative samples and provided evidence directly related to the populations of comparison: persons born between 1945 and 1965 living in the United States and the general population (1, 29, 30). These studies, as well as a recent CDC analysis of 1999 to 2008 National Health and Nutrition Examination Survey (NHANES) data, found that the proportion of persons born between 1945 and 1965 with HCV antibody was higher than that of the general population. The NHANES analysis specifically found that the anti-HCV prevalence in the 1945 to 1965 birth cohort was 3.25% and that it was much lower (0.8%) among adults aged 20 years or older who were born outside of the birth cohort.

Several studies examined treatment effectiveness and the relationship between achieving an SVR with treatment and clinical outcomes. Of note, in chronic HCV infection spontaneous viral clearance is highly unlikely and SVR can currently be achieved only by an interferon-based treatment regimen. Newer direct-acting antiviral agents increase the chance of SVR from an average of 41.3% for pegylated interferon and ribavirin therapy to nearly 70% with triple therapy (pooled risk difference, 28% [95% CI, 24% to 32%] [data not shown]) (31–35).

One observational study (31), the highest-quality evidence available relevant to HCV infection–related mortality among persons born during 1945 to 1965, found that achieving SVR with treatment was associated with lower risk for all-cause mortality (unadjusted relative risk, 0.46 [CI, 0.14 to 0.51]). The study compared persons who responded to therapy with those who did not. It did not address a screened population or an untreated population. Differences in stage of liver disease between the groups had the potential to bias findings. However, adjusted analysis for baseline prognostic factors, including the presence of cirrhosis, showed a substantial association between lower risk for mortality and SVR in patients with genotype 1 (relative risk, 0.7 [CI, 0.59 to 0.83]) and lower risk for mortality among patients with SVR and genotypes 2 and 3.

We found 30 observational studies that examined the relationship between achieving SVR with treatment and developing HCC. Our meta-analysis of these data found that achieving a treatment-related SVR was associated with a reduction in the risk for HCC among persons at all stages of liver disease (adjusted hazard ratio, 0.24 [CI, 0.18 to 0.31]), as well as among those with advanced liver disease (adjusted hazard ratio, 0.23 [CI, 0.16 to 0.35]) (36). We rated the certainty of these findings as moderate-quality evidence because of the large magnitude of effect.

Studies report that many adverse events associated with HCV treatment can lead to treatment discontinuation or other illnesses. Typical adverse events included infections, anemia, rash, pruritus, disabling fatigue, fever, nausea, diarrhea, muscle aches, and mood disorders that can rarely lead to suicides. More than 98% of patients undergoing treatment have at least 1 adverse event; however, almost all adverse events resolve when therapy is discontinued (33). Adding new direct-acting antiviral agents increases the risk for adverse events leading to discontinuation of treatment by about 3% from an average rate of 9.7% in previously untreated patients (pooled risk difference, 3% [CI, 0% to 7%] [data not shown]) (31–35).

One previously published systematic review examined the effect of HCV testing and treatment on patients' QOL (36). Based on the Short Form-36 vitality subscore, patients receiving testing and treatment had a mean QOL score of 6.6 points higher than that of patients in the control group, suggesting that those who received testing and treatment had a higher QOL (**Table 2**).

Recommendation 2: The CDC recommends that all persons identified with HCV infection should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment services for HCV infection and related conditions (Grade: strong recommendation; moderate-quality evidence).

A meta-analysis of 22 randomized, controlled trials published in 2010 examined the effects of a brief alcohol intervention versus no intervention on reduction of alcohol use (37). Patients who had a brief alcohol reduction intervention had a mean reduction of alcohol consumed per week of 38.42 g (CI, 30.91 to 65.44) compared with those in the control group. We rated this evidence moderate quality due to indirectness because the studies did not specifically examine patients with HCV infection (**Table 3**).

Table 2. **GRADE Evidence Profile for Observational Data Examining the Relationship Between Achieving SVR With Treatment and Outcomes**

Outcome	Participants (Studies), *n*	Quality of Evidence	Relative Effect Hazard Ratio (95% CI)	Risk With Failed or No Treatment	Anticipated Absolute Effect With Achieving SVR (95% CI)	Findings
All-cause mortality	16 868 (1)	Low*	0.7 (0.59–0.83)	119 deaths per 1000 persons	34 fewer deaths per 1000 persons (19–47)	Achieving SVR was associated with a lower risk for all-cause mortality
HCC	25 906 (12)	Moderate†	0.24 (0.18–0.31)	10 HCC incidents per 1000 persons	8 fewer HCC incidents per 1000 persons (7–8)	Achieving SVR was associated with a decreased incidence of HCC
QOL	5978 (7)	Low	–	–	The mean QOL associated with the SVR–vitality subscore in the intervention groups was 6.6 points higher than that of patients not achieving SVR‡	Achieving SVR was associated with an increased QOL

GRADE = Grading of Recommendations Assessment, Development, and Evaluation; HCC = hepatocellular carcinoma; HCV= hepatitis C virus; QOL = quality of life; SVR= sustained virologic response.
* This observational study controlled for baseline status of cirrhosis and other variables.
† Most of these observational studies controlled for baseline severity of liver disease (e.g., presence of cirrhosis) and other important confounders, such as hepatitis B virus infection. Quality of evidence was rated up because of large relative risk effect.
‡ CI not provided. Effect was reported as significant. Minimally clinically important difference estimated to be 4.2 (range, 3–5). Effect size results were 0.2 (range, 0.15–0.25). According to Cohen, small effect sizes are ≤0.2; moderate, 0.5; and large, ≥0.8.

DISCUSSION

The CDC now recommends 1-time HCV testing for all persons born during 1945 to 1965. These recommendations augment the CDC's 1998 and 1999 recommendations based on risk and medical indication and are not meant to replace them. We judged that the benefits of testing and treating persons with HCV infection are greater than the harms. Although certain harms (that is, worry or anxiety while waiting for test results, insurability, liver biopsy complications, and severe adverse events during treatment) can be detrimental to patients, the benefits associated with diagnosis and effective treatment include SVR, which is associated with reductions in HCC and all-cause mortality.

The CDC also recommends that all infected persons receive alcohol screening and counseling as indicated. Brief alcohol screenings are effective in reducing alcohol use and maintaining that reduction for 1 year or more. Because alcohol is known to accelerate progression of liver disease (38), screening to evaluate the level of alcohol consumption followed by counseling to reduce or cease alcohol use can avoid this acceleration. Screening tools shown to be effective in eliciting history of alcohol use from patients include the Alcohol Use Disorders Identification Test and are available from the National Institute on Alcohol Abuse and Alcoholism (http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide.htm). The World Health Organization has published intervention tools to help patients reduce alcohol use (www.who.int/substance_abuse/activities/sbi/en/index.html). Although the screening and intervention may be uncomfortable or cause anxiety, the benefits of alcohol reduction for persons with HCV infection outweigh those harms. Finally, the CDC recommends that all infected persons receive medical care (for example, hepatitis A and B virus vaccinations as needed and medical monitoring of disease progression), but detailed care and treatment recommendations are beyond the scope of these guidelines. The patient and provider should make treatment decisions considering such factors as disease stage, genotype, comorbid conditions, and adverse events of therapy.

Table 3. **GRADE Evidence Profile for Brief Alcohol Screening and Intervention**

Outcome	Participants (Studies), *n*	Quality of Evidence	Relative Effect (95% CI)	Risk With Failed or No BAI	Anticipated Absolute Effect With Failed or No BAI (95% CI)	Findings
Alcohol use	5860 (22 randomized, controlled trials)	Moderate*	NA	The mean quantity of drinking alcohol in the control groups was 313 g/wk†	The mean quantity of drinking alcohol in the intervention groups was 38.42 g/wk lower than in the control groups (65.44–30.91 lower)	A BAI was associated with a reduction in grams of alcohol consumed

BAI = brief alcohol intervention; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; NA = not available.
* Quality of evidence was rated down because of indirectness of populations (HCV-infected patients not the primary target).
† 21 trials reported the following findings about baseline alcohol consumption: range, 89–456 g/wk, and overall mean, 313 g/wk (26 standard U.S. drinks [approximately 12 g each]/wk and an average of 3.7 drinks/d).

The U.S. Preventive Services Task Force (USPSTF) and the CDC both issue preventive recommendations using evidence-based methods that include evaluating available data on a topic and drawing conclusions on the basis of the strength of the evidence. However, several differences exist between the organizations, including their affiliation, target audience, and scope. Congress created the USPSTF in 1984 as an independent panel of clinical experts to evaluate and make recommendations for preventive services to be delivered in the context of primary care. The USPSTF is not a government agency—it makes recommendations that are independent of the Department of Health and Human Services. The CDC is an operating division of the Department of Health and Human Services and clears all preventive recommendations with other Department of Health and Human Services agencies as appropriate. The USPSTF focuses on the primary care setting and provider–patient interactions and considers the harms and benefits (generally, reduced morbidity and mortality) to the patient directly resulting from a given intervention. The CDC has a broader public health focus that includes diverse settings outside of primary care and considers not only the benefits and harms of an intervention but also the potential harms of an absence of public health action and of future transmission of disease.

The USPSTF's HCV screening recommendations and the CDC's birth cohort recommendation are not in direct conflict, and updated USPSTF recommendations are expected within a year. In 2004, the USPSTF found insufficient evidence to recommend for or against HCV screening among high-risk persons (for example, persons who have ever injected drugs) and against routine testing for all asymptomatic adults (39). The CDC's recommendation for 1-time HCV testing is only for persons born during 1945 to 1965, not for all adults. The CDC's recommendation is, to a large degree, built upon an intermediate measure (SVR) and its strong association with reductions in HCC and all-cause mortality.

The USPSTF prefers data from randomized, controlled trials that begin with randomization into screened and nonscreened groups and follow participants through to morbidity and mortality, yet these data are not available. Although these types of studies provide the most conclusive evidence about the benefits and harms of a screening intervention, they also are resource-intensive and require long periods of follow-up. The CDC based its HCV testing recommendations on the prevalence in the target population, the many persons who are unaware of their infection status, potential benefits of care and treatment, and projections of increasing morbidity and mortality in the absence of an intervention.

From the Centers for Disease Control and Prevention, Division of Viral Hepatitis, Atlanta, Georgia, and Louis Stokes Veterans Affairs Medical Center and University Hospitals—Case Medical Center, Cleveland, Ohio.

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Requests for Single Reprints: Bryce D. Smith, PhD, 1600 Clifton Road, MS G-37, Atlanta, GA 30333; e-mail, BSmith6@cdc.gov.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Dr. Smith, Ms. Morgan, Mr. Beckett, and Drs. Holtzman and Ward: 1600 Clifton Road, MS G-37, Atlanta, GA 30333.
Dr. Falck-Ytter: 10701 East Boulevard, Cleveland, OH 44106.

Author Contributions: Conception and design: B.D. Smith, R.L. Morgan, G.A. Beckett, Y. Falck-Ytter, J.W. Ward.
Analysis and interpretation of the data: B.D. Smith, R.L. Morgan, G.A. Beckett, Y. Falck-Ytter, D. Holtzman.
Drafting of the article: B.D. Smith, R.L. Morgan, G.A. Beckett.
Critical revision of the article for important intellectual content: B.D. Smith, R.L. Morgan, G.A. Beckett, Y. Falck-Ytter, D. Holtzman, J.W. Ward.
Final approval of the article: B.D. Smith, R.L. Morgan, D. Holtzman, J.W. Ward.
Statistical expertise: R.L. Morgan, Y. Falck-Ytter.
Obtaining of funding: J.W. Ward.
Administrative, technical, or logistic support: R.L. Morgan.
Collection and assembly of data: R.L. Morgan, Y. Falck-Ytter.