Overview of draft CDC recommendations for perinatal hepatitis C testing

Lakshmi Panagiotakopoulos, MD, MPH

Medical Epidemiologist, Prevention Branch

Division of Viral Hepatitis

December 6, 2022

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**

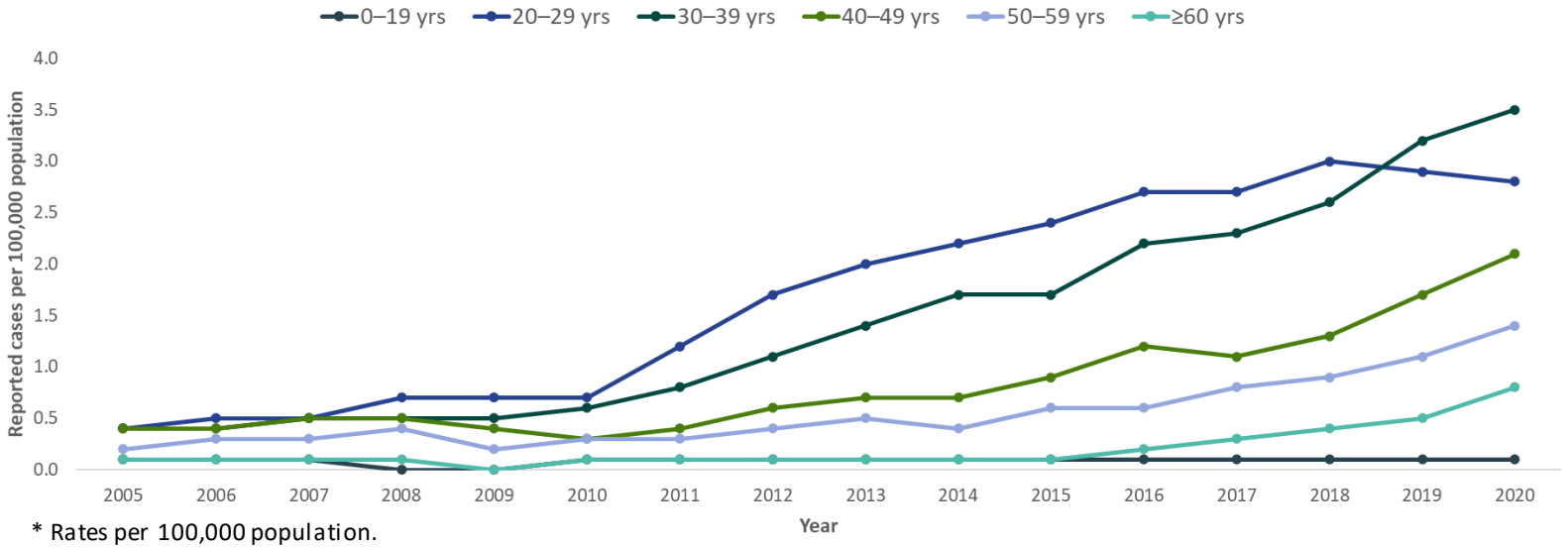
Risk behaviors	Risk identified	No risk identified	Risk data missing
Injection drug use	1,017	523	3,258
Multiple sexual partners	167	352	4,279
Surgery	142	713	3,942
Sexual contact	83	336	4,379
Needlestick	64	706	4,028
Men who have sex with men	44	258	2,803
Household contact (non-sexual)	17	402	4,379
Dialysis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

- **In children, most infections are acquired perinatally**

Source: https://www.cdc.gov/hepatitis/statistics/2020surveillance/index.htm

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



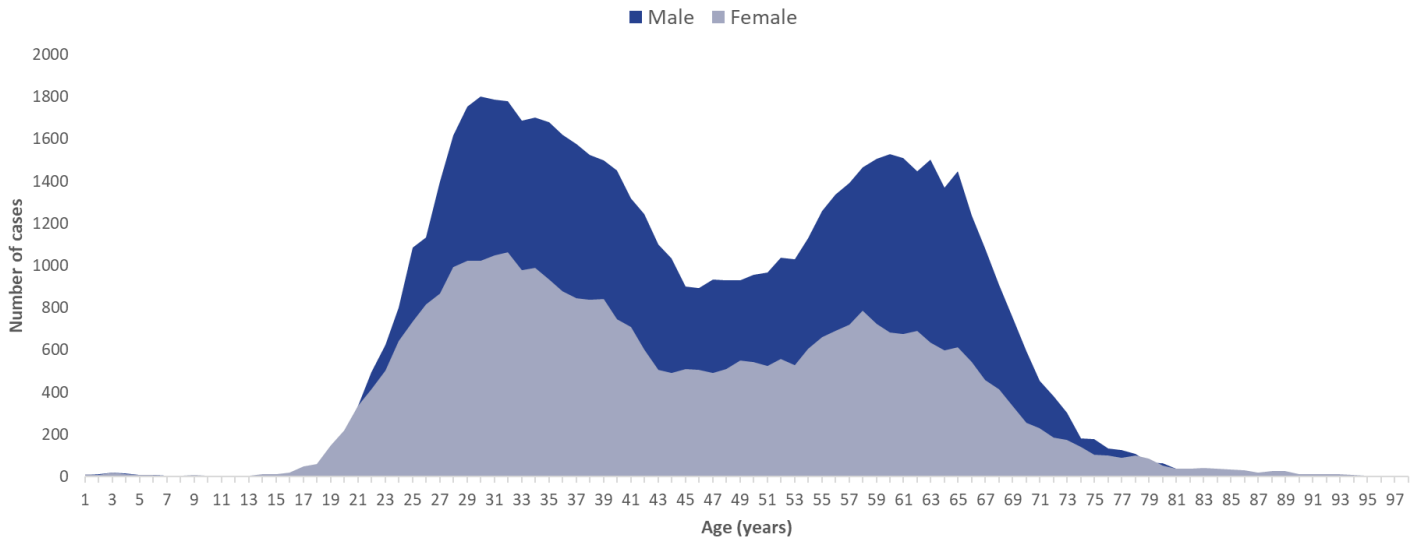
* Rates per 100,000 population.

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

Source: https://www.cdc.gov/hepatitis/statistics/2020surveillance/index.htm

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/.

Source: https://www.cdc.gov/hepatitis/statistics/2020surveillance/index.htm

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

2018

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

March 2020

U.S. Preventive Services Task Force recommends screening all adults aged 18–79, including pregnant adults

April 2020

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

May 2021

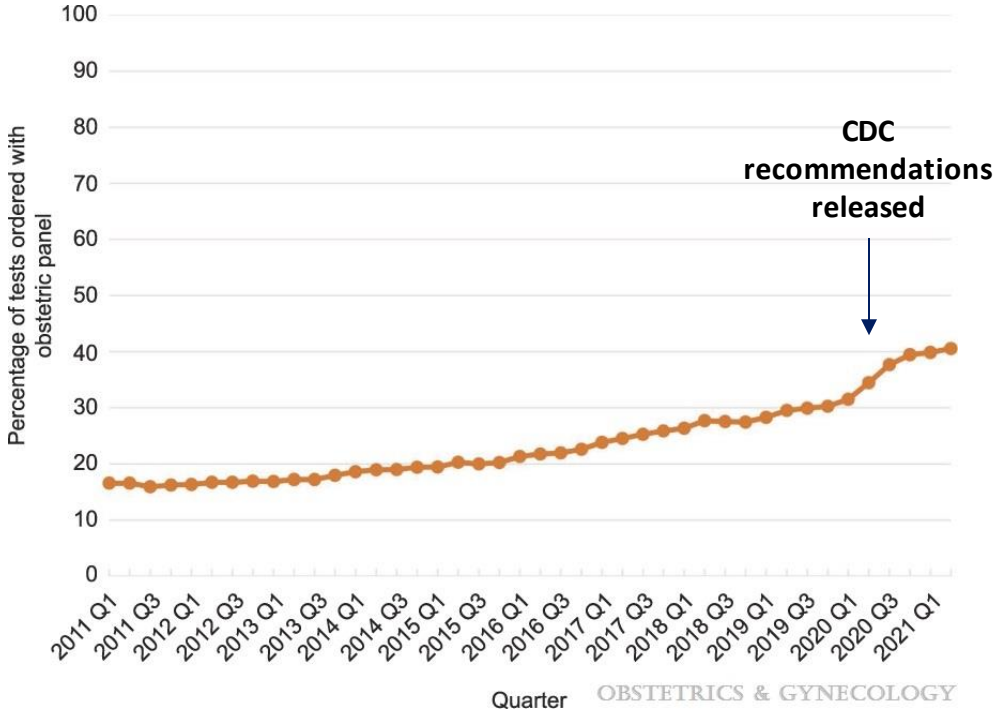
American College of Obstetricians and Gynecologists recommends screening all pregnant persons during each pregnancy

June 2021

Society for Maternal-Fetal Medicine recommends screening all pregnant persons during each pregnancy

*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

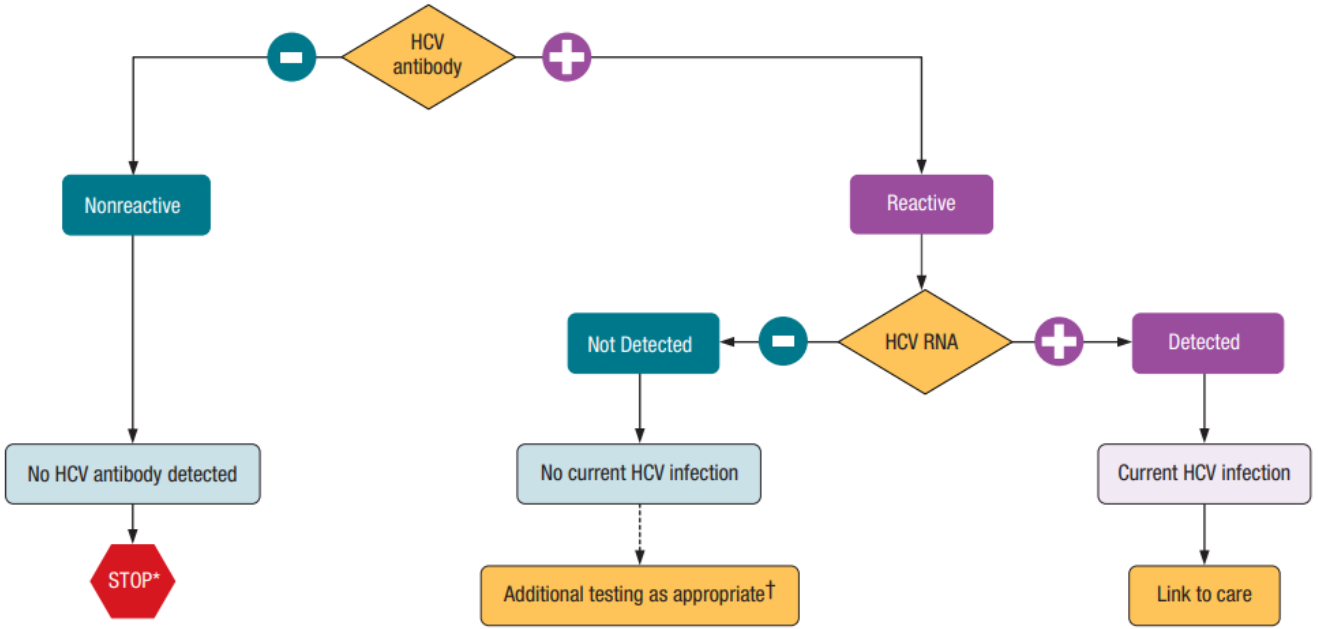


- **Hepatitis C antibody testing among pregnant persons increased from 16.6% in 2011 to 40.6% in 2021**

Kaufman, Harvey W.; Osinubi, Ademola; Meyer, William A. III; Khan, Mohammed; Huang, Xiaohua; Panagiotakopoulos, Lakshmi; Thompson, William W.; Nelson, Noele; Wester, Carolyn. Obstetrics & Gynecology140(1):99-101, July 2022.

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

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention



* 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.

Source: CDC. Testing for HCV infection: An update of guidance for clinicians and laboratorians. MMWR 2013;62(18).

Perinatal transmission

- **Large systematic review and meta-analysis of 109 articles[1]**
  - 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[2]**
  - 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

1. Benova, L., et al., *Vertical transmission of hepatitis C virus: systematic review and meta-analysis.* Clin Infect Dis, 2014. **59**(6): p. 765-73
2. Ades, A.E., et al., Overall vertical transmission of HCV, transmission net of clearance, and timing of transmission. Clin Infect Dis, 2022.

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]

1. Gowda C, Smith S, Crim L, Moyer K, Sánchez PJ, Honegger JR. Nucleic Acid Testing for Diagnosis of Perinatally-Acquired Hepatitis C Virus Infection in Early Infancy. Clin Infect Dis. 2020 Jul 8:ciaa949.
2. Source: https://www.hcvguidelines.org/unique-populations/children

Linkage to care and loss to follow up

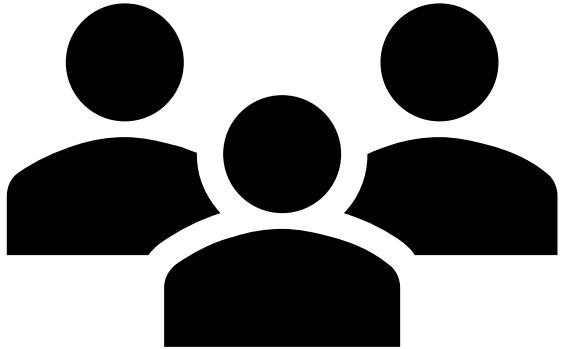
- **For HCV-exposed infants**
  - Surveillance data showed that out of 537 exposed infants, 84 (16%) had HCV testing and 4 had confirmed HCV infection[1]
    - Additional 23 children expected to have HCV infection were not identified at 20 months of age
  - One retrospective study comparing testing strategies 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 age[2]

1. Kuncio DE, Newbern EC, Johnson CC, Viner KM. Failure to Test and Identify Perinatally Infected Children Born to Hepatitis C Virus-Infected Women. Clin Infect Dis. 2016 Apr 15;62(8):980-5
2. Gowda C, Smith S, Crim L, Moyer K, Sánchez PJ, Honegger JR. Nucleic Acid Testing for Diagnosis of Perinatally-Acquired Hepatitis C Virus Infection in Early Infancy. Clin Infect Dis. 2020 Jul 8:ciaa949.

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:**
  - https://www.regulations.gov/docket/CDC-2022-0116/document

Source: https://www.cdc.gov/hepatitis/policy/ISIreview/index.htm

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

Measure	Median % (range)	No. of studies informing estimates
Pregnant persons*		
Proportion tested for HCV	47.5 (0.7–93.7)	14
Prevalence of reactive anti-HCV or diagnosis	1.0 (0.1–70.8)	34
Prevalence of detectable HCV RNA†	67.6 (29.6–80.2)	8
Perinatally exposed children		
Proportion tested for HCV§	26.5 (8.6–53.1)	11
Rate of perinatal transmission	4.8 (1.0–11.1)	12
Proportion of children linked to care¶	37.4 (1.9–100)	4
Proportion of children with CHC who achieved SVR12 after DAA treatment	98.1 (97.1–98.9)	5

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.

* All estimates among pregnant persons include studies reviewed in: Schillie S, Wester C, Osborne M, Wesolowski L, Ryerson AB. CDC recommendations for hepatitis C screening among adults—United States, 2020. MMWR Recomm Rec 2020;69:1–17.

† HCV RNA positivity among those who are anti-HCV reactive.

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

¶ Children exposed to perinatal hepatitis C who were referred to or attended an HCV-related appointment.

TABLE 1. Summary of literature review related to perinatal hepatitis C testing, prevalence, and linkage to care

Measure	Median % (range)	No. of studies informing estimates
Pregnant persons*		
Proportion tested for HCV	47.5 (0.7–93.7)	14
Prevalence of reactive anti-HCV or diagnosis	1.0 (0.1–70.8)	34
Prevalence of detectable HCV RNA†	67.6 (29.6–80.2)	8
Perinatally exposed children		
Proportion tested for HCV§	26.5 (8.6–53.1)	11
Rate of perinatal transmission	4.8 (1.0–11.1)	12
Proportion of children linked to care¶	37.4 (1.9–100)	4
Proportion of children with CHC who achieved SVR12 after DAA treatment	98.1 (97.1–98.9)	5

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.

* All estimates among pregnant persons include studies reviewed in: Schillie S, Wester C, Osborne M, Wesolowski L, Ryerson AB. CDC recommendations for hepatitis C screening among adults—United States, 2020. MMWR Recomm Rec 2020;69:1–17.

† HCV RNA positivity among those who are anti-HCV reactive.

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

¶ 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**

1. Goyal, N.K., et al., Well-Child Care Adherence After Intrauterine Opioid Exposure. Pediatrics, 2020. 145(2).
2. Towers, C.V. and K.B. Fortner, *Infant follow-up postdelivery from a hepatitis C viral load positive mother.* J Matern Fetal Neonatal Med, 2019. **32**(19): p. 3303-3305.

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

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

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; ¶ 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**

NR NONRULEMAKING DOCKET

CDC Recommendations for Hepatitis C Testing Among Perinatally Exposed Infants and Children

Created by the **Centers for Disease Control and Prevention**

Share | Subscribe

Docket Details | Browse Documents 3

REFINE RESULTS

Only show documents open for comment (1)

Document Type

- Supporting & Related Material (2)
- Notice (1)

Posted

- Last 7 Days (3)
- Last 15 Days (3)
- Last 30 Days (3)
- Last 90 Days (3)
- Custom Dates

Comments Due

- Next 90 Days (1)
- Custom Dates

SEARCH RESULTS

SORT BY Comments Due (Newer-Older)

Search

NOTICE

Notice - CDC Recommendations for Hepatitis C Testing Among Perinatally Exposed Infants and Children

Agency Centers for Disease Control and Prevention | **Posted** Nov 22, 2022 | **ID** CDC-2022-0116-0001

Comment

Comments Due Jan 27, 2023

SUPPORTING & RELATED MATERIAL

Draft Guidelines_CDC Recommendations for Hepatitis C Testing Among Perinatally Exposed Infants and Children

Agency Centers for Disease Control and Prevention | **Posted** Nov 22, 2022 | **ID** CDC-2022-0116-0002

SUPPORTING & RELATED MATERIAL

Appendix and Supplementary Tables_CDC Recommendations for Hepatitis C Testing Among Perinatally Exposed Infants and Children

Agency Centers for Disease Control and Prevention | **Posted** Nov 22, 2022 | **ID** CDC-2022-0116-0003

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/ 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)
TTY: 1-888-232-6348 www.cdc.gov