CDC Recommendations for Hepatitis C Testing Among Perinatally Exposed Infants and Children — United States, 2023

SUPPLEMENTARY APPENDIX

Supplementary appendix 1: Recommendation development staff and conflicts of interest

Steering Committee

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No CDC staff were deemed to have a conflict of interest.

External Peer reviewers

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Supplementary appendix 2: Peer review comments and responses

A summary of substantive peer reviewer comments is presented below, by recommendation section. While individual comments are not attributed to specific reviewers, all peer reviewers are listed in the main document and acknowledged for their contributions. Minor editorial comments may not be reflected, and correction of typos and other clarifying edits may have been made.

Methodology

- All reviewers stated the report included all relevant studies and was complete, agreed with the methodology, believed the report correctly summarized the available evidence and that the report clearly identified and characterized scientific uncertainties and limitations.
- Five reviewers offered suggestions regarding how the findings of the report could be made clearer (*see comments below).*

Recommendations

- Five reviewers believed CDC came to the right conclusions based on the evidence presented.
- One reviewer believed that CDC came to the right conclusion in some ways, but not in others (*see comments below)*.

What can be done to make the recommendations clearer?

- Three reviewers offered suggestions for making the recommendations statement clearer *(see comments below).*

Potential impact and implementation

- Three reviewers believed the implementation of the recommendations would reduce the burden of hepatitis C among perinatally exposed infants and children in the United States.
- Two reviewers were unsure if the recommendations would result in a reduction of the burden of hepatitis C among perinatally exposed infants and children in the United States.
- One reviewer did not believe the recommendations would reduce the burden of hepatitis C among perinatally exposed infants and children in the United States (*see comments below).*

Specific comments, by section of the recommendation

Introduction

- [Reviewer 1] Recommended providing a range for perinatal HCV transmission around 7%.
    - Estimates from the two referenced studies were added to the introduction and 7% was changed to 6-7% in the summary to indicate the range.
- [Reviewer 1] recommended providing a range of HCV-exposed infants who are not tested for chronic HCV infection after birth.
    - The range was not provided in the introduction since the studies are heterogenous and were more closely examined in the summary of the literature.

Background

- [Reviewer 1] recommended moving the supplementary background material into the main document.
    - This information is now included in the main document.

HCV description and transmission

- [Reviewer 1 and reviewer 3] emphasized that perinatal HCV transmission among persons co-infected with HIV and HCV is specifically higher among those with poorly controlled HIV and recommended adding references to this section.
    - The work group agreed with the comment and added additional detail and references. Additionally, higher transmission rates among those with HCV/HIV co-infection and poorly controlled HIV infection were specified.

Methods

- [Reviewer 1] questioned how this document would evaluate cirrhosis and death in exposed infants.
    - There are limited data on long term outcomes in children with perinatal hepatitis C; these data are summarized in the section titled "clinical features and natural history of perinatally acquired HCV infection". Much of these data are descriptive. However, it is known that earlier diagnosis of perinatal hepatitis C and curative treatment before development of complications will decrease morbidity and mortality related to chronic hepatitis C. Undiagnosed and subsequently untreated chronic hepatitis C can lead to cirrhosis, liver transplant, and death related to complications of chronic hepatitis C.
- [Reviewer 6] requested acknowledgements of potential sources of data/studies from regions where hepatitis C is endemic, such as Egypt.
    - Since these recommendations will apply to populations within the United States, the evidence used in developing the recommendations, including the prevalence and testing rates for hepatitis C in pregnancy and among perinatally exposed infants and children, were primarily from the United States. International studies are included in the background and when evaluating the harms of perinatal HCV testing.

Summary of the literature

- [Reviewer 1 and reviewer 2] questioned the range of 0.1-70.8% anti-HCV reactive among pregnant persons. Reviewer 1 suggested adding interquartile ranges and reviewer 2 suggested a footnote or description of where providers can access state or county prevalence information.
    - These numbers were taken directly from the referenced CDC recommendations and vary significantly based on the population tested as evident in the supplementary tables. Interquartile ranges were added to all estimates in Table 1 and a link to the viral hepatitis surveillance report with detailed epidemiologic information was added to the background.

Table 1

- [Reviewer 1] recommended adding a column for the number of subjects available for analysis of each outcome. The reviewer also pointed out the ranges for the medians are very broad and suggested an interquartile range (IQR) may be more helpful. The reviewer also questioned if all the studies were done in the United States.
    - More details on the included studies, including the total number of subjects is available in the supplementary tables. IQRs were added to table 1. As stated in the methods, the literature review only included articles with US data. This has been clarified in the title of Table 1.
- [Reviewer 1] questioned how the authors distinguished between false positive HCV tests and spontaneous clearance of perinatal HCV.
    - This can be distinguished based on the timing of the tests and sequential results. However, this information was not always available.

Cost-effectiveness Considerations

- [Reviewer 1] requested the addition of Incremental Cost-Effectiveness Ratio when describing the cost effectiveness study.
    - ICERs from the study were added.

Recommendations

- [Reviewer 2] recommended additions to the recommendation statement. “It may be worth stating somewhere in the document that if the clinical picture changes or there are signs or laboratory findings consistent with hepatitis C later in childhood, it is reasonable to retest, as very rare false negative tests are possible, as is postnatal acquisition of disease through other means.”
    - This statement was added in the patient follow up section of the recommendations.

- [Reviewer 2] suggested modifying the language of the recommendations from, "although there was perinatal hepatitis C transmission" to "although there was likely perinatal hepatitis C transmission" to account for the possibility of persistent presence of maternal antibody.
    - Language of the recommendation was edited as suggested.
- [Reviewer 1] raised concerns about referring children to pediatric specialists, especially given lack of access in rural communities. "Shouldn't general pediatricians and primary care providers be included as potential treating providers?"
    - The recommendations are not limited to pediatric specialists. For clarification, wording has been changed to, "managed in consultation with a health care provider with expertise in pediatric hepatitis C management."
- [Reviewer 1] expressed hope that "we can develop tests that would reliably detect potential infants with chronic HCV infection at birth before discharge from the hospital. For example, infants at high risk for perinatal HIV are screened with HIV DNA tests. I believe testing before hospital discharge may be the most reliable way of identifying infants at risk for chronic HCV given the low rate of testing in the first 18 months of life."

    - Advancement in infant testing is needed to optimally implement the recommendations. Testing for HCV RNA at birth, however, can lead to false positive and false negative results and would not reliably capture children who go on to develop chronic hepatitis C (Mast EE, 2005, Risk factors for perinatal transmission of hepatitis C virus [HCV] and the natural history of HCV infection acquired in infancy).
- [Reviewer 4] was concerned that there was not enough evidence that changing recommendations would impact liver outcomes and that recommendations should not be different than what liver societies currently recommend.
    - Earlier diagnosis with effective HCV RNA testing will lead to parents and guardians of perinatally infected children becoming aware of the diagnosis earlier. This will increase the likelihood that care will be established so that treatment can be initiated at age 3 years, prior to the development of liver complications. Many jurisdictions and institutions are already starting to test earlier due to the loss to follow up that occurs by age 18 months. As the evidence on earlier testing is just starting to emerge, the hope is that other pediatric and adult liver and infectious disease societies will align in their recommendations.
- [Reviewer 5] questioned whether a positive antibody and negative HCV NAT after 18 months of age represented persistent maternal antibody or cleared infection.
    - After 18 months of age, the two scenarios would be indistinguishable without having earlier RNA testing to document transmission with cleared infection. The persistence of maternal antibody after 18 months of age is <2% (Mast EE, 2005, Risk factors for perinatal transmission of hepatitis C virus [HCV] and the natural history of HCV infection acquired in infancy), therefore, this scenario is less

common than a spontaneously cleared infection. The wording of the statement was edited for accuracy and clarity.

- [Reviewer 1] expressed concerned that the document does not address strategies to improve medical engagement in postpartum people with chronic HCV infection who often have significant factors such as maternal substance abuse, relative poverty, and lack of access to care in rural communities that results in loss to care.
    - There are many barriers to hepatitis C care for both postpartum patients and their infants beyond the timing and type of test recommended. However, the goal of these recommendations is to increase testing of exposed infants among primary care providers by optimizing the timing and type of testing recommended. Infants and children who are HCV RNA positive should be managed in consultation with a health care provider with expertise in pediatric hepatitis C management, which is not limited to a specialist or physician. While these recommendations will not capture infants who never present for well-child visits, it is expected to increase the number of infants with perinatal HCV transmission who are identified early on. Medical engagement in postpartum care is critical, but outside the scope of these recommendations.
- [Reviewer 3] recommended mentioning changes in NAT assays due to substantial difference in performance characteristics between prior PCR assays and current real-time PCR methods, which impact confidence in negative tests.
    - Added information about older, less sensitive tests in many studies characterizing intermittent viremia and current test performance.
- [Reviewer 5] expressed concerns about building confidence in recommendations for a single test when other guidelines recommend multiple tests.
    - This is a new recommendation based on the higher performance of newer NAT for HCV RNA tests and data supporting its use in perinatally exposed children. The included supporting evidence has been expanded for clarity, and the recommendation statement has been updated to clarify situations in which a provider may consider additional testing.
- [Reviewer 1 and reviewer 5] recommended continued surveillance and monitoring of perinatal HCV infection to monitor loss to follow up and more accurately identify barriers to screening, diagnosis, and treatment of children with perinatal HCV infection.
    - The work group agreed there is a need for more data on earlier HCV RNA testing. Much of the data included in the recommendations are from smaller studies and extrapolated from well-child visit attendance in the general population and in the population of children born to persons who use opiates. Ongoing surveillance is critical. State and local health departments and individual institutions that have recommended earlier testing are expected to publish data on success rates. CDC plans to continue surveillance through systems such as Surveillance for Emerging Threats to Mothers and Babies Network (SET-NET), which funds jurisdictions to monitor perinatal infections, including hepatitis C. The future directions section has been updated to indicate the importance of evaluating whether an earlier diagnosis leads to higher treatment and cure rates.

Clinical considerations

- [Reviewer 2] recommended consistently recommending HCV RNA testing for children with unknown exposure status.
    - HCV RNA testing among children with unknown exposure status has been added to the clinical considerations section.
- [Reviewer 2 and reviewer 5] recommended more clarification on children of mothers with unknown status, including removing risk factor requirement.
    - Risk factors have been removed from the statement, and testing has been recommended at age 2-6 months with HCV RNA for all infants born to pregnant persons with unknown HCV status who cannot subsequently be tested.

Future directions

- [Reviewer 3] suggested adding "If DAA treatments are approved for pregnant persons and widely used, the resulting clearance of maternal viremia during pregnancy will likely lead to fewer children becoming infected. This could obviate the need for follow-up testing."
    - This wording was added, however, the last sentence was not included as any infant born to a pregnant person with a positive HCV RNA during pregnancy would be recommended for testing, even if treatment was administered during pregnancy.

General comments

- [Reviewer 3] suggested working with industry partners to find assays for use in young children, including those that are more amendable to small volume samples (i.e., heelsticks or fingersticks).
    - The work group agreed this would be important to advance implementation of the recommendations.
- [Reviewer 4] acknowledged the dependance of these recommendations on testing during pregnancy and the importance of collaboration with obstetricians and pediatricians in following these recommendations.
    - Testing of pregnant persons and communication between obstetric and pediatric providers is critical in identifying perinatally exposed children. This will be emphasized in implementation of the recommendations.
- [Reviewer 5] recommended addressing immigrant, and internationally adopted children.
    - Specific recommendations for screening internationally adopted children are available in the CDC yellow book: https://wwwnc.cdc.gov/travel/yellowbook/2020/family-travel/international-adoption. In the systematic review of the literature, there was no specific evidence for this population, however, the current CDC recommendations would apply: all adults ≥18 and all pregnant persons should be screened as recommended in the

2020 CDC recommendations: https://www.cdc.gov/mmwr/volumes/69/rr/rr6902a1.htm.

- Furthermore, these current perinatal hepatitis C testing recommendations state that all children born to persons with unknown hepatitis C status whose birth parent cannot be tested would benefit from being tested as well.

- [Reviewer 6] requested a table displaying the PPV and NPV of HCV RNA testing at 2-6 months of age.
  - The information from this single study was not added to a specific table, however, the PPV and NPV of HCV RNA testing at age 2-6 months is available in the text under "diagnosis of HCV infection among pregnant persons and perinatally infected children" and in the referenced article by Gowda et al.

Supplementary Appendix 3: Public comments and responses

During November 22, 2022-Jan 27, 2023, opportunity for reaction and feedback to the draft recommendation was provided through a public comment period and an informational webinar open to the public. CDC received a total of 22 public comments on the draft document from the general public, providers, advocacy groups, industry, medical professional associations, think-tanks and a public health department. Comment themes and CDC responses are summarized below. Some comments echo themes from the peer review and are provided in the public comments section as well for completeness.

HCV RNA testing at age 2-6 months: CDC received 12 comments fully supporting testing infants of exposed pregnant persons with NAT for HCV RNA at age 2-6 months. Two comments were critical of the approach and recommended keeping the current recommendation of anti-HCV testing at age ≥18 months, suggesting approaches of using the same health care provider to prevent loss to follow up and limiting earlier testing to those in whom there is a concern for loss to follow up. One comment was against any testing of perinatally exposed infants and children below age 3 years due to the lack of approved treatment.

- Current testing approaches including the recommendation for anti-HCV testing for all perinatally exposed children at age ≥18 months have been shown throughout the recommendations document to be poorly implemented with the majority of exposed children being lost to follow up. Earlier HCV RNA testing for infants at risk for loss to follow up currently exist in the majority of testing recommendations, however, testing rates remain low. Furthermore, as perinatally exposed infants may be separated from their birth families or have multiple barriers to accessing a single health care provider early in life, recommending the use of the same healthcare provider would be expected to have a minimal impact on testing rates of exposed infants.

Children born to pregnant persons with unknown HCV status: CDC received 5 comments regarding the recommendation to test infants born to pregnant persons with unknown HCV status during pregnancy. Two comments suggested a stronger recommendation for infants born to pregnant persons with unknown HCV status in pregnancy. One comment indicated that children in foster care with no maternal risk factors can be screened on a case-to-case basis. Another comment stated all infants with an unknown HCV exposure status should be tested at age 2-6 months, without a requirement for risk factor assessment in the birth parent. The fifth comment encouraged stronger language for testing the birthing parent prior to delivery hospital discharge if status during pregnancy was unknown, but to recommend testing the infant if birth parent testing is incomplete.

- Clinical considerations for children born to pregnant persons with unknown HCV exposure during pregnancy has been updated to recommend: "children whose birth parent's hepatitis C status is unknown… would also benefit from being tested starting at age 2 months with a NAT for HCV RNA or at age ≥18 months with an anti-HCV test with reflex to NAT for HCV RNA."

Testing during pregnancy: CDC received 4 comments requesting more clarification on testing for HCV infection in pregnancy and management of infants. Three of these comments requested clarification on how to manage an exposed infant born to a pregnant person with one positive and one negative test during pregnancy (e.g., pregnant person treated during pregnancy with subsequent viral clearance) or in situations of an acute infection during pregnancy in which the pregnant person was initially HCV RNA negative and then infected without being retested around the time of delivery. One comment requested more guidance on linkage to care of pregnant persons with HCV infection in the postpartum period.

- Language in the recommendation has been updated to clarify that a confirmed infection during pregnancy is considered any detectable HCV RNA at any time during pregnancy, regardless of subsequent clearance, in the recommendation statement and footnote. Language has also been added to the clinical considerations section about testing infants in cases where acute infections acquired during pregnancy are suspected and the birth parent cannot be retested. Linkage to care of pregnant persons in the postpartum period is outside the scope of these recommendations.

Follow up after a positive test: CDC received 4 comments related to infant follow up after a positive NAT for HCV RNA at age 2-6 months. One comment was fully supportive of the recommendation to refer infants to a provider with expertise in management of pediatric HCV infection. Two of these comments encouraged stronger language allowing all providers with expertise treating hepatitis C in children, including primary care providers and mid-level providers, to manage these children, especially in rural areas where subspecialty care may be lacking. One of the comments recommended measures to keep infants with positive tests engaged in care until they can be treated, including with yearly NAT for HCV RNA for monitoring. One of the comments encouraged arranging follow up for exposed children prior to discharge from the birth hospitalization.

- The work group agreed all providers can manage children with hepatitis C, including in rural areas in which sub-specialty care may not be accessible. Wording on follow up after a positive HCV RNA test has been updated to recommend management in consultation with a provider with expertise in pediatric hepatitis C management.

Follow up after a negative test: CDC received 4 comments with concerns about a lack of follow up HCV testing following a negative NAT for HCV RNA at age 2-6 months due to the possibility of intermittent viremia or a false negative test. One comment acknowledged these would be very rare situations and suggested additional language "clarifying that if there are signs or laboratory findings consistent with hepatitis C later in childhood, it is reasonable to retest, as very rare false negative tests are possible, as is postnatal acquisition of disease through other means."

- The work group reviewed the evidence on currently used HCV RNA tests noting that studies describing intermittent viremia were conducted using HCV RNA tests that were less sensitive. The work group concluded the evidence supports the use of a single HCV

RNA test to rule out perinatal HCV transmission at age 2-6 months, and updated the wording of the recommendations to allow for additional follow-up "if clinical symptoms, signs, or laboratory findings consistent with hepatitis C appear later in childhood because rare false-negative test results and postnatal acquisition of HCV infection through other means are possible."

Testing siblings of infants perinatally infected with HCV: CDC received 3 comments suggesting a stronger recommendation to test siblings of perinatally exposed infants (i.e., all siblings of exposed infants to be tested with recommendations consistent with main recommendations). Two of the comments also suggested clearer language around the recommendation for siblings.

- Language on testing siblings of exposed infants and children has been updated and is consistent with the main recommendations.

Stigma and harms of HCV testing: CDC received 3 comments expressing concerns about stigma related to diagnosis of perinatal HCV infection and other harms of testing. These comments included concerns about early diagnosis in the context of spontaneous clearance, potential investigations into parental drug use and the child welfare system and labeling and discrimination at school. Potential solutions presented included repeating HCV RNA testing to monitor for clearance, conducting parental interviews related to stigma and reluctance to seek care, and educating providers and parents about the implications of a positive test.

- The work group agreed on the importance of addressing stigma associated with a diagnosis of hepatitis C and implications for children and has included this information in future directions. The patient follow-up section recommends confirming chronic infection prior to treatment initiation: "To confirm chronic hepatitis C, children who test positive [at or after age 2 months] should be retested with a NAT for HCV RNA before beginning treatment, which can be started as early as age 3 years." While recommendations to routinely repeat HCV RNA testing to monitor for clearance is outside the scope of this recommendation (i.e., clinical management), it is described in AASLD-IDSA guidelines: https://www.hcvguidelines.org/unique-populations/children.

Abstract and background: CDC received 3 comments specifically related to the abstract and background sections of the recommendations. One comment requested additional information on gaps in knowledge regarding perinatal HCV transmission (including the spectrum of illness of HCV, extrahepatic manifestations and their impact on perinatal transmission, timing of perinatal transmission, and the impact of "transient infections" on long term outcomes in children). Another commenter requested defining reflex testing in the abstract due to its public health importance and adding denominators to the commercial laboratory study presented.

- Definition of reflex testing was added to the abstract and background. Further information on gaps in knowledge were not added to the background as the recommendations document is not intended to be all-encompassing. Denominator data for the commercial laboratory study was added where available.

Implementation of testing: CDC received 2 comments regarding implementation of testing. One comment from industry expressed concerns about the lack of US approved standalone HCV RNA diagnostic tests, and that current recommendations would be for off-label use in perinatally exposed infants. This commenter suggested establishing partnerships to overcome this barrier. One comment suggested CDC work with companies to lower the cost of HCV RNA tests and to evaluate the safety and efficacy of treatment below 3 years of age.

- The work group is aware of this barrier and will continue having discussions with industry and regulatory agencies to facilitate implementation of infant testing. Evaluation of the safety and efficacy of treatment in children younger than age 3 years is outside the scope of these recommendations.

Retesting prior to treatment: CDC received 2 comments requesting clarification that children with perinatal HCV infection be retested at age 3 years when they become eligible for curative antiviral therapy.

- This was added to the patient follow-up section.

Breastfeeding: CDC received 2 comments regarding language related to breastfeeding infants perinatally exposed to HCV. In one comment, a suggestion was made to add information to the figure encouraging providers to counsel postpartum persons regarding the risk of breastfeeding with cracked or bleeding nipples. Another comment recommended including information on the safety of breastfeeding in communication materials.

- Considerations for retesting infants with undetectable HCV RNA at or after 2 months of age now mentions postnatal acquisition of disease. Information on communication materials related to breastfeeding has been added to future directions.

Communication materials: CDC received 2 comments with suggestions for communication materials and resources. These included information about financial reimbursement, a directory of providers who specialize in treating hepatitis C in children, and guidance on informed consent and related counseling.

- These items will be considered when planning communications following release of the recommendations and were added to the future directions section of the document.

Gendered terminology: CDC received one comment expressing concerns about gendered terminology in the document and suggested the use of "birthing parent" rather than "birth mother."

- Mother has been changed to birth parent.

Future directions: CDC received one comment on the importance of increasing funding to jurisdictions to support existing hepatitis infrastructure, increased collaboration with providers, parents and or caregivers, social services, harm reduction agencies, and increased action towards reducing inequalities.

- The work group agreed and has included this information in future directions.

Treatment of family members: CDC received one comment suggesting additional anticipatory guidance encouraging family members of exposed infants to be treated to prevent future household transmission.

- Anticipatory guidance for family members is outside the scope of the CDC testing recommendations.

Wording of recommendation statement: CDC received one comment with suggestions for wording of the main recommendation statement. This comment emphasized consistency in language and questioned why exposed children aged ≥18 months are recommended for an anti-HCV test with reflex NAT for HCV RNA rather than a NAT for HCV RNA (without anti-HCV testing).

- HCV RNA tests are more expensive than anti-HCV tests. The cost-effectiveness benefit of testing at age 2-6 months with a NAT for HCV RNA relates to the significant loss to follow up that occurs when testing is postponed to age 18 months. Using a more expensive test (i.e., HCV RNA) at age 18 months would be associated with excess cost, without the benefit of testing more exposed children and preventing long term outcomes associated with morbidity and mortality related to undiagnosed hepatitis C. By 18 months, ≥98% of infants have lost maternal antibody (Mast et al, 2005) and children with a negative antibody test will not require reflex NAT for HCV RNA testing.

Presentation of data: CDC received one comment on the presentation of data from the literature review. Due to the wide variety of estimates in heterogenous studies, a suggestion was made to include information on where providers can access state or county level information about HCV infection prevalence.

- This information has been added, along with interquartile ranges to further characterize the range of estimates.