Use of GRADE Methodology to Guide Development of CDC's Hepatitis C Virus Infection Testing Recommendations for Persons Born during 1945 through 1965 in the United States

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BACKGROUND

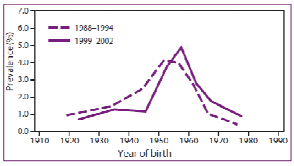
Burden of Hepatitis C Virus (HCV) Infection in the United States

- In the U.S., 3.2 million persons are living with HCV infection[1]
- In 2007, deaths associated with HCV surpassed those from HIV[2]
- Few HCV-infected persons are tested and many are unaware of their infection[3]
- Recommendations for testing of demographic sub-populations with a high HCV prevalence, such as persons born in the 1945-1965 birth cohort, might improve access to HCV testing

Current CDC HCV Testing Recommendations

- In 1998, CDC developed *Recommendations for Prevention and Control of Hepatitis C Virus Infection and HCV-Related Chronic Disease*[4] to address risk-based transmission methods
- Recent evidence suggests that, in addition to risk-based testing, a birth-year based testing strategy could identify previously unidentified cases of HCV infection (Figure 1)

Figure 1. Prevalence of HCV antibody, by year of birth — National Health and Nutrition Examination Survey, United States, 1988–1994 and 1999–2002[1]



Standards for High-Quality Guideline Development

- In 2011, the Institute of Medicine published a set of standards to follow when developing rigorous and trustworthy clinical practice guidelines[5]:
  - Be based on a systematic review of the existing evidence;
  - Be developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups;
  - Consider important patient subgroups and patient preferences, as appropriate;
  - Be based on an explicit and transparent process that minimizes distortions, biases, and conflicts of interest;
  - Provide a clear explanation of the logical relationships between alternative care options and health outcomes, and provide ratings of both the quality of the evidence and the strength of recommendations; and
  - Be reconsidered and revised as appropriate when important new evidence warrants modifications of recommendations.

METHODS

Methodology

- The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework[6] was used to
  - Assess the quality of the evidence
  - Determine the strength of the recommendations

Research Questions

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

Two-stage Review

- Formative review
  - Conduct a literature search for birth-year-based HCV trends
- Systematically review evidence
  - Once evidence was identified for screening persons born during 1945-1965, systematic reviews were conducted on patient-important outcomes

External Involvement

- 35-person work group (composed of clinicians, academicians, methodologists, patient advocacy groups, persons from state and local health departments, and other federal agencies) provided input throughout the development process
- Three peer reviewers reviewed the draft recommendations
- Document was posted for a two-week public comment period
- Comments were reviewed and modifications made, as needed

Search Strategy

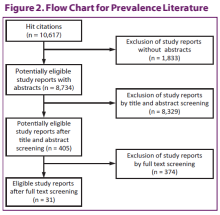
- Prevalence data
  - English-language studies published during 1995-2011
  - Databases searched: MEDLINE, EMBASE, Sociological Abstracts, the Cochrane Library, CINAHL, DARE
- Patient-important Outcomes
  - Mortality, SVR, SAEs, QoL, Transmission, Brief Alcohol Interventions
    - English-language studies (including previously published systematic reviews and meta-analyses) published during 1995-2011
    - Database searched: MEDLINE
  - HCC
    - English-language studies published during 1946-2011
    - Databases searched: MEDLINE, EMBASE, Web of Science, the Cochrane Library, CINAHL, DARE

RESULTS

Review of Prevalence Data

- The formative review identified 3 studies (out of 31) providing best evidence from nationally representative data used to support a birth-year-based HCV testing strategy and effective birth years to target (Figure 2)
- HCV prevalence among persons born 1945-1965 was 3.25% compared with 0.8% among persons born outside of those years

Figure 2. Flow Chart for Prevalence Literature



Review of Patient-Important Outcomes

- Patient-important outcomes:
  - All-cause mortality
  - Hepatocellular carcinoma (HCC)
  - Sustained virologic response (SVR)
  - Serious adverse events (SAEs)
  - Quality of Life (QoL)
  - Brief Alcohol Interventions
- Separate literature reviews were conducted for each patient-important outcome
- Previously published systematic reviews were identified for SVR, SAEs, QoL, Brief Alcohol Interventions
- One study was identified as providing the most relevant and highest-quality evidence for All-cause Mortality
- A meta-analysis of 30 identified studies was conducted for HCC

Evidence Profiles

Table 1. GRADE Evidence Profile for HCV Testing followed by Antiviral Treatment Versus No Antiviral Treatment[7]

Outcome	Participants (number of studies)	Quality of evidence	Relative effect (95% CI)	Risk with Failed or No Treatment	Anticipated Absolute Effect with Viral Eradication (95% CI)	Findings
All-cause Mortality	16 868 (1)	Low[1]	HR, 0.7 (0.59-0.83)	119 deaths per 1000	34 fewer deaths per 1000 (19-47)	Achieving viral eradication was associated with a lower risk of all-cause mortality
Hepatocellular Carcinoma	25 752 (12)	Moderate[2]	HR, 0.24 (0.19-0.31)	10 HCC incidents per 1000	8 fewer HCC incidents per 1000 (7-8)	Achieving viral eradication was associated with a decreased incidence of developing HCC
Quality of Life	5978 (7)	Low	-	-	The mean QOL associated with SVR - vitality sub-score in the intervention groups was 6.6 higher[3]	Receiving HCV testing and treatment was associated with an increased quality of life among persons with HCV

[1] This observational study controlled for baseline status of cirrhosis and other variables

[2] Most observational studies controlled for baseline liver disease severity and other important confounders. Quality of evidence rated up due to large relative risk effect

[3] CI not provided. Effect was reported as significant. Minimally clinically important difference estimated to be 4.2 (range, 3-5). Effect size results: 0.3; no CI given; according to Cohen, small effect sizes are in the 0.2 and less range; moderate 0.5; large 0.8 and larger range.

Table 2. GRADE Evidence Profile for HCV Testing followed by a Brief Alcohol Intervention (BAI) Versus No Intervention[7]

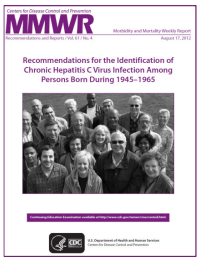
Outcome	Participants (number of studies)	Quality of evidence	Relative effect (95% CI)	Risk with Failed or No BAI	Anticipated Absolute Effect with Failed or No BAI (95% CI)	Findings
Brief Alcohol Interventions	5860 (22 randomized controlled trials)	Moderate[1]	NA	The mean quantity of drinking alcohol (g/week) in the control groups was 313 grams of alcohol a week[2]	The mean quantity of drinking alcohol (g/week) in the intervention groups was 38.42 lower (65.44 to 30.91 lower)	A brief alcohol intervention was associated with a reduction in grams of alcohol consumed.

[1] Quality of evidence rated down due to indirectness of populations (HCV infected patients not the primary target)

[2] 21 trials reported baseline alcohol consumption: range 89 to 456 g / week; overall mean 313 g / week (26 standard US drinks (~12 g each) per week; 3.7 average a day).

Determining the Strength of the Recommendations

- Quality of the Evidence
  - Based on the GRADE evidence profiles the quality of the evidence was deemed Moderate
- Benefits and Harms
  - The benefits associated with testing and receiving treatment were determined to outweigh potential harms (e.g., worry/anxiety while waiting for test results, concerns about insurability, liver biopsies)
- Values and Preferences
  - Available data are limited regarding the acceptability of HCV testing in the U.S.
  - Testing preferences should be addressed during discussions between the patient and physician
- Resource Implications
  - This testing strategy will reduce future costs, by avoiding HCV-related morbidity and mortality medical expenditures



Final Recommendations

- Adults born during 1945–1965 should receive one-time testing for HCV without prior ascertainment of HCV risk **(Strong Recommendation, Moderate Quality of Evidence)**, and
- 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 **(Strong Recommendation, Moderate Quality of Evidence)**.

DISCUSSION

Implementation of the methodology

- GRADE provided a rigorous and transparent framework for:
  - Development of the research questions;
  - Identification of outcomes critical for decision-making;
  - Assessment of the quality of the evidence;
  - Production of evidence profiles;
  - Determination of the strength of the recommendations; and
  - Presentation of the final recommendations.
- This framework
  - Provided a standardized approach when assessing both randomized trials and observational studies;
  - Strengthened the rigor of evidence upon which CDC recommendations are based; and
  - Aligned the development of these recommendations with the IOM standards
- Stakeholder involvement throughout the development process increased acceptability of the recommendations

Implications

- CDC recommends, in addition to current risk-based testing strategies, that persons born during 1945-1965 receive HCV testing and a brief alcohol screening and intervention, as indicated
- GRADE provides a suitable framework for the development of evidence-based recommendations

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