Overview of draft CDC recommendations for perinatal hepatitis C testing

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Disclaimer

- This presentation is distributed solely for the purpose of predissemination review. These materials have not been formally disseminated by the Centers for Disease Control and Prevention. Draft materials shared for review do not represent and should not be construed to represent any agency determination or policy.
Overview

- Welcome and introduction – Dr. Amy Sandul
- Presentation – Dr. Lakshmi Panagiotakopoulos
  - Perinatal hepatitis C in the United States
  - Methods of guideline development
  - Proposed recommendation language
  - Process for providing feedback
- Question and Answer period
- Closing remarks – Dr. Carolyn Wester
Introduction

- The purpose of this webinar is to:
  - Present the draft of the perinatal hepatitis C testing recommendations
  - Describe how to provide feedback via the Federal Register Notice (FRN)

- These slides will be posted on: https://www.cdc.gov/hepatitis/policy/ISIreview/index.htm
Introduction (cont.)

- All participants will be muted for the duration of the webinar
- Please add any questions about the FRN process or clarification about the guidelines in the Q&A box
  - These questions will be answered at the end of the presentation
- CDC highly encourages review of the draft recommendations and feedback
  - All public comments must be submitted through the FRN
Perinatal Hepatitis C in the United States
Risk factors for hepatitis C virus (HCV) infection

- In adults, injection drug use is the most commonly reported risk factor for acute infection

<table>
<thead>
<tr>
<th>Risk behaviors</th>
<th>Risk identified</th>
<th>No risk identified</th>
<th>Risk data missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection drug use</td>
<td>1,017</td>
<td>523</td>
<td>3,258</td>
</tr>
<tr>
<td>Multiple sexual partners</td>
<td>167</td>
<td>352</td>
<td>4,279</td>
</tr>
<tr>
<td>Surgery</td>
<td>142</td>
<td>713</td>
<td>3,942</td>
</tr>
<tr>
<td>Sexual contact</td>
<td>83</td>
<td>336</td>
<td>4,379</td>
</tr>
<tr>
<td>Needlestick</td>
<td>64</td>
<td>706</td>
<td>4,028</td>
</tr>
<tr>
<td>Men who have sex with men</td>
<td>44</td>
<td>258</td>
<td>2,803</td>
</tr>
<tr>
<td>Household contact (non-sexual)</td>
<td>17</td>
<td>402</td>
<td>4,379</td>
</tr>
<tr>
<td>Dialysis patient</td>
<td>69</td>
<td>964</td>
<td>3,765</td>
</tr>
<tr>
<td>Occupational</td>
<td>9</td>
<td>923</td>
<td>3,866</td>
</tr>
<tr>
<td>Transfusion</td>
<td>1</td>
<td>885</td>
<td>3,912</td>
</tr>
</tbody>
</table>

- In children, most infections are acquired perinatally

Acute HCV infections have more than quadrupled in the past decade

Rates* of reported cases† of acute hepatitis C virus infection, by age group — United States, 2005–2020

*Rates per 100,000 population.

†Reported confirmed cases. For the case definition, see https://ndc.services.cdc.gov/conditions/hepatitis-c-acute/.

Chronic HCV infections highest among reproductive aged adults

Number of newly reported* chronic hepatitis C virus infection cases† by sex and age — United States, 2020

* During 2020, cases of chronic hepatitis C were either not reportable by law, statute, or regulation; not reported; or otherwise, unavailable to CDC from Arizona, Delaware, District of Columbia, Hawaii, Indiana, Kentucky, Nevada, North Carolina, Rhode Island, and Texas.

† Only confirmed, newly diagnosed, chronic hepatitis C cases are included. For the complete case definition, see https://ndc.services.cdc.gov/conditions/hepatitis-c-chronic/.

Timeline of HCV screening recommendations during pregnancy in the United States, 2018–2021

**March 2020**
U.S. Preventive Services Task Force recommends screening all adults ≥18 and all pregnant persons during each pregnancy.*

**April 2020**
CDC recommends screening all adults ≥18 and all pregnant persons during each pregnancy.*

**May 2021**
American College of Obstetricians and Gynecologists recommends screening all pregnant persons during each pregnancy.

**June 2021**
Society for Maternal-Fetal Medicine recommends screening all pregnant persons during each pregnancy.

2018
American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) recommend universal screening during pregnancy.

*except in settings where the prevalence of HCV infection is <0.1%
HCV testing among pregnant persons before and after 2020 CDC universal screening recommendations

- Hepatitis C antibody testing among pregnant persons increased from 16.6% in 2011 to 40.6% in 2021

Recommended Testing Sequence for Identifying Current Hepatitis C Virus (HCV) Infection

HCV antibody

Nonreactive

No HCV antibody detected

STOP*

Reactive

HCV RNA

Not Detected

No current HCV infection

Additional testing as appropriate†

Detected

Current HCV infection

Link to care

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* For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody is recommended. For persons who are immunocompromised, testing for HCV RNA can be considered.

† To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV antibody assay can be considered. Repeat HCV RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.

Perinatal transmission

- **Large systematic review and meta-analysis of 109 articles**
  - Transmission risk from HCV-antibody positive, RNA positive
    - **5.8%** (95% CI 4.2-7.8%) with no HIV infection
    - **10.5%** (95% CI 7.6-15.2%) with HIV co-infection

- **Statistical reanalysis of data including 1,749 children in 3 prospective cohorts**
  - Corrected for infections that might have cleared before being detected
    - **7.2%** (95% CI 5.6-8.9%) with no HIV infection
    - **12.1%** (95% CI 8.6-16.8%) with HIV co-infection

Assessment of perinatal HCV transmission

- **2–6 months of age: earliest time for HCV RNA test**
  - Single test is diagnostic of perinatal transmission: sensitivity 100% (95% CI 87.5-100%); specificity 100% (95% CI 98.3-100%)\(^1\)
  - Can have false negative and positive results before 2 months of age

- **18 months of age: earliest time for anti-HCV test**
  - Antibody test will detect passively transferred maternal antibody prior to 18 months

- **3 years of age: earliest age for FDA approved DAA treatment**
  - Repeat HCV RNA prior to initiating treatment\(^2\)

2. Source: https://www.hcvguidelines.org/unique-populations/children
Linkage to care and loss to follow up

- For HCV-exposed infants
  - Surveillance data showed that out of 537 exposed infants, 84 (16%) had HCV testing and 4 had confirmed HCV infection¹
    - Additional 23 children expected to have HCV infection were not identified at 20 months of age
  - One retrospective study comparing testing strategies in exposed infants showed that only 30% of infants with a negative HCV RNA at 2 months of age returned for subsequent HCV antibody testing at 18 months of age²

Methods
CDC perinatal HCV guidelines work group

- Discussed research questions
- Conducted systematic reviews
- Assessed the quality of evidence
- Considered literature review, cost-effectiveness analysis, implementation feasibility, public health implications, equitable access to testing
Research question

- **Population:** Infants and children perinatally exposed to HCV
- **Intervention:** Nucleic acid test (NAT) for HCV ribonucleic acid (RNA) during age 2-6 months
- **Comparison:** HCV antibody with reflex* NAT for HCV RNA at age ≥ 18 months
- **Outcomes:** Increased identification of HCV infections, increased linkage to care and treatment, decreased cirrhosis and deaths attributable to HCV infection

*A NAT for HCV RNA performed on specimens that are anti-HCV reactive*
Perinatal HCV testing systematic review

- Examined:
  - HCV infection prevalence among pregnant people and perinatally exposed children
  - Loss to follow up among perinatally exposed children
  - Benefits and harms of testing perinatally exposed children

- Reviewed evidence from 01/01/2001 - 06/08/2021
External review

- **Peer reviewers nominated by:**
  - American Academy of Pediatrics
  - American Association for the Study of Liver Diseases
  - American College of Obstetricians and Gynecologists
  - American Academy of Family Physicians
  - North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

- **Federal Register Notice:**

Cost-effectiveness analysis
De novo cost-effectiveness analysis informed guidelines

- No prior cost-effectiveness studies comparing perinatal HCV testing approaches were identified
- Used economic analysis framework to compare:
  - Current strategy: anti-HCV with reflex NAT for HCV RNA at 18 months
  - Comparison: single NAT for HCV RNA during age 2-6 months
  - Additionally: universal testing strategies for both options
- Outcomes: diagnosed infections, treated or cured infections, hepatocellular carcinoma, liver transplants, liver-related deaths

Hall et al. Cost-effectiveness of strategies to identify children with perinatally acquired HCV infection [under review]
Compared with current practice, testing with NAT for HCV RNA at age 2-6 months was:

- **Effective**
  - Increased number of perinatally exposed infants diagnosed with HCV infection
  - Improved health outcomes

- **Cost-saving**
  - Population level difference in cost of $469,671

Universal testing strategies diagnosed more infections, but has an increased total cost of $38-$129 million

Hall et al. Cost-effectiveness of strategies to identify children with perinatally acquired HCV infection [under review]
Cost-effectiveness analysis findings

- **Sensitivity analysis:**
  - Approximately 45% of persons are screened during pregnancy
  - As this number increases, universal testing of infants and children becomes less cost-effective

- **Conclusions:**
  - Testing known perinatally exposed infants with NAT for HCV RNA at age 2-6 months was the only strategy that was cost-saving and resulted in better health outcomes

Hall et al. Cost-effectiveness of strategies to identify children with perinatally acquired HCV infection [under review]
Systematic review results
TABLE 1. Summary of literature review related to perinatal hepatitis C testing, prevalence, and linkage to care

<table>
<thead>
<tr>
<th>Measure</th>
<th>Median % (range)</th>
<th>No. of studies informing estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pregnant persons</strong>&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion tested for HCV</td>
<td>47.5 (0.7–93.7)</td>
<td>14</td>
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<tr>
<td>Prevalence of reactive anti-HCV or diagnosis</td>
<td>1.0 (0.1–70.8)</td>
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<tr>
<td>Prevalence of detectable HCV RNA&lt;sup&gt;†&lt;/sup&gt;</td>
<td>67.6 (29.6–80.2)</td>
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<td><strong>Perinatally exposed children</strong></td>
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<td></td>
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<tr>
<td>Proportion tested for HCV&lt;sup&gt;§&lt;/sup&gt;</td>
<td>26.5 (8.6–53.1)</td>
<td>11</td>
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<td>Rate of perinatal transmission</td>
<td>4.8 (1.0–11.1)</td>
<td>12</td>
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<tr>
<td>Proportion of children linked to care&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>37.4 (1.9–100)</td>
<td>4</td>
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<td>Proportion of children with CHC who achieved SVR12 after DAA treatment</td>
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**Abbreviations:** Anti-HCV = hepatitis C virus antibody; CHC = chronic hepatitis C; DAA = direct acting antiviral; HCV = hepatitis C virus; RNA = ribonucleic acid; SVR12 = sustained virologic response 12 weeks post-treatment.


<sup>†</sup> HCV RNA positivity among those who are anti-HCV reactive.

<sup>§</sup> Perinatally exposed children tested with an anti-HCV test or NAT for HCV RNA.

<sup>‡</sup> Children exposed to perinatal hepatitis C who were referred to or attended an HCV-related appointment.
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* Children exposed to perinatal hepatitis C who were referred to or attended an HCV-related appointment.
Summary of evidence

- Rates of hepatitis C among reproductive-aged adults have been increasing
- Perinatal HCV transmission occurs in approximately 7% of exposed infants and children
- Systematic review showed only 26.5% of perinatally exposed infants and children are tested for HCV infection
- Many children with chronic infection are lost to follow up
Justification for testing at 2-6 months

- NAT for HCV RNA at 2-6 months is highly sensitive and specific for diagnosing perinatal HCV transmission

- More children attend well visits in the first 6 months of life than at 18 months\(^1,2\)

- Early diagnosis of perinatal HCV transmission at 2-6 months is cost-saving and cost-effective in preventing morbidity and mortality from chronic hepatitis C complications

Proposed recommendation language
Perinatal HCV testing recommendations

- CDC recommends HCV testing for all infants and children born to pregnant persons with confirmed or probable HCV infection
  - Confirmed HCV infection: any HCV RNA detected in pregnancy
  - Probable HCV infection: anti-HCV test reactive in pregnancy in the absence of HCV RNA results
Perinatal HCV testing recommendations (cont.)

- Perinatally exposed infants should receive a NAT for HCV RNA at age 2-6 months to identify children who might go on to develop chronic HCV infection
  - Infants with detectable HCV RNA: refer to health care provider with expertise in pediatric hepatitis C management
  - Infants with undetectable HCV RNA: no further follow-up needed
Other considerations

- Infants and children aged 7-17 months who are perinatally exposed to HCV and have not previously been tested should receive a NAT for HCV RNA

- Children aged ≥ 18 months who are perinatally exposed to HCV and have not previously been tested should receive an anti-HCV test with reflex* to NAT for HCV RNA

*A NAT for HCV RNA performed automatically on specimens that are anti-HCV reactive
### Comparison with recommendations from other organizations

<table>
<thead>
<tr>
<th>Organization</th>
<th>NAT for HCV RNA at age ≥ 2-6 months</th>
<th>Confirm anti-HCV at age ≥ 18 months</th>
<th>Anti-HCV with reflex* NAT for RNA at age ≥ 18 months</th>
<th>Re-test for HCV RNA prior to initiating treatment</th>
<th>Test siblings</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDSA/AASLD (2020)</td>
<td>Consider†</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>AAP (2021)</td>
<td>Consider</td>
<td>Yes</td>
<td>Yes</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>AAFP (2010)</td>
<td>Yes§</td>
<td>---</td>
<td>Yes</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>NASPGHAN (2020)</td>
<td>Consider¶</td>
<td>---</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CDC (proposed)</td>
<td>Yes**</td>
<td>No</td>
<td>If not tested previously</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviations: AAFP = American Association of Family Physicians; AAP = American Academy of Pediatrics; AASLD = American Association for the Study of Liver Diseases; anti-HCV = hepatitis C virus antibody; HCV = hepatitis C virus; HCV RNA = HCV ribonucleic acid; IDSA = Infectious Diseases Society of America; NASPGHAN = North American Society for Pediatric Gastroenterology, Hepatology & Nutrition; NAT = Nucleic Acid Test.

* A NAT for HCV RNA performed on specimens that are anti-HCV reactive; † Consider at age 2–12 months; ‡ AAFP recommendations based on a National Institutes of Health consensus statement (which is now retired). These guidelines recommend NAT for HCV RNA on two separate occasions between age 2–6 months or anti-HCV testing at age ≥15 months; § AAFP recommendations at age 2 months if requested by family; recheck at age 12 months to confirm chronic hepatitis C; ¶ Consider at age 2 months if requested by family; recheck at age 12 months to confirm chronic hepatitis C; **NAT for HCV RNA can be done through age 17 months; at age ≥18 months, recommend anti-HCV testing with reflex to NAT for HCV RNA if not previously tested.
Federal Register Notice

▪ Visit https://www.regulations.gov/docket/CDC-2022-0116/document to view the full document draft and to submit a comment
  – Comment period is open through January 27, 2023

▪ All comments will be considered and responded to by the CDC workgroup
Next steps

- Winter 2022/23: Review and respond to external peer review and FRN comments

- Winter 2023: Supplemental literature review

- Spring 2023: Submit revised guidelines to CDC clearance

- Summer 2023: MMWR publication (tentative)
Acknowledgements

Guideline workgroup and steering committee

- Jessica Brown
- Erin Conners
- Laura Cooley
- Monique Foster
- Noele Nelson
- Karina Rapposelli
- Amy Sandul
- Carolyn Wester

Other CDC Consultation and Support

- DVH policy and communications
- Guidelines and Recommendations Activity
- Strategic Business Initiatives Unit
- MMWR Serials Team

Cost-effectiveness modeling

- Eric Hall
- Monica Trigg
- Taiwo Abimbola
Questions and Answers

- Please add any questions about the FRN process or clarification about the guidelines in the Q&A box below

- Visit [https://www.regulations.gov/docket/CDC-2022-0116/](https://www.regulations.gov/docket/CDC-2022-0116/) to view the full document draft and to submit a comment
  - Comment period is open through 01/27/2023
For more information, contact CDC
1-800-CDC-INFO (232-4636)

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.