Hepatitis C Screening Guideline Development Group
Background to recommendation 2: Children born to women who are HCV positive

The purpose of this document is to provide the background information to the formulation of recommendations by the Guideline Development Group (GDG).

Not all evidence in this document is presented in the National Clinical Guideline.

The National Clinical Guideline is available from: http://health.gov.ie/national-patient-safetyoffice/ncec/national-clinical-guidelines/

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Contents

History of development of the recommendation

Date	Process	Outcome
02/06/2015	Recommendations from quality appraised national and international guidelines reviewed	Agreed to adopt/adapt evidence from existing guidelines
14/12/2016	GDG subgroup meeting to undertake considered judgement process	Formulation of recommendation
January 2017	Consultation with the Rainbow Clinic	
24/01/2017	Review of subgroup recommendation by GDG	Agreed to adopt Rainbow Clinic recommendation
25/04/2017	Consultation feedback reviewed by GDG	No changes to recommendations
June – July 2017	Editing	Recommendation reworded in final editing process

Considered judgement process

The considered judgment form completed by the GDG subgroup in formulating the recommendations is presented below. Please note the final wording of the recommendation may have changed after review of the GDG, after the consultation process, or during the editing process.

Date of meeting: 14/12/2016
Attendees: ER, PF, LT, CDG, OC, JL, SD
Not in attendance but reviewed evidence and provided commentary: RD

Table 1: Considered judgement form

1. What is the question being addressed?
Q2. Who should be offered screening for Hepatitis C? c. Should the following contacts of known cases of hepatitis C be screened? iii. **Children born to HCV infected mothers**
2. What evidence is being considered to address this question and why? (This section will explain the approach taken to address this question and what GDG members are being asked to consider)
Relevant guidelines – quality appraised (section 3) Additional literature relevant to the Irish context (section 5)
3. What is the body of evidence? Source of evidence: (tick all that apply) ✓ Guidelines Primary literature □ Other □ ; specify: _____
Irish Guidelines **Rainbow clinic practice guide, Dublin, 2015.** Testing infants born to infected women permits early identification and linkage to medical services for infected children and reassurance to parents in the event that infection is excluded. Overall, HCV will be transmitted to 3–7% of infants born to mothers who are HCV antibody positive. Reported maternal risk factors for HCV vertical transmission include active hepatitis C infection, higher hepatitis C viral loads, elevated maternal serum transaminases and HIV co-infection. The highest transmission rates are found in women who are co-infected with HIV with rates as high as 20% reported from co infected women in the pre HAART era. Twenty percent of infants infected through vertical transmission clear HCV infection spontaneously, usually by 5-6 years of age. Follow up of HCV Exposed Infants: 1. If mother is both HCV Ab and PCR positive test baby at 6 weeks and 6 months for HCV Ab and PCR and test at 18 months for Ab, 2. If mother is HCV Ab positive but PCR negative test baby at 18 months for HCV Ab and PCR, 3. Infants who are HCV PCR positive at any time or who are HCV antibody positive at or after 18 months of age should be referred to the Rainbow clinic. (Preventing perinatal transmission: a practical guide to the antenatal and perinatal management of HIV, hepatitis B, hepatitis C, herpes simplex and syphilis (1)) **Current International Hepatitis C Guidelines**

WHO, 2016 Children born to mothers infected with HCV should be offered screening. The risk of vertical (mother-to-child) transmission is approximately 4-8% and is substantially higher in infants born to HIV-infected mothers (10.8–25%). (World Health Organization, Guidelines for the screening, care and treatment of persons with hepatitis C infection (2)). *HIQA Quality Score of 148*

NICE, 2013 Primary care practitioners should promote the importance of hepatitis C testing for children who may have been exposed to hepatitis C at birth or during childhood. Babies born to mothers infected with hepatitis C should be tested for HCV. (The National Institute for Health and Care Excellence, Hepatitis B and C: Ways to Promote and Offer Testing to People at Increased Risk of Infection (3)). *HIQA Quality Score of 148*

AASLD, 2016 Children born to HCV-infected women should be offered screening for HCV. (American Association for the Study of Liver Diseases, Recommendations for Testing, Managing, and Treating Hepatitis C (4)). *HIQA Quality Score of 134.5*

SIGN, 2013 Children whose mother is known to be infected with HCV should be offered screening for HCV. Infants born to women who are HCV positive and HCV RNA negative do not need to be tested. The aim of testing infants born to women with hepatitis C is not primarily to identify all children to whom the virus has been transmitted, but to identify those at risk of persistent infection and its long term consequences. Infants born to women who are HCV antibody positive will test positive for HCV antibody at birth. Infants who are not infected become negative for HCV antibody between six and 20 months of age. Around 80% will be negative by 12 months of age. Positive results for viral RNA by NAT may be obtained in the early months of life in children who subsequently become negative and lose HCV antibody. Some infected infants may not become HCV RNA positive until 12 months of age or older. One study indicates that the sensitivity of a positive reverse transcriptase polymerase chain reaction (RT PCR) result obtained on two occasions between two and six months of life in predicting infection is 81% (95% CI: 58 - 97%). Infants of mothers with HIV co-infection who are consistently positive for viral RNA may have negative HCV antibody tests between 12 and 18 months of age. In children born to women infected with HCV, an HCV antibody test should be performed at 12 months of age or older to identify the minority of children who are infected. In children whose mothers are co-infected with HIV, and in infants found to be HCV antibody positive after 12 months, an HCV RNA test should be performed, and if positive, confirmed on a second sample. If information regarding the risk of HCV infection in an individual child is required before 12 months of age, an HCV RNA test and retest can be performed after two months of age. Further testing is still required to make a definitive diagnosis. (Scottish Intercollegiate Guidelines Network, Management of Hepatitis C A National Clinical Guideline (5)). HIQA Quality Score of 127.7

US Preventive Services Taskforce, 2013 Screen for hepatitis C virus infection: persons at high risk of infection, and adults born between 1945-1965. The most important risk factor for HCV infection is past or current injection drug use. Additional risk factors include..... being born to an HCV infected mother. (United States Preventive Services Taskforce, Screening for Hepatitis C Virus Infection in Adults (6)). *HIQA Quality Score of 117*

KASL, 2014 Screening should be offered for children born to mothers infected with HCV. (The Korean Association for the Study of the Liver, KASL Clinical Practice Guidelines: Management of Hepatitis C (7)). *HIQA Quality Score of 111*

CDC, 2015- **webpage** Persons for whom HCV testing is recommended-children born to HCV positive women. (Viral hepatitis - hepatitis C information [Internet](8)).

CDC, 1998 Children born to HCV-positive women should be tested routinely for HCV-infection based on a recognized exposure. (Centers for Disease Control and Prevention, Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection and HCV-Related Chronic Disease (9)). *HIQA Quality Score of 98*

BASHH, 2015 (update of 2008 guideline) Arrange screening for hepatitis C of children who have been born to HCV+ women if the child was not tested previously
(1A)Test children born to viraemic women. (British Association for Sexual Health and HIV, United Kingdom National Guideline on the Management of the Viral Hepatitides A, B & C 2015 (10)) *HIQA Quality Score of 97*

SASLT, 2012 Children born to HCV-infected mothers offered screening. (Saudi Association for the Study of Liver diseases and Transplantation, SASLT Practice Guidelines: Management of Hepatitis C Virus Infection (11)). *HIQA Quality Score of 95.3*

North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) 2012 HCV screening is recommended for Children born to HCV-infected mothers. In the setting of known vertical transmission, siblings should be screened for vertical transmission of HCV infection as well. (North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, NASPGHAN Practice Guidelines: Diagnosis and Management of Hepatitis C Infection in Infants, Children, and Adolescents (12)). *HIQA Quality Score of 88*

IUSTI/WHO Euro, 2010 Children born to mothers infected with HCV are recommended for HCV screening. (The International Union Against Sexually Transmitted Infections/WHO Europe, European Guideline for the Management of Hepatitis B and C Virus Infections (13)). *HIQA Quality Score of 66.3*

4. What is the quality of the evidence? To be considered if primary literature was reviewed (also apply where appropriate to guidelines)

4.1. How reliable are the studies in the body of evidence?

If there is insufficient evidence to answer the key question go to section 11. Comment here on any issues concerning the quantity of evidence available on this topic and its methodological quality.

A number of high quality guidelines addressed this question.

4.2. Are the studies consistent in their conclusions – comment on the degree of consistency within the available evidence. Highlight specific outcomes if appropriate. If there are conflicting results highlight how the group formed a judgement as to the overall direction of the evidence

There is consistency in recommending hepatitis C testing for infants born to women with HCV infection. The rainbow clinic guidelines differ from other guidelines in also recommending testing (at 18 months) for babies born to women who test HCV antibody positive but RNA negative. There is inconsistency surrounding the type of test or the infant age at which it should be done. No detailed recommendations are provided for testing children who are beyond infancy at the time the mother is first known to be HCV infected.

4.3. Generalisability – are the patients in the studies similar to our target population for this guideline? is it reasonable to generalise

Yes

4.4. Applicability - Is the evidence applicable to Ireland? Is the intervention/action implementable in Ireland?

Yes

4.5. Are there concerns about publication bias? Comment here on concerns about all studies coming from the same research group, funded by industry etc

Not relevant

5. Additional information for consideration

5.1. Additional literature if applicable e.g. Irish literature

Two studies, one in Ireland and one in Ireland and the UK, looked at the risk of vertical transmission.

Gibb et al in a prospective cohort study in the UK and Ireland between 1994-1999 determined the overall vertical transmission rate of HCV to be 6.7% (95% CI of 4.1 - 1.2%) (14). The vertical transmission rate for women co-infected with HIV is 3.8 times higher (p=0.06).

A study from Healy et al reported on the outcomes of 314 infants born to 296 HCV positive women between 1994 and 1999 in the three main Dublin maternity hospitals (15). The infants were monitored for a median of 18 months. Infection status was ascertained for 173 babies with 11 found to be infected. The transmission rate calculated based only on those patients of known outcome was 6.4% (95 CI: 2.8-10%) and the minimum vertical transmission rate, i.e. where it was assumed that all indeterminate status are lost to follow up were uninfected, was 3.5% (1.5-5.5%, 95% CI). The rate of vertical transmission was 3.4 times higher for HIV co-infected women, viral load was generally not available. HCV genotype did not influence transmission risk.

One study which included an Irish cohort looked at testing in infants (14). This study was carried out between 1994 and 1999. It is considered in the SIGN recommendations from 2013. An estimated 50% of uninfected children became seronegative by 8 months of age, with only 5% still having detectable maternal antibody at 13 months. The specificity of PCR was estimated to be 97% (95% CI: 96–99) and was unrelated to age at testing. PCR sensitivity, by contrast, was clearly age dependent. Estimated sensitivity was 22% (7–46) before 1 month of age and 97% (85–100) after that age. This finding has implications for testing policy. First, there is little value in undertaking RNA PCR tests in the first month of life because of low sensitivity. Second, a negative RNA PCR result after 1 month of age almost certainly rules out infection; with the assumption of a transmission risk of 6·7%, only one in every 400 negative RNA PCR results after 1 month of age is a false result in an infected child. Third, after a positive PCR result, the revised risk of infection is about 73% and a repeat test is advisable, although results labelled as false positive could also include infants who clear infection and lose antibody. All these values should be used as a general guide only, because specificity and sensitivity vary between laboratories. Confirmatory serological tests should be delayed until at least 12–15 months because before this age detection of maternal antibody is common.

5.2. Relevant national policy/strategy/practice

National HCV strategy Ireland, 2011 (16) (HIQA quality score 98) Babies born to hepatitis C infected mothers should be screened for hepatitis C infection. Vertical transmission rates are in the order of 5%, with higher rates

reported where mothers are co-infected with HIV. Diagnosis of hepatitis C infection soon after birth can be difficult and prolonged follow-up is necessary to make a definitive diagnosis.

5.3. Epidemiology in Ireland if available and applicable

NA

6. Potential impact of recommendation

6.1. Benefit versus harm

What factors influence the balance between benefit versus harm? Take into account the likelihood of doing harm or good. Do the desirable effects outweigh the undesirable effects?

Benefits:

- Detection of infants with persistent viraemia which will enable linkage to care

Harms:

- In women who are truly anti-HCV positive and RNA negative there is no risk of transmission to the baby. However, occasionally some women have a transient or fluctuating viraemia or might become reinfected during pregnancy. Therefore, not screening the infants of these women may miss a very small number of cases.
- If first testing is recommended at 12 months of age or older, as the evidence suggests is appropriate, some infants might be lost to follow up.
- However, interpretation of tests earlier than this is difficult and some infants will spontaneously clear the virus. Testing earlier than 12 months of age may results in undue anxiety amongst parents. When considering benefit versus harm due regard must be given to any recommendations on the type of test and timing of test to minimise false positive and false negative test results, and the detection of cases who would otherwise clear infection during infancy.
- Opportunity cost.

6.2. What are the likely resource implications and how large are the resource requirements? Consider cost effectiveness, financial, human and other resource implications

No formal health economic assessments were retrieved on screening for HCV infection in children born to infected mothers.

Currently, in the absence of national guidelines on HCV screening for children born to infected mothers it is likely that the majority of children are screened. However, it is unknown what specific testing policy is being applied. Therefore it is possible with the implementation of these recommendations that either a slight increase or decrease in testing may result, which may have some resource implications.

6.3. Acceptability – Is the intervention/ option acceptable to key stakeholders?

Screening of children is likely to be acceptable to parents. However, parents might be anxious to know if transmission has occurred earlier. Parents may not understand the difficulty with interpretation of tests in younger babies and the lack of clinical need to test early in infancy.

The proposed recommendation differs from the current guidance set out by the Rainbow Clinic, the principal referral centre for infected children. The rationale for the recommendation will need to be communicated with stakeholders to ensure acceptance.

6.4. Feasibility - Is the intervention/action implementable in the Irish context?

Yes it is highly likely to be feasible and implementable. Current practice is to screen such children but there may be variability in timing across the country.

6.5. What would be the impact on health equity?

If the principle of proportionate universalism[1] underpins the implementation of the recommendations then there will be a positive impact on health equity.
Children who will be eligible for screening are more likely to be from vulnerable demographic groups. If the recommendation is accompanied with a pathway to ensure screening occurs i.e resource to put a place a system to follow up children and ensure they are not lost to follow up there may be a positive impact on health equity.

7. What is the value judgement? How certain is the relative importance of the desirable and undesirable outcomes? Are the desirable effects larger relative to undesirable

Recent advances in treatment options for hepatitis C make treatment more acceptable and more successful. Treatment with the new DAAs which are now available results in cure in the majority of patients with shorter duration of treatment and less side effects than previous treatments. However at present the cost of these treatments is high.

Screening enables early detection, referral for assessment and treatment where indicated. Without screening children infected with HCV may go undetected for a considerable length of time due to the asymptomatic nature of HCV infection. Individuals often do not present until symptomatic, which is usually indicative of severe liver damage. Early treatment and cure will confer personal, social, and economic benefits. Early treatment and cure will also reduce the risk of transmission to others. A treatment programme exists in Ireland allowing children with HCV access to the new treatment regimes which have greater acceptability and very high cure rates.

While the likelihood of transmission from mother to infants is low it is important to detect infected children and link them to care and treatment. The aim is to identify those with persistent infection and not all those to whom the virus was transmitted.

While parents may be anxious to know if transmission has occurred earlier than 12 months of age, the interpretation of the tests is difficult earlier. Also spontaneous clearance does occur. Also treatment will not be commenced in infancy and the risk of transmission from the infant to others is extremely low.

8. Final Recommendations

√ Strong recommendation
□ Condi□onal/ weak recommenda□on

Text:
Children born to mothers who are HCV infected (RNA or antigen positive) should be tested by a HCV antibody test at 12 months of age or older. If antibody positive, HCV RNA or antigen should be tested to confirm infection. Infected children should be referred to a specialist paediatric infectious disease service.

[1] Proportionate universalism is the resourcing and delivering of universal services at a scale and intensity proportionate to the degree of need.

Children born to mothers who are antibody positive but RNA or antigen negative should have a HCV antibody test at 18 months.

If testing is required before 12 months of age, a HCV RNA test and re-test could be done after two months of age. However, further testing is still required to make a definitive diagnosis.

If a woman is found to be infected with hepatitis C, any previous children should be tested unless the woman was known to be uninfected at the time of their delivery.

9. Justification

There is a small risk of transmission of HCV between an infected mother and infant during the perinatal period. There is no risk of transmission if a mother is RNA negative at the time of delivery. However, 0ccasionally some women test HCV antibody positive and RNA negative, but have a transient or fluctuating viraemia. There is also the possibility that some women may become re-infected during pregnancy. Therefore, although recognising that there is no risk of vertical transmission in women who are HCV antibody positive and truly RNA negative, the guidelines recommend screening babies of all women who are HCV antibody positive.

Screening is not recommended until 12 months of age or older due to difficulty in interpreting the results prior to that age and the absence of clinical benefit in diagnosing earlier than this.

10. Implementation considerations

Infants may be lost to follow up given the time period between birth and the recommended screening age. Also some of these infants will be from a vulnerable population. Therefore, additional support may be required to ensure that the children are followed up.

Also, as many GPs do not take bloods on infants or toddlers, and regional paediatric services do not always offer a GP phlebotomy service, screening may require attendance at a paediatric OPD. A clear pathway from the time of diagnosis or booking of the mother in the antenatal period to the time the child is screened needs to be developed. Incorporation of such a protocol into the proposed perinatal hepatitis B programme may facilitate follow up of these infants.

The proposed recommendation is not consistent with current Rainbow guidelines. Implementation will require consultation with the Rainbow clinic and communication to those currently following Rainbow clinic guidelines.

11. Recommendations for research

List any aspects of the question that have not been answered and should therefore be highlighted as an area in need of further research.

Consultation feedback

Feedback received from Professor Karina Butler, Rainbow Clinic, outlining the updated recommendations of the Rainbow Clinic and the experiences of the Rainbow clinic in managing the follow up of children born in HCV positive women.

Review by GDG

The GDG considered the feedback provided by the Rainbow Clinic. While the GDG recognises that there is not a direct clinical benefit to early detection of infection in infants, the GDG recommends adopting the Rainbow Clinic guidelines on the basis that they have proven to be acceptable and feasible, and that the early testing schedule will link the child and family into care and support subsequent follow-up.

Final recommendation

Recommendation 2

2.1. Infants of HCV-RNA positive women should be tested for HCV-RNA at six weeks and six months of age and, if both are negative, anti-HCV at ≥ 18 months of age.

2.2. Infants who are HCV-RNA positive at any time, or who are anti-HCV positive at or after 18 months of age, should be referred to the Rainbow Clinic.

2.3. Infants of anti-HCV positive but HCV-RNA negative women, where eradication of infection, either spontaneously or by treatment is not assured (i.e. by serial negative HCV-RNA tests), should be tested for anti-HCV at ≥ 18 months of age.

2.4. Infants of anti-HCV positive but HCV-RNA negative women where eradication of infection, either spontaneously or by treatment is assured (i.e. persistent negative HCV-RNA and no ongoing risk for reinfection), should be managed as infants of uninfected women and do not require follow-up.

Quality/level of evidence: low to moderate
Strength of recommendation: strong

Recommendation 3

3.1. If a woman is found to have current or resolved HCV infection, any previous children she has given

Quality/level of evidence: low to moderate
Strength of recommendation: strong

References List

1. Butler K, Ferguson W, Goode M, Lyons F. Preventing perinatal transmission: a practical guide to the antenatal and perinatal management of HIV, hepatitis B, hepatitis C, herpes simplex and syphilis. Dublin: The Rainbow Clinic; 2015. Available from: https://www.hse.ie/eng/about/Who/clinical/natclinprog/obsandgynaeprogramme/guidelines/non%20prog%20guidelines/PPT.pdf.
2. World Health Organization. Guidelines for screening, care and treatment care of persons with hepatitis C infection. Updated version, April 2016. Geneva: WHO; 2016. Available from: http://apps.who.int/iris/bitstream/10665/205035/1/9789241549615_eng.pdf?ua=1.
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12. Mack CL, Gonzalez-Peralta RP, Gupta N, Leung D, Narkewicz MR, Roberts EA, et al. NASPGHAN practice guidelines: Diagnosis and management of hepatitis C infection in infants, children, and adolescents. J Pediatr Gastroenterol Nutr. 2012;54(6):838-55.
13. Brook G, Soriano V, Bergin C. European guideline for the management of hepatitis B and C virus infections, 2010. Int J STD AIDS. 2010;21(10):669-78.
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15. Healy CM, Cafferkey MT, Conroy A, Dooley S, Hall WW, Beckett M, et al. Outcome of infants born to hepatitis C infected women. Ir J Med Sci. 2001;170(2):103-6.
16. Health Service Executive. National Hepatitis C Strategy 2011-2014. Dublin: HSE; 2012. Available from: https://www.hse.ie/eng/services/Publications/HealthProtection/HepCstrategy.pdf.

Appendices

Evidence search and results

International and national guidelines

HCV guidelines identified, reviewed, and quality appraised as described in the National Clinical Guideline.

Other guidelines reviewed

The Rainbow Clinic guideline *Preventing perinatal transmission: a practical guide to the antenatal and perinatal management of HIV, hepatitis B, hepatitis C, herpes simplex and syphilis* was identified by expert members of the GDG for inclusion.

Grey literature

Nil used.

Primary literature

Specific literature review not undertaken. Literature identified through for other key questions (e.g. antenatal screening) was included as background information when relevant.