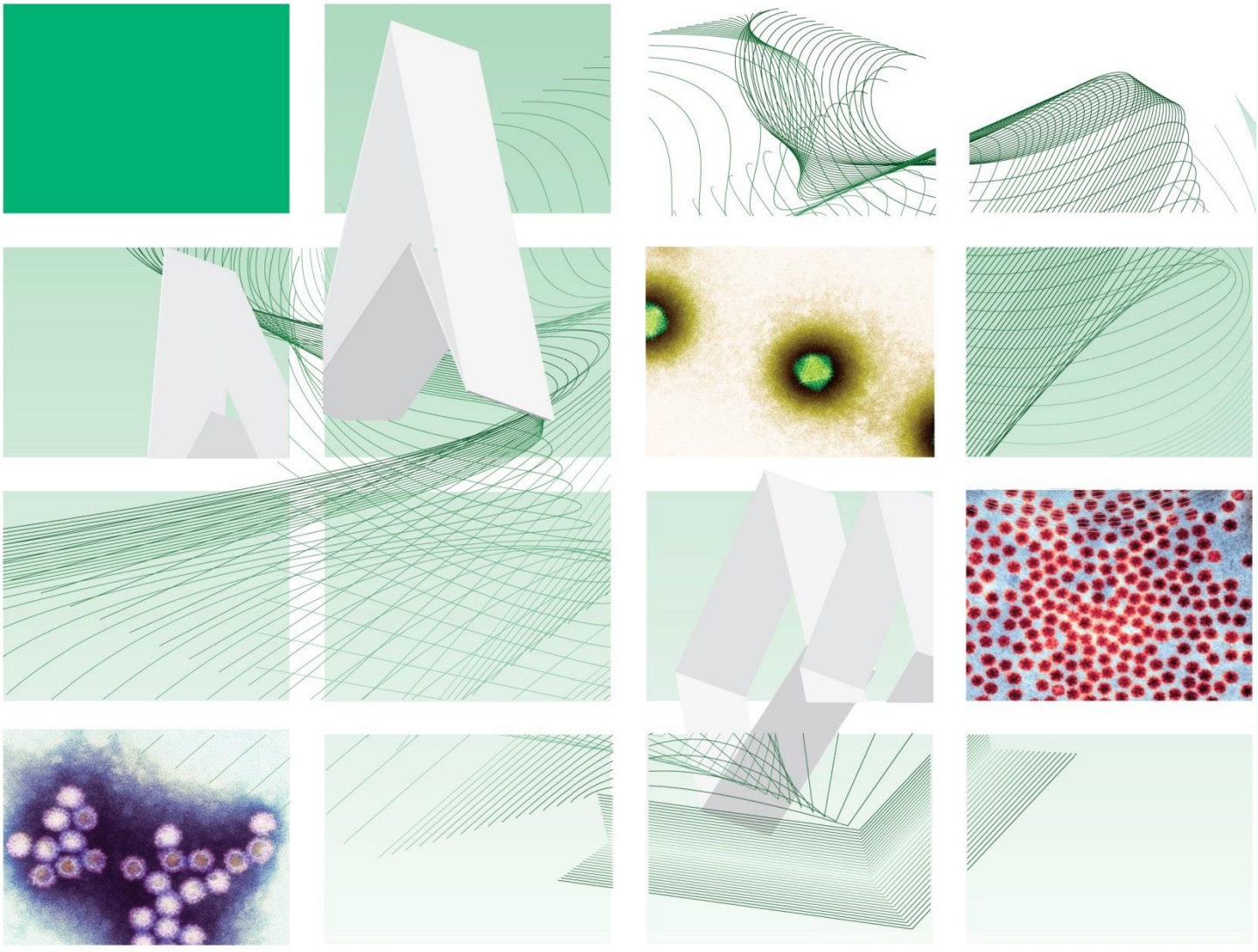
Public Health England

NHS

UK Standards for Microbiology Investigations

Vertical and perinatal transmission of hepatitis C



NICE accredited
www.nice.org.uk/accreditation

"NICE has renewed accreditation of the process used by **Public Health England (PHE)** to produce **UK Standards for Microbiology Investigations**. The renewed accreditation is valid until **30 June 2021** and applies to guidance produced using the processes described in **UK standards for microbiology investigations (UKSMIs) Development process, S9365', 2016**. The original accreditation term began in **July 2011.**"

Issued by the Standards Unit, Microbiology Services, PHE

Virology | V 8 | Issue no: 3 | Issue date: 03.12.18 | Page: 1 of 23

Acknowledgments

UK Standards for Microbiology Investigations (UK SMIs) are developed under the auspices of Public Health England (PHE) working in partnership with the National Health Service (NHS), Public Health Wales and with the professional organisations whose logos are displayed below and listed on the website https://www.gov.uk/uk-standards-for-microbiology-investigations-smi-quality-and-consistency-in-clinical-laboratories. UK SMIs are developed, reviewed and revised by various working groups which are overseen by a steering committee (see https://www.gov.uk/government/groups/standards-for-microbiology-investigations-steering-committee).

The contributions of many individuals in clinical, specialist and reference laboratories who have provided information and comments during the development of this document are acknowledged. We are grateful to the medical editors for editing the medical content.

For further information please contact us at:

Standards Unit
National Infection Service
Public Health England
61 Colindale Avenue
London NW9 5EQ

E-mail: standards@phe.gov.uk

Website: https://www.gov.uk/uk-standards-for-microbiology-investigations-smi-quality-and-consistency-in-clinical-laboratories

PHE publications gateway number: 2018033

UK Standards for Microbiology Investigations are produced in association with:

Logos correct at time of publishing.

Contents

"NICE has renewed accreditation of the process used by **Public Health England (PHE)** to produce **UK Standards for Microbiology Investigations**. The renewed accreditation is valid until **30 June 2021** and applies to guidance produced using the processes described in **UK standards for microbiology investigations (UKSMIs) Development process, S9365', 2016**. The original accreditation term began in **July 2011."**

Amendment table

Each UK SMI method has an individual record of amendments. The current amendments are listed on this page. The amendment history is available from standards@phe.gov.uk.

New or revised documents should be controlled within the laboratory in accordance with the local quality management system.

Amendment No/Date.	4/03.12.18
Issue no. discarded.	2
Insert Issue no.	3
Anticipated next review date*	03.12.21
Section(s) involved	**Amendment**
Whole document.	An introduction has been added to this document along with background information for Hepatitis C virus and a link to the UK SMI V 5 document. Document updated to include sections: Technical Limitations, Safety Considerations, Public Health Management and Report Comments. Updated flowchart. References updated.

*Reviews can be extended up to five years subject to resources available.

UK SMI[#]: scope and purpose

Users of UK SMIs

Primarily, UK SMIs are intended as a general resource for practising professionals operating in the field of laboratory medicine and infection specialties in the UK. UK SMIs also provide clinicians with information about the available test repertoire and the standard of laboratory services they should expect for the investigation of infection in their patients, as well as providing information that aids the electronic ordering of appropriate tests. The documents also provide commissioners of healthcare services with the appropriateness and standard of microbiology investigations they should be seeking as part of the clinical and public health care package for their population.

Background to UK SMIs

UK SMIs comprise a collection of recommended algorithms and procedures covering all stages of the investigative process in microbiology from the pre-analytical (clinical syndrome) stage to the analytical (laboratory testing) and post analytical (result interpretation and reporting) stages. Syndromic algorithms are supported by more detailed documents containing advice on the investigation of specific diseases and infections. Quality guidance notes describe laboratory processes which underpin quality, for example assay validation.

Standardisation of the diagnostic process through the application of UK SMIs helps to assure the equivalence of investigation strategies in different laboratories across the UK and is essential for public health surveillance, research and development activities.

Equal partnership working

UK SMIs are developed in equal partnership with PHE, NHS, Royal College of Pathologists and professional societies. The list of participating societies may be found at https://www.gov.uk/uk-standards-for-microbiology-investigations-smi-quality-and-consistency-in-clinical-laboratories. Inclusion of a logo in an UK SMI indicates participation of the society in equal partnership and support for the objectives and process of preparing UK SMIs. Nominees of professional societies are members of the Steering Committee and working groups which develop UK SMIs. The views of nominees cannot be rigorously representative of the members of their nominating organisations nor the corporate views of their organisations. Nominees act as a conduit for two way reporting and dialogue. Representative views are sought through the consultation process. UK SMIs are developed, reviewed and updated through a wide consultation process.

Quality assurance

NICE has accredited the process used by the UK SMI working groups to produce UK SMIs. The accreditation is applicable to all guidance produced since October 2009. The process for the development of UK SMIs is certified to ISO 9001:2008. UK SMIs represent a good standard of practice to which all clinical and public health

[#] Microbiology is used as a generic term to include the two GMC-recognised specialties of Medical Microbiology (which includes Bacteriology, Mycology and Parasitology) and Medical Virology.

microbiology laboratories in the UK are expected to work. UK SMIs are NICE accredited and represent neither minimum standards of practice nor the highest level of complex laboratory investigation possible. In using UK SMIs, laboratories should take account of local requirements and undertake additional investigations where appropriate. UK SMIs help laboratories to meet accreditation requirements by promoting high quality practices which are auditable. UK SMIs also provide a reference point for method development. The performance of UK SMIs depends on competent staff and appropriate quality reagents and equipment. Laboratories should ensure that all commercial and in-house tests have been validated and shown to be fit for purpose. Laboratories should participate in external quality assessment schemes and undertake relevant internal quality control procedures.

Patient and public involvement

The UK SMI working groups are committed to patient and public involvement in the development of UK SMIs. By involving the public, health professionals, scientists and voluntary organisations the resulting UK SMI will be robust and meet the needs of the user. An opportunity is given to members of the public to contribute to consultations through our open access website.

Information governance and equality

PHE is a Caldicott compliant organisation. It seeks to take every possible precaution to prevent unauthorised disclosure of patient details and to ensure that patient-related records are kept under secure conditions. The development of UK SMIs is subject to PHE Equality objectives https://www.gov.uk/government/organisations/public-health-england/about/equality-and-diversity.

The UK SMI working groups are committed to achieving the equality objectives by effective consultation with members of the public, partners, stakeholders and specialist interest groups.

Legal statement

While every care has been taken in the preparation of UK SMIs, PHE and the partner organisations, shall, to the greatest extent possible under any applicable law, exclude liability for all losses, costs, claims, damages or expenses arising out of or connected with the use of an UK SMI or any information contained therein. If alterations are made by an end user to an UK SMI for local use, it must be made clear where in the document the alterations have been made and by whom such alterations have been made and also acknowledged that PHE and the partner organisations shall bear no liability for such alterations. For the further avoidance of doubt, as UK SMIs have been developed for application within the UK, any application outside the UK shall be at the user's risk.

The evidence base and microbial taxonomy for the UK SMI is as complete as possible at the date of issue. Any omissions and new material will be considered at the next review. These standards can only be superseded by revisions of the standard, legislative action, or by NICE accredited guidance.

Suggested citation for this document

Public Health England. (2018). Vertical and perinatal transmission of hepatitis C. UK Standards for Microbiology Investigations. V 8 Issue 3. https://www.gov.uk/uk-standards-for-microbiology-investigations-smi-quality-and-consistency-in-clinical-laboratories

Scope of document

Type of specimen

Blood, serum or plasma

This algorithm outlines the laboratory screening for HCV infection in babies born to hepatitis C virus (HCV) infected mothers[1]. Infection may be acquired through vertical or perinatal transmission[2,3]. Only babies born from mothers who are HCV RNA positive require routine testing, however babies born from mothers who are HCV RNA negative, anti-HCV positive may be tested dependent on local policy. Transmission from HCV RNA negative mothers is rare, but has been documented in some studies[4-6].

CE marked assays should be validated and verified prior to use. If assays are to be used outside the scope for which the manufacturer has designated for its use, these should be validated, and shown to be fit for purpose by the laboratory to suit its needs. For more information on CE marking, refer to the IVD Directive and for more information on validation of these CE marked assays, refer to UK SMI Q 1: Evaluations, validations and verifications of diagnostic tests.

Refer to UK SMIs, S 1: Acute infective hepatitis and V 5: Screening for hepatitis C infection for further information regarding clinical presentations of acute infective hepatitis and associated tests.

This UK SMI should be used in conjunction with other UK SMIs.

Abbreviations

Abbreviation	Definition
HCV	hepatitis C virus (complete infectious virion)
Anti-HCV	Antibody to HCV
NAAT	nucleic acid amplification test

Definitions

For all antigen, antibody and nucleic acid amplification test (NAAT) testing the following definitions apply:

During testing process

Reactive – Initial internal-stage positive result pending confirmation.

Not reactive – Initial internal-stage negative result.

Equivocal – Result is not clearly positive or negative. Further testing is required.

The term ‘equivocal’ may be different for various platforms eg ‘indeterminate’.

Inhibitory – The term ‘inhibitory’ may be different for various platforms eg ‘invalid’.

Reporting stage

These terms are used for final or preliminary reports.

Detected – Report-stage confirmed reactive result.

Not detected – Report-stage not reactive result.

Indeterminate – Reactive result that cannot be confirmed.

Inhibitory – The term ‘inhibitory’ may be different for various platforms eg ‘invalid’.

Introduction

Hepatitis C is a blood-borne viral infection predominantly transmitted through contact with infected blood. In the UK, hepatitis C is primarily acquired through injecting drug use. Other modes of transmission include vertical transmission (mother to child), sharing of contaminated devices for non-injection drug use, exposure to infected blood through occupational and other means, and sexual intercourse.

Hepatitis C virus causes both acute and chronic infection. Acute HCV infection is usually asymptomatic and spontaneous clearance occurs within six months of infection in 15–45% of infected individuals in the absence of treatment. Almost all the remaining 55–85% of persons will harbour HCV and are considered to have chronic HCV infection. If left untreated, chronic HCV infection can cause liver cirrhosis, liver failure and hepatocellular carcinoma[7].

Pregnant women who are infected with hepatitis C virus carry an approximately 5% risk of transmission from mother to infant and this is higher in infants born to HIV-infected mothers (17-25%)[7]. Hepatitis C virus can be transmitted to the infant in utero or during the peripartum period. Infection during pregnancy is associated with increased risk of adverse foetal outcomes, including foetal growth restriction and low birthweight[8].

HCV infection requires an initial serologic test followed by a HCV RNA test to confirm the presence of viraemia. World Health Organization (WHO) recommends that HCV testing be performed on individuals who are part of a population with high HCV seroprevalence or who have a history of HCV risk exposure and/or behaviour.

Laboratory diagnosis

Pregnant women who are at increased risk for hepatitis C infection should be tested at their prenatal visits by testing for anti-HCV antibodies. If the initial results in pregnant women with on-going risk factors for hepatitis C infection are negative, this should be repeated later on in the third trimester[7,8]. It should be noted that routine testing of pregnant women for HCV infection is currently not recommended[9].

Infants infected with HCV should be monitored and assessed clinically every 6-12 months to identify any risks of progressive liver fibrosis during childhood[3].

Technical information/limitations

Limitations of UK SMIs

The recommendations made in UK SMIs are based on evidence (eg sensitivity and specificity) where available, expert opinion and pragmatism, with consideration also being given to available resources. Laboratories should take account of local requirements and undertake additional investigations where appropriate. Prior to use, laboratories should ensure that all commercial and in-house tests have been validated and are fit for purpose.

Specimen containers[10,11]

UK SMIs use the term “CE marked leak proof container” to describe containers bearing the CE marking used for the collection and transport of clinical specimens. The requirements for specimen containers are given in the EU in vitro Diagnostic Medical Devices Directive (98/79/EC Annex 1 B 2.1) which states: “The design must allow easy handling and, where necessary, reduce as far as possible contamination of and leakage from, the device during use and, in the case of specimen receptacles, the risk of contamination of the specimen. The manufacturing processes must be appropriate for these purposes”.

1 Safety considerations[10-27]

1.1 Specimen collection, transport and storage[10,11,19,20,23,26,27]

Use aseptic technique.

Collect adequate and appropriate specimens in appropriate CE marked leak proof containers and transport in sealed plastic bags.

Compliance with postal, transport and storage regulations is essential.

This guidance should be supplemented with local COSHH and risk assessments.

Refer to current guidance on the safe handling of all organisms documented in this UK SMI.

1.2 Specimen processing

Laboratory procedures that give rise to infectious aerosols must be conducted in a microbiological safety cabinet[13].

Refer to current guidance on the safe handling of all organisms documented in this UK SMI.

The above guidance should be supplemented with local COSHH and risk assessments.

2 Specimen transport, storage and retention[10,11]

2.1 Optimal transport and storage conditions

Specimens should be collected in appropriate CE marked leak proof containers and transported in sealed bags.

Specimens should be transported and processed according to manufacturer's instructions or local validation data[28].

If processing is delayed, refrigeration is preferable to storage at ambient temperature[28].

Note: Specimens for NAAT can be stored long-term at -20° or -70°C to minimise RNA loss[29].

Samples should be retained in accordance with The Royal College of Pathologists guidelines 'The retention and storage of pathological records and specimens'[30].

Public health management

Hepatitis C is a notifiable disease and laboratories should ensure that the Health Protection teams are notified of any new cases in line with national public health legislation[31]. Hepatitis C is usually asymptomatic for many years after infection, numerous individuals therefore remain undiagnosed.

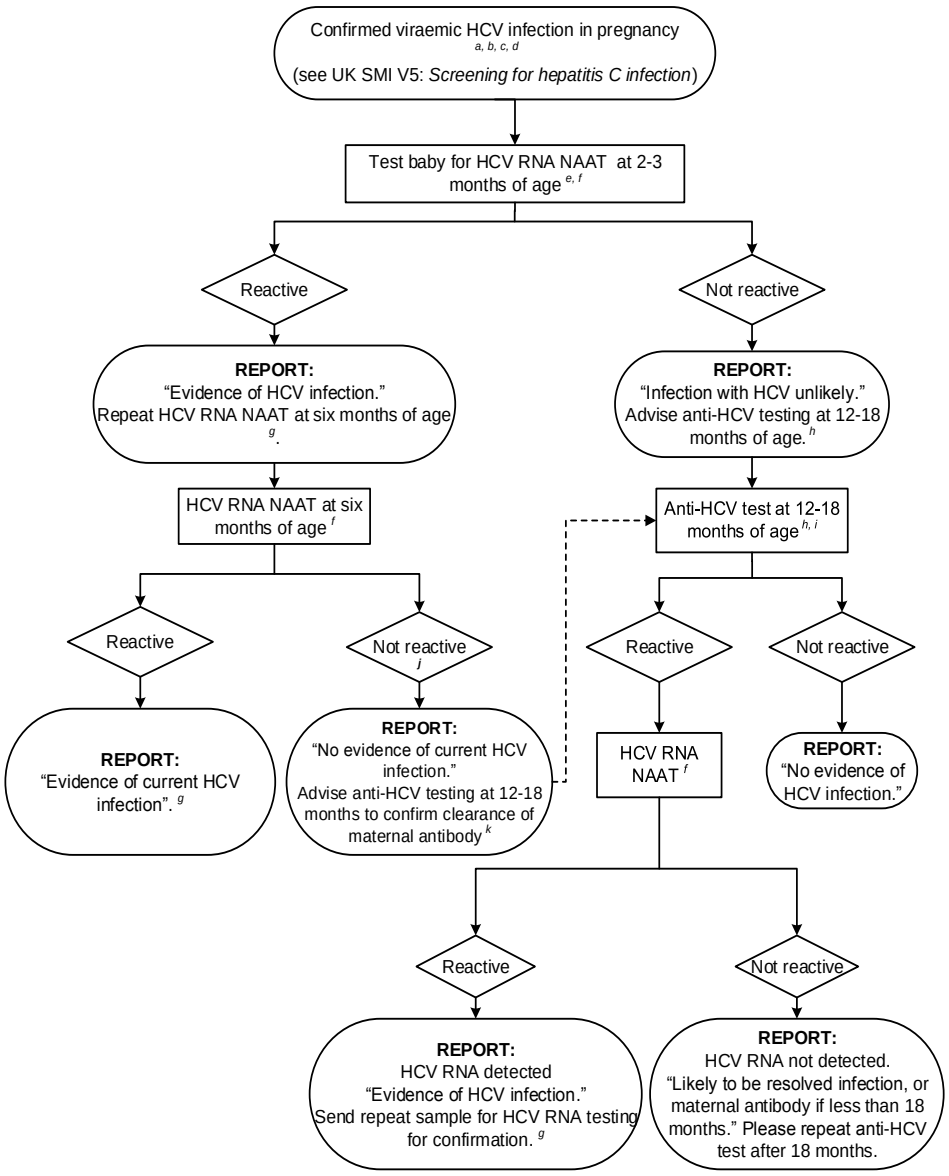
For information regarding notification to PHE (or equivalent in the devolved administrations) refer to section 'notification to PHE, or equivalent in the devolved administrations'.

For further information on public health management refer to PHE guidance: https://www.gov.uk/government/collections/hepatitis-c-guidance-data-and-analysis and www.gov.uk/government/publications/hepatitis-b-and-c-local-surveillance-standards.

In addition to reporting new positive diagnoses to PHE Health Protection Teams, participating laboratories should also report into sentinel surveillance programmes for HCV.

In the UK, guidance for hepatitis C infected health care workers (HCW) is available[32]. See link: https://www.gov.uk/guidance/bloodborne-viruses-in-healthcare-workers-report-exposures-and-reduce-risks.

Vertical and perinatal transmission of hepatitis C infection[1,33,34]



Footnotes

a) Transmission of hepatitis C from HCV RNA positive mother to baby occurs in 3-6%. Most cases occur as a result of perinatal transmission, usually during birth, although in utero transmission has been suggested in up to one-third of infections[35]. The transmission rate is increased 3 to 4 fold in HIV-HCV co-infection and with prolonged rupture of membranes[36]. Transmission via breastfeeding is rare[37,38]. For women with on-going risk factors for HCV who have a negative RNA test, consideration should be given to a further confirmatory NAAT test in the third trimester. It should also be noted that consideration should be given to investigate previous pregnancies or partner of current HCV positive mothers.

b) For women who have acquired infection during pregnancy, but have cleared viraemia, the baby should be followed up as described in this algorithm.

c) For babies born to a woman who has injected drugs, if the mother is unavailable to consent for testing and there is evidence of suspected HCV infection, test the baby for HCV antibody and follow the algorithm if the baby is HCV antibody positive. If the baby is HCV antibody negative then this is highly predictive of absence of infection providing the exposure risk is more than 6 months ago[5].

d) Mothers with evidence of hepatitis C antibodies who are stably HCV RNA negative are highly unlikely to transmit HCV to the baby[4-6]. Babies born from HCV RNA PCR negative, anti-HCV positive mothers do not require routine testing[3].

e) It should be noted that other guidelines do not always advocate early NAAT testing in children[3].

f) HCV RNA assay target sensitivity level of 15 IU/mL or lower[39].

g) Advise referral to Paediatric Hepatologist or Paediatric Infectious Disease Specialist for further assessment/ treatment.

h) Combined HCV antigen/antibody assays can also be used[40,41]. These assays generally have a sensitivity of ~1000-5000 IU/mL and may therefore miss about 3% of viraemia cases[42-46]. Precise analytical sensitivity and clinical sensitivity varies from assay to assay, and should be carefully assessed before the assay is put into service[47-52]. If antigen negative, ensure that NAAT test is performed.

   Note: However, if HCV antigen only assays are used, NAAT will be required.

i) A negative HCV RNA NAAT result may be observed in infected children with fluctuations in viraemia, therefore an anti-HCV test should be carried out between 12–18 months[53,54].

j) Might reflect resolution of infection (>25% resolve), fluctuating RNA level or a laboratory error.

k) Request repeat sample. Laboratories may wish to repeat discordant results.

Report comments

The final result should be able to distinguish active HCV infection from resolved infection using a combination of antibody, antigen and NAAT tests.
Following an initial (first sample) positive result, it is best practice to request a repeat sample.

Investigation of hepatitis C infection in babies of women confirmed as HCV during pregnancy using both NAAT and Anti- HCV test				
	HCV NAAT at 2-3 mths	**HCV NAAT at 6 mths**	**Interpretative comments**	**Notes**
1	RNA detected	RNA detected	**At 2-3 months,** HCV RNA detected. Evidence of HCV infection. Repeat HCV NAAT at 6 months. Advise referral to Paediatric Hepatologist or Paediatric Infectious Disease Specialist for further assessment/treatment. **At 6 months,** HCV RNA detected. Evidence of current HCV infection. Advise referral to Paediatric Hepatologist or Paediatric Infectious Disease Specialist for further assessment/treatment. Hepatitis A and B vaccine recommended if appropriate.	In the case of suspected acute hepatitis C or in immunocompromised patients, HCV RNA testing should be part of the initial evaluation. Please ensure hepatitis B vaccination status is known and vaccination given if needed. Consider requesting HCV genotyping and other BBV testing unless already performed[7].
2.	RNA detected	RNA not detected	**At 2-3 months,** HCV RNA detected. Evidence of HCV infection. Request repeat sample for HCV NAAT at 6 months. Advise referral to Paediatric Hepatologist or Paediatric Infectious	

			Disease Specialist for further assessment/treatment. **At 6 months,** HCV RNA not detected. No evidence of current HCV infection. Request repeat sample for retesting. Advise anti-HCV testing at 12-18 months to confirm clearance of maternal antibody.	
3	RNA not detected	Not tested	**At 2- 3 months,** HCV RNA not detected. Infection with HCV unlikely. Advise anti-HCV testing at 12-18 months.	

Following a negative HCV RNA result at 2-3mths of age, testing for HCV antibodies using Anti-HCV test at 12-18 months

	Anti-HCV Test at 12-18mths	**Interpretative comments**	**Notes**
4	Detected	HCV antibody detected. Request HCV RNA NAAT to confirm evidence of infection.	HCV antibody positive result may indicate past HCV infection. EASL 2016 recommend that "*Anti-HCV positive, HCV RNA negative individuals should be retested for HCV RNA 3 months later to confirm definitive clearance*"[39]. Suggest a repeat sample to confirm HCV antibody status. Please note that undetectable HCV RNA does not exclude current infection because viraemia may be intermittent. Suggest testing a follow-up blood for HCV NAAT to investigate possible fluctuating viraemia[39,55].
5	Not detected	HCV antibody not detected. No evidence of HCV	

		infection.	
Confirmation of Anti-HCV test performed at 12-18 months using HCV RNA NAAT			
	HCV NAAT at 12-18 mths	**Interpretative comments**	**Notes**
6	RNA detected	HCV RNA detected. Evidence of HCV infection. Send repeat sample for HCV RNA testing for confirmation. Advise referral to Paediatric Hepatologist or Paediatric Infectious Disease Specialist for further assessment/treatment.	
7	RNA not detected	HCV RNA not detected. Likely to be resolved infection or maternal antibody if less than 18 months. Please repeat anti-HCV test after 18 months.	

Notification to PHE[56,57], or equivalent in the devolved administrations[58-61]

The Health Protection (Notification) regulations 2010 require diagnostic laboratories to notify Public Health England (PHE) when they identify the causative agents that are listed in Schedule 2 of the Regulations. Notifications must be provided in writing, on paper or electronically, within seven days. Urgent cases should be notified orally and as soon as possible, recommended within 24 hours. These should be followed up by written notification within seven days.

For the purposes of the Notification Regulations, the recipient of laboratory notifications is the local PHE Health Protection Team. If a case has already been notified by a registered medical practitioner, the diagnostic laboratory is still required to notify the case if they identify any evidence of an infection caused by a notifiable causative agent.

Notification under the Health Protection (Notification) Regulations 2010 does not replace voluntary reporting to PHE. The vast majority of NHS laboratories voluntarily report a wide range of laboratory diagnoses of causative agents to PHE and many PHE Health protection Teams have agreements with local laboratories for urgent reporting of some infections. This should continue.

Note: The Health Protection Legislation Guidance (2010) includes reporting of Human Immunodeficiency Virus (HIV) & Sexually Transmitted Infections (STIs), Healthcare Associated Infections (HCAIs) and Creutzfeldt–Jakob disease (CJD) under 'Notification Duties of Registered Medical Practitioners': it is not noted under 'Notification Duties of Diagnostic Laboratories'.

https://www.gov.uk/government/organisations/public-health-england/about/our-governance#health-protection-regulations-2010

Other arrangements exist in Scotland[58,59], Wales[60] and Northern Ireland[61].

References

Modified GRADE table used by UK SMIs when assessing references

Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) is a systematic approach to assessing references. A modified GRADE method is used in UK SMIs for appraising references for inclusion. Each reference is assessed and allocated a grade for strength of recommendation (A-D) and quality of the underlying evidence (I-VIII). A summary table which defines the grade is listed below and should be used in conjunction with the reference list.

Quality/certainty of evidence	Types of evidence
A Strongly recommended	I Evidence from randomised controlled trials, meta-analysis and systematic reviews
B* Recommended but other alternatives may be acceptable	II Evidence from non-randomised studies
	III Evidence from documents describing techniques, methods or protocols
C* Weakly recommended: seek alternatives	IV Non-analytical studies, eg case reports, reviews, case series
D Never recommended	V Expert opinion and wide acceptance as good practice but with no study evidence
	VI Required by legislation, code of practice or national standard/ guideline
	VII Letter /short communication /editorials /conference communication
	VIII Electronic citation

1. Davison SM, Mieli-Vergani G, Sira J, Kelly DA. Perinatal hepatitis C virus infection: diagnosis and management. ArchDisChild 2006;91:781-5. **B, IV**

2. European association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. JHepatol 2011;55:245-64. **A, VI**

3. Scottish Intercollegiate Guidelines Network. SIGN 133: Management of Hepatitis C. 2013. **A, VI**

4. Resti M, Azzari C, Mannelli F, Moriondo M, Novembre E, de MM et al. Mother to child transmission of hepatitis C virus: prospective study of risk factors and timing of infection in children born to women seronegative for HIV-1. Tuscany Study Group on Hepatitis C Virus Infection. BMJ 1998;317:437-41. **B, II**

5. Tovo PA, Pembrey LJ, Newell ML. Persistence rate and progression of vertically acquired hepatitis C infection. European Paediatric Hepatitis C Virus Infection. JInfectDis 2000;181:419-24. **B, II**

6. Thomas SL, Newell ML, Peckham CS, Ades AE, Hall AJ. A review of hepatitis C virus (HCV) vertical transmission: risks of transmission to infants born to mothers with and without HCV viraemia or human immunodeficiency virus infection. IntJEpidemiol 1998;27:108-17. **B, IV**

7. World Health Organization. Guidelines for the screening, care and treatment of persons with hepatitis C infection. 2014. 1-122. **A, VI**

8. Society for Maternal-Fetal Medicine, Hughes BL, Page CM, Kuller JA. Hepatitis C in pregnancy: screening, treatment, and management. Am J Obstet Gynecol 2017;217:B2-B12. **B, IV**

9. World Health Organization. WHO guidelines on hepatitis B and C testing. 2017. 1-204. **A, VI**

10. European Parliament. UK Standards for Microbiology Investigations (UK SMIs) use the term "CE marked leak proof container" to describe containers bearing the CE marking used for the collection and transport of clinical specimens. The requirements for specimen containers are given in the EU in vitro Diagnostic Medical Devices Directive (98/79/EC Annex 1 B 2.1) which states: "The design must allow easy handling and, where necessary, reduce as far as possible contamination of, and leakage from, the device during use and, in the case of specimen receptacles, the risk of contamination of the specimen. The manufacturing processes must be appropriate for these purposes". 1998. **A, VI**

11. Official Journal of the European Communities. Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on *in vitro* diagnostic medical devices 1998. 1-37. **A, VI**

12. Advisory Committee on Dangerous Pathogens. Infections at work: Controlling the risks. Her Majesty's Stationery Office 2003. **A, VI**

13. Advisory Committee on Dangerous Pathogens. Biological agents: Managing the risks in laboratories and healthcare premises. Health and Safety Executive 2005. **A, VI**

14. Advisory Committee on Dangerous Pathogens. Biological Agents: Managing the Risks in Laboratories and Healthcare Premises. Appendix 1.2 Transport of Infectious Substances - Revision. Health and Safety Executive 2008. **A, VI**

15. Advisory Committee on Dangerous Pathogens. The Approved List of Biological Agents. Health and Safety Executive 2013. 1-35. **A, VI**

16. British Standards Institution (BSI). BS EN12469 - Biotechnology - performance criteria for microbiological safety cabinets 2000. **A, VI**

17. British Standards Institution (BSI). BS 5726:2005 - Microbiological safety cabinets. Information to be supplied by the purchaser and to the vendor and to the installer, and siting and use of cabinets. Recommendations and guidance. 2005. 1-14. **A, VI**

18. Centers for Disease Control and Prevention. Guidelines for Safe Work Practices in Human and Animal Medical Diagnostic Laboratories. MMWR Surveill Summ 2012;61:1-102. **B, V**

19. Department for Transport. Transport of Infectious Substances, 2011 Revision 5. 2011. **A, VI**

20. Department of Health. Transport of Infectious Substances. Best Practice Guidance for Microbiology Laboratories. Department of Health. 1-13. 2007. **A, VI**

21. Health and Safety Executive. Five Steps to Risk Assessment: A Step by Step Guide to a Safer and Healthier Workplace. HSE Books,. 2002. **A, VI**

22. Health and Safety Executive. A Guide to Risk Assessment Requirements: Common Provisions in Health and Safety Law. HSE Books,. 2002. **A, VI**

23. Health and Safety Executive. Safe use of pneumatic air tube transport systems for pathology specimens. 2009. **A, VI**

24. Health and Safety Executive. Control of Substances Hazardous to Health Regulations. The Control of Substances Hazardous to Health Regulations 2002 (as amended). Approved Code of Practice and guidance L5 (sixth edition). HSE Books,. 2013. **A, VI**

25. Health Services Advisory Committee. Safe Working and the Prevention of Infection in Clinical Laboratories and Similar Facilities. HSE Books 2003. **A, VI**

26. Home Office. Anti-terrorism, Crime and Security Act. 2001. **A, VI**

27. World Health Organization. Guidance on regulations for the Transport of Infectious Substances 2017-2018. 2017. **A, VI**

28. Baron EJ, Miller JM, Weinstein MP, Richter SS, Gilligan PH, Thomson RB, Jr. et al. A Guide to Utilization of the Microbiology Laboratory for Diagnosis of Infectious Diseases: 2013 Recommendations by the Infectious Diseases Society of America (IDSA) and the American Society for Microbiology (ASM). ClinInfectDis 2013;57:e22-e121. **B, V**

29. Baleriola C, Johal H, Jacka B, Chaverot S, Bowden S, Lacey S et al. Stability of hepatitis C virus, HIV, and hepatitis B virus nucleic acids in plasma samples after long-term storage at -20 degrees C and -70 degrees C. J Clin Microbiol 2011;49:3163-7. **B, II**

30. The retention and storage of pathological records and specimens (5th edition). The Royal College of Pathologists.; 2015. p. 1-59. **A, VI**

31. National Institute for Health and Care Excellence. Hepatitis B and C: ways to promote and offer testing to people at increased risk of infection. 2012. 1-97. **A, VI**

32. Department of Health. Hepatitis C infected health care workers. 08/2002. **A, VI**

33. Resti M, Bortolotti F, Vajro P, Maggiore G. Guidelines for the screening and follow-up of infants born to anti-HCV positive mothers. DigLiver Dis 2003;35:453-7. **B, IV**

34. Dunn DT, Gibb DM, Healy M, Goodall RL, Butler K, Cafferkey M et al. Timing and interpretation of tests for diagnosing perinatally acquired hepatitis C virus infection. PediatrInfectDisJ 2001;20:715-6. **B, II**

35. Mok J, Pembrey L, Tovo PA, Newell ML. When does mother to child transmission of hepatitis C virus occur? ArchDis Child Fetal Neonatal Ed 2005;90:F156-F60. **B, II**

36. Pembrey L, Newell ML, Tovo PA. The management of HCV infected pregnant women and their children European paediatric HCV network. J Hepatol 2005;43:515-25. **B, IV**

37. Indolfi G, Resti M. Perinatal transmission of hepatitis C virus infection. J Med Virol 2009;81:836-43. **B, IV**

38. Arshad M, El Kamary SS, Jhaveri R. Hepatitis C virus infection during pregnancy and the newborn period--are they opportunities for treatment? J Viral Hepat 2011;18:229-36. **B, IV**

39. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2016. . J Hepatol 2016:1-42. **A, VI**

40. Ansaldi F, Bruzzone B, Testino G, Bassetti M, Gasparini R, Crovari P et al. Combination hepatitis C virus antigen and antibody immunoassay as a new tool for early diagnosis of infection. JViral Hepat 2006;13:5-10. **B, II**

41. Tillmann HL. Hepatitis C virus core antigen testing: role in diagnosis, disease monitoring and treatment. World JGastroenterol 2014;20:6701-6. **B, IV**

42. Gaudy C, Thevenas C, Tichet J, Mariotte N, Goudeau A, Dubois F. Usefulness of the hepatitis C virus core antigen assay for screening of a population undergoing routine medical checkup. JClinMicrobiol 2005;43:1722-6. **B, II**

43. Hayashi K, Hasuike S, Kusumoto K, Ido A, Uto H, Kenji N et al. Usefulness of a new immuno-radiometric assay to detect hepatitis C core antigen in a community-based population. JViral Hepat 2005;12:106-10. **B, II**

44. Leary TP, Gutierrez RA, Muerhoff AS, Birkenmeyer LG, Desai SM, Dawson GJ. A chemiluminescent, magnetic particle-based immunoassay for the detection of hepatitis C virus core antigen in human serum or plasma. JMed Virol 2006;78:1436-40. **B, II**

45. Ravera G, Bottaro LC, Franceschini M, Morando A, De PM, Zare M et al. Reliability and diagnostic use of a test for the search of the hepatitis C virus Ag (AgHCV). Hepatogastroenterology 2006;53:753-6. **B, II**

46. Tobler LH, Stramer SL, Lee SR, Baggett D, Wright D, Hirschkorn D et al. Performance of ORTHO HCV core antigen and trak-C assays for detection of viraemia in pre-seroconversion plasma and whole blood donors. Vox Sang 2005;89:201-7. **B, II**

47. Chakravarti A, Chauhan MS, Dogra G, Banerjee S. Hepatitis C virus core antigen assay: can we think beyond convention in resource limited settings? BrazJInfectDis 2013;17:369-74. **B, II**

48. Gu S, Liu J, Zhang H, Gu B, Lai H, Zhou H et al. Core antigen tests for hepatitis C virus: a meta-analysis. MolBiol Rep 2012;39:8197-208. **B, I**

49. Kamili S, Drobeniuc J, Araujo AC, Hayden TM. Laboratory diagnostics for hepatitis C virus infection. ClinInfectDis 2012;55 Suppl 1:S43-S8. **B, IV**

50. Kuo YH, Chang KC, Wang JH, Tsai PS, Hung SF, Hung CH et al. Is hepatitis C virus core antigen an adequate marker for community screening? JClinMicrobiol 2012;50:1989-93. **B, II**

51. Ottiger C, Gygli N, Huber AR. Detection limit of architect hepatitis C core antigen assay in correlation with HCV RNA, and renewed confirmation algorithm for reactive anti-HCV samples. JClinVirol 2013;58:535-40. **B, II**

52. Medici MC, Furlini G, Rodella A, Fuertes A, Monachetti A, Calderaro A et al. Hepatitis C virus core antigen: analytical performances, correlation with viremia and potential applications of a quantitative, automated immunoassay. JClinVirol 2011;51:264-9. **B, II**

53. Polywka S, Pembrey L, Tovo PA, Newell ML. Accuracy of HCV-RNA PCR tests for diagnosis or exclusion of vertically acquired HCV infection. J Med Virol 2006;78:305-10. **B, II**

54. England K, Pembrey L, Tovo PA, Newell ML. Excluding hepatitis C virus (HCV) infection by serology in young infants of HCV-infected mothers. Acta Paediatr 2005;94:444-50. **C, II**

55. European Association for Study of L. EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol 2015;63:199-236. **A, VI**

56. Public Health England. Laboratory Reporting to Public Health England: A Guide for Diagnostic Laboratories. Public Health England 2016. 1-29. **A, VI**

57. Department of Health. Health Protection Legislation (England) Guidance. 1-112. 2010. **A, VI**

58. Scottish Government. Public Health (Scotland) Act. 2008. **A, VI**

59. Scottish Government. Public Health etc. (Scotland) Act 2008. Implementation of Part 2: Notifiable Diseases, Organisms and Health Risk States. 2009. **A, VI**

60. The Welsh Assembly Government. Health Protection Legislation (Wales) Guidance. 2010. **A, VI**

61. Home Office. Public Health Act (Northern Ireland) 1967 Chapter 36. 1967. **A, VI**