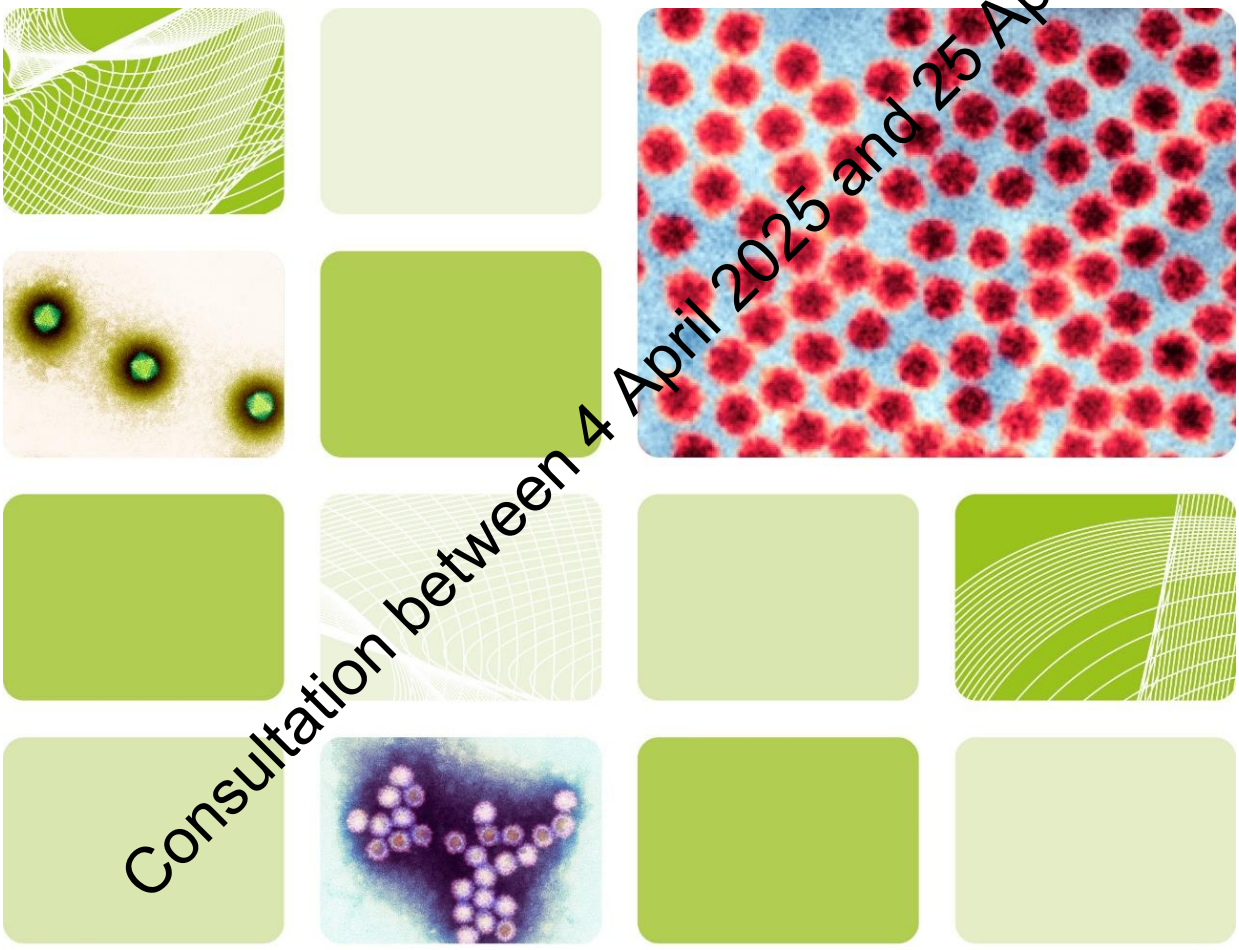
UK Health Security Agency

UK Standards for Microbiology Investigations

Laboratory diagnosis of hepatitis C virus



Consultation between 4 April 2025 and 25 April 2025

Issued by the Standards Unit, Specialised Microbiology and Laboratories, UKHSA

Acknowledgments

UK Standards for Microbiology Investigations (UK SMIs) are developed under the auspices of UKHSA working in partnership with the partner organisations whose logos are displayed below and listed on the UK SMI website. UK SMIs are developed, reviewed and revised by various working groups which are overseen by a 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.

UK SMIs are produced in association with:

Displayed logos correct as of December 2024.

Contents

Amendment table

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

Any alterations to this document should be controlled in accordance with the local document control process.

Amendment number/date	x/dd.mm.yy
Issue number discarded	
Insert issue number	
Anticipated next review date*	dd.mm.yy
Section(s) involved	**Amendment**

*Reviews can be extended up to 5 years where appropriate

1 General information

View general information related to UK SMIs.

2 Scientific information

View scientific information related to UK SMIs.

3 Scope of document

This UK SMI provides a detailed review of initial and supplemental laboratory-based serological and Nucleic Acid Amplification Tests (NAAT) for the detection and exclusion of Hepatitis C virus (HCV). Refer to UK SMI S 1: Acute infective hepatitis for further information regarding clinical presentations of acute infective hepatitis and associated tests.

This document covers the different types of samples - whole blood, plasma and serum and the various methods of collection including venous and capillary blood sampling and dried blood spot (DBS) collection. It also addresses testing in specific patient groups. In addition, the algorithms aim to assist clinicians and laboratories in their decision making, by providing a framework for testing and the interpretation of results. Reporting criteria for commonly obtained test results are also provided.

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 Quality-related guidance

This UK SMI is intended for use in the laboratory diagnosis of HCV infection within healthcare settings. It is not intended to cover:

- testing of blood prior to organ or blood donation (refer to the SaBTO Guidance on the microbiological safety of human organs, tissues and cells used in transplantation).
- testing methods or strategies commonly used in community testing such as POCT testing, self-sampling, or self-testing.
- testing of specimens other than blood, plasma and serum obtained by venepuncture, such as oral fluid and saliva.
- ongoing monitoring tests used for those with a confirmed diagnosis of HCV.

For the investigation and management of occupational exposure, refer to UKHSA (formerly PHE) and HSE guidelines (2-5).

For blood-borne virus (BBV) testing following dialysis away from base (DAFB), refer to DHSC guidelines (6).

For the management and treatment of Hepatitis C, refer to the EASL recommendations on treatment of hepatitis C and BHIVA guidelines for the management of hepatitis viruses in adults infected with HIV (7,8).

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

Abbreviations

Abbreviation	Definition
HCV	hepatitis C virus
BBV	Blood-borne viruses
DBS	Dried blood spot
POCT	Point of care testing
PWID	People who inject drugs
NAAT	Nucleic acid amplification test
DAAs	Direct-acting antivirals

Definitions

For all antibody and NAAT testing, the following definitions apply:

Reporting stage for serology

These terms are used for final or preliminary reports.

Reactive – Report-stage confirmed reactive result.

Not reactive – Report-stage not reactive result.

Equivocal – Reactive result that cannot be confirmed.

Reporting stage for molecular assays

These terms are used for final or preliminary reports.

Scenarios	Qualitative result	Quantitative actual value	Quantitative Log10 of actual value
1	Detected	Actual value	Calculated log from actual value of the assay
2	Detected	Below the lower limit of detection of the assay	Calculated to the lower limit of the assay value
3	Detected	Above the upper limit of detection of the assay	Calculated to the upper limit of the assay value
4	Not detected	Below the lower limit of detection of the assay	Calculated to the lower limit of the assay value
5	Inhibitory	Not applicable	Not applicable
6	Insufficient	Not applicable	Not applicable
7	Invalid	Not applicable	Not applicable

4 Introduction

In the UK, hepatitis C virus infection remains a significant public health concern. The UK government has aligned its national efforts with the WHO's goal of eliminating HCV (and HBV) globally as a public health threat by 2030. In 2016 the UK government committed to the WHO's Global Health Sector Strategy on Viral Hepatitis (GHSS) and in May 2022 adopted the updated 2022-2030 strategy.

Significant progress has been made towards the elimination of HCV across the UK (9-12). Improvements in testing, including the use of point-of-care testing (POCT) in hard-to-reach areas, and opt-out testing programmes in emergency departments along with accessible treatments such as direct-acting antivirals (DAAs) are key drivers in hepatitis C elimination efforts (13-17). These advancements, if continued at the current rate, are predicted to achieve an 80% reduction in chronic HCV by 2030 compared to 2015 as the baseline (18,19).

4.1 Hepatitis C Virus (HCV)

Hepatitis C virus (HCV) is a blood-borne virus of the *Flaviviridae* family and a member of the Hepacivirus genus (20-22). It is a single stranded, positive sense enveloped RNA virus with a genome of approximately 9600 bases (20). There are eight genotypes of HCV (1 to 8) to date, each with multiple subtypes that are distributed worldwide (23-26). The most common genotypes in the UK are HCV genotypes 1 and 3 (27,28).

4.2 Stages of HCV infection

New acute HCV infections are usually asymptomatic (85 - 90% cases) and therefore acute infection is rarely diagnosed. Around 30% (15 - 45%) of infected persons spontaneously clear the virus within 6 months of infection without any treatment (21,29-31). Spontaneous viral clearance is rare beyond 4 to 6 months of infection, therefore HCV RNA detectable for longer than 6 months is defined as Chronic HCV infection (21,29-31). Levels of HCV RNA remain relatively stable over time in chronically infected patients.

HCV reinfection is defined as the reappearance of HCV RNA at least 6 months after a sustained viral clearance (SVR) with a different HCV genotype or strain (7).

4.3 HCV diagnostic approaches

Routine laboratory diagnosis of established infection is commonly based upon the detection of antibodies for the virus using serological methods, followed by the detection of the virus using HCV RNA NAAT on the same sample to confirm viraemia (20,32-37).

The approach to HCV infection diagnosis and monitoring is tailored to individual patient circumstances, considering factors such as immune status, pregnancy, and risk behaviours. In the UK, since the introduction of screening of blood and blood-derived products, HCV is most common in people who inject drugs (PWID), with 10% and 70% antibody prevalence for those injecting for 2 years and 15 years respectively (18,19,38). This is especially the case within PWID populations in prison or those experiencing homelessness.

Antibodies to HCV are detected using first line Enzyme Linked Immunosorbent Assays (ELISA), Enzyme Immunoassays (EIA), Chemiluminescent Immunoassays (CLIA) or in the past with second line immunoblots (39). Assays have been developed to detect antibodies to an increasing range of viral proteins, from second generation (core proteins and non-structural proteins 3 and 4), third generation (also with non-structural protein 5) and now fourth generation (also with HCV capsid antigen) (35,40).

The diagnosis of recently acquired or chronic HCV infection is based on the detection of HCV RNA by a qualitative or both qualitative and quantitative molecular methods (7). An HCV RNA assay with target sensitivity level of 15 IU/mL or lower is recommended (7). Reflex NAAT testing is recommended to streamline the HCV care pathway (41-43). Molecular methods are recommended over HCV core antigen testing for confirmation due to the higher rates of false negatives and lower sensitivity compared to HCV RNA NAAT (44-46). Therefore, hepatitis C core antigen testing will not be discussed further within this document.

4.4 Types of HCV diagnostic tests and markers of infection

- **HCV RNA** is a marker of replicating virus in peripheral blood. HCV RNA may be detected as early as 1 to 3 weeks after initial infection, approximately 1 month before the appearance of total HCV antibodies.
- **Immunoglobulin G (IgG) antibodies** emerge after IgM antibodies and persist throughout the course of HCV infection. Most assays are designed to detect IgG which become detectable at approximately 8 to 12 weeks following exposure (47).

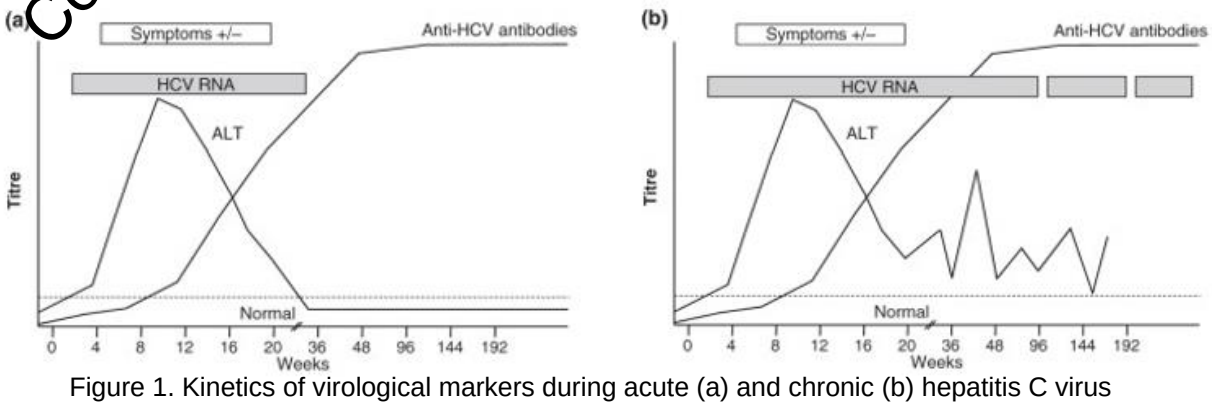


Figure 1. Kinetics of virological markers during acute (a) and chronic (b) hepatitis C virus (HCV) infection (1).

5 Technical information and limitations

5.1 Sample types and collection methods:

Dried Blood Spots (DBS) and capillary blood samples have been adapted for use in HCV serology and qualitative NAAT for HCV diagnosis. (48-51). These samples are useful in identifying individuals with chronic HCV but may have a lower sensitivity for monitoring therapeutic response (48,52). Therefore, appropriate local validation and/or verification is required prior to their use to ensure accuracy and effectiveness in both diagnostic and monitoring context.

5.2 Immunoassays:

HCV antibody tests:

The limitations of antibody tests primarily arise when they are used alone, particularly in low-risk groups or in immunocompromised individuals. In populations with low exposure risk, a low-level positive result may be reflective of a false positive (53). In addition, antibodies can take a long time to develop, typically around 5 to 12 weeks in the immunocompetent and several months in immunocompromised leading to delayed detection. This may limit the clinical utility of antibody tests during the window period, and in immunocompromised patients due to delayed or absent seroconversion (53,54). In addition, antibody tests cannot distinguish between historical HCV infection with sustained viral clearance and reinfection with a different HCV genotype.

Individuals who are immunocompromised or with risk factors should undergo HCV RNA detection with PCR (53-55).

5.3 Molecular methods

HCV RNA is a marker of active viral replication, but low-level results should be interpreted with caution as they may have various causes including intermittent viraemia, assay variability and antiviral treatment response. Laboratories should provide detailed quantification for more informed clinical interpretation. When low-level positivity is observed, careful evaluation is required with further testing or clinical correlation as appropriate.

In addition, when samples with low viral load are diluted to bring them within the assay's quantifiable range, there is a risk that viral concentration could either fall below the detection threshold or be at the lower limit of detection. For example, a negative HCV RNA after a 2-fold dilution may suggest that the original viral load was too low to be detected after dilution, making current infection extremely unlikely. Reporting the dilution factor helps clinicians make a more informed decision, particularly in low-level positive results or low viral loads.

NAAT Inhibition:

It has been recognised that samples may contain substances that can inhibit amplification, potentially causing false negative results (33). It is recommended to use an inhibition control in NAAT testing (1). Internal and cellular controls exist within most commercial kits. Many NAATs are able to remove inhibitory substances during the nucleic acid extraction process. In duplex or multiplex assays, where several targets may be detected, competitive inhibition may be observed. The test manufacturers' instructions should be followed as they may contain a list of substances which have been identified as inhibitory through verification and validation. The laboratory may consider regular monitoring of inhibition levels and positive rates.

Contamination:

The risk of contamination should always be considered when using NAAT.

See also UK SMI Q 4 Good laboratory practice when performing molecular amplification assays.

6 Safety considerations

The section covers specific safety considerations related to this UK SMI and should be read in conjunction with the general safety considerations (56-74).

6.1 Specimen collection, transport, and storage

Use aseptic technique to collect blood.

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.

6.2 Specimen handling and processing

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

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.

7 Methodology

7.1 Pre-testing considerations

WHO recommends that all adults have access to and be offered HCV testing with linkage to prevention, care and treatment services with more focused testing for individuals at increased risk of infection (21). Additionally, in settings where the general population has an HCV antibody seroprevalence of ≥ 2% or ≥ 5% (21). WHO also recommends blood donor screening, as well as focused or targeted testing of specific high-risk groups, including migrants from endemic regions, health-care workers, people who inject drugs (PWID), people in prisons and other closed settings, men who have sex with men (MSM), sex workers and HIV-infected persons (21).

Targeted and more frequent hepatitis C screening in people who are at increased risk of infection is also strongly recommended by UK bodies such as UKHSA, British HIV Association, British Association of Sexual Health and HIV, and National Institute for Health and Care Excellence to address the need to improve rates of earlier diagnosis (8,18,21,36).

Specific groups are usually routinely screened for HCV by specialist service providers. These include blood, organ or tissue donors, end-stage kidney disease patients and healthcare workers following occupational exposure.

It should be noted that routine testing of pregnant women for HCV infection is currently not recommended. However, pregnant women at increased risk of infection should be tested.

7.1.1 Specimen type

Whole blood, serum or plasma DBS or finger capillary

Note: Venous blood is the preferred specimen for hepatitis C virus testing. However, alternative sample types can also be used. DBS or finger capillary samples can be used in HCV serology and qualitative NAAT for HCV diagnosis.

Use of specific sample types in individual assays is subject to local verification and validation requirements, alongside the manufacturer's instructions.

7.1.2 Specimen collection and processing:

For safety considerations refer to Section 6.

Venous blood is the preferred specimen for HCV testing. DBS and capillary blood samples are increasingly employed in hard-to-access populations such as in prisons and in people who inject drugs (PWID).

Use of specific sample types in individual assays is subject to local verification and validation requirements, alongside the manufacturer's instructions.

Specimens collected in EDTA, or serum separator tubes are generally acceptable for testing. Please refer to manufacturer instructions for specimen acceptability.

Providing adequate sample volume is essential for maintaining test sensitivity and accuracy. If a sub-optimal volume is provided (perhaps due to dilution) this must be reported, and a repeat sample requested.

Refer to local laboratory protocols or the manufacturer's instructions for specific requirements on serum or plasma separation for NAAT.

7.1.3 Specimen transport, storage, and retention

For safety considerations refer to Section 6.

Specimens should be transported and processed as soon as possible (75). If processing is delayed, refrigeration is preferable to storage at ambient temperature (75).

Note: Specimens for NAAT can be stored long-term at - 20° or - 70°C to minimise RNA loss (76).

Samples should be retained in accordance with The Royal College of Pathologists guidelines 'The retention and storage of pathological records and specimens' (73).

7.1.4 Test selection:

The choice of test can be influenced by risk factors.

Please note that HCV RNA NAAT is recommended as the initial test in certain patient populations or situations to avoid missing cases of HCV infections. This ensures early detection and appropriate management.

Immunocompetent people:

The initial screening assay should be a 3rd or 4th generation antibody assay which if positive should be followed by a confirmatory HCV RNA NAAT. People at risk of acute HCV infection or HCV reinfection – screen using HCV RNA NAAT. There is no need for second antibody assay because it is of very little clinical utility.

Immunocompromised people:

Screen using HCV RNA NAAT.

For immunosuppression definitions, refer to UKHSA guidelines on post exposure prophylaxis for varicella or shingles.

Pregnant women and infected babies:

Pregnant women who are at increased risk for hepatitis C virus infection should be tested at their prenatal visits by testing for HCV antibodies. If the initial results in pregnant women with on-going risk factors for hepatitis C virus infection are negative, this should be repeated later in the third trimester (77,78). It should be noted that routine testing of pregnant women for HCV infection is currently not recommended (79).

Mothers with evidence of hepatitis C virus antibodies who are stably HCV RNA negative are highly unlikely to transmit HCV to the baby (80-82). Babies born from HCV RNA NAAT negative, HCV antibody positive mothers do not require routine testing (83).

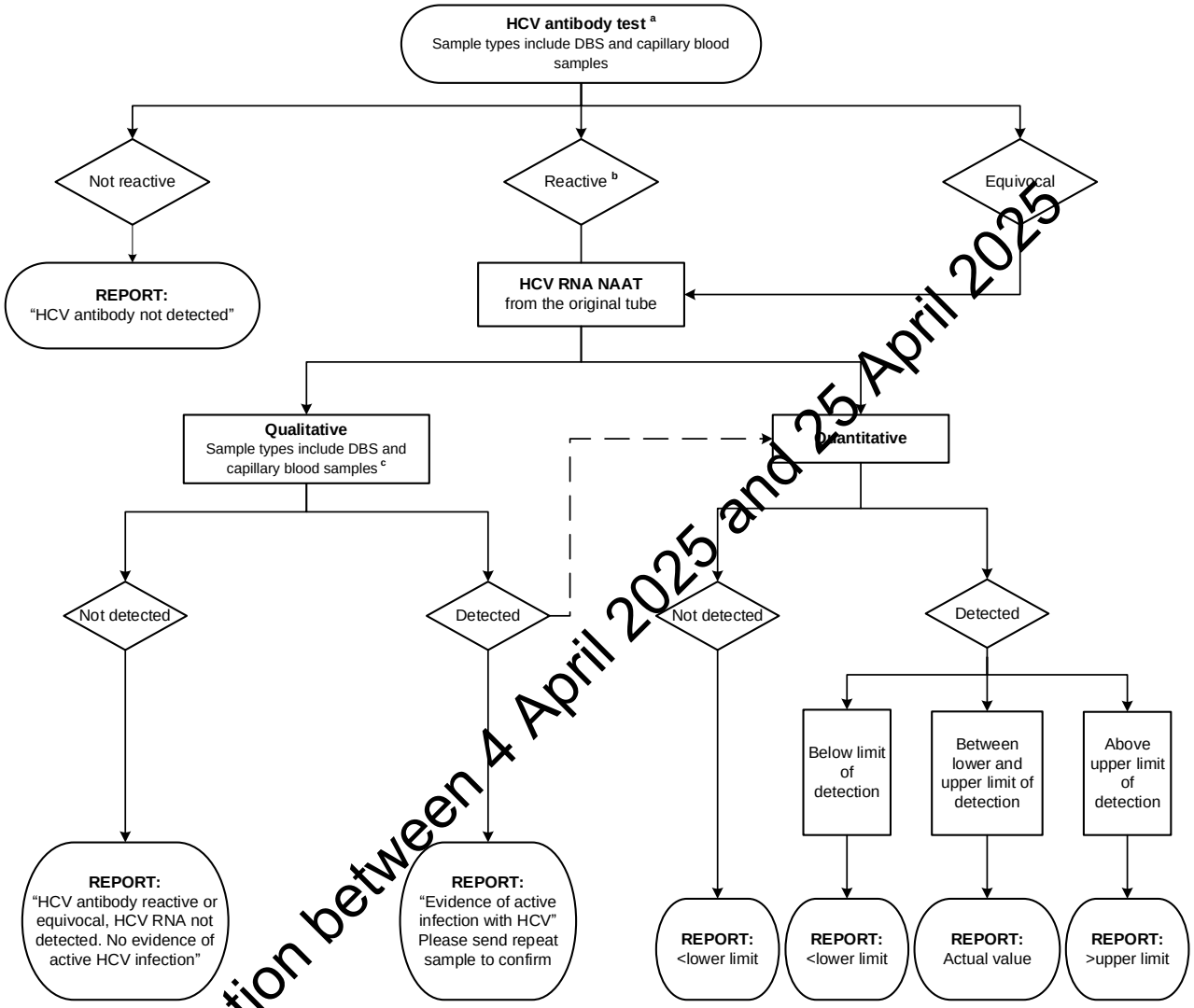
For women who have acquired infection during pregnancy, but have cleared viraemia, the baby should be followed up as described in algorithm 7.3. It should also be noted that consideration should be given to investigate previous pregnancies or partner of current HCV positive mothers.

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 algorithm 7.3 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 (81).

A negative HCV RNA NAAT result in babies may reflect resolution of infection (>25% resolved), fluctuating RNA level or a lab error. Therefore, an antibody test should be performed between 12 - 18 months (84,85). Please note that other guidelines do not always advocate early NAAT testing in children (83).

Infants infected with HCV should be monitored and assessed clinically every 6 - 12 months to identify any risks of progressive liver fibrosis during childhood (83,86).

7.2 Investigation of hepatitis C infection by HCV antibody testing confirmed by HCV RNA NAAT (7,33,37,87)



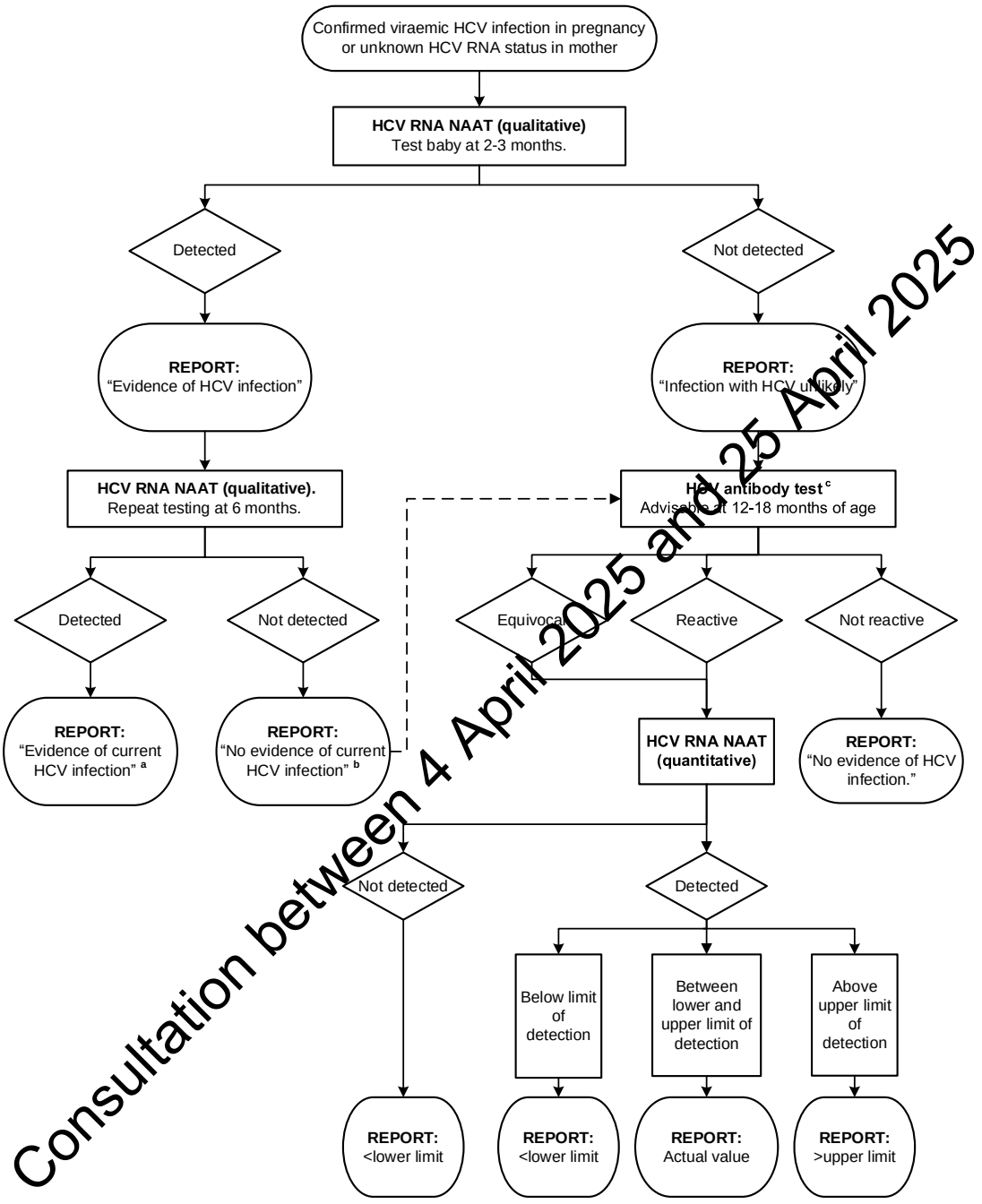
Footnotes:

a) Screening directly with HCV RNA NAAT is required for certain patient groups, particularly those who are immunocompromised or when the risk of recent or ongoing infection is high, as NAAT is more reliable in these cases than HCV antibody testing.

b) Report at this stage as an interim report if additional testing will be delayed and the result may have immediate significance for patient management; suggested wording "Initial HCV antibody reactive. Hepatitis C RNA result to follow".

c) Follow up with quantitative HCV RNA NAAT is recommended for both DBS and capillary blood samples to assess viral load and guide treatment decision.

7.3 Mother-to-child transmission of hepatitis C infection (88-90)



Footnotes:

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

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

c) If antigen/antibody assays are to be used, they should be carefully assessed, and antigen negative results followed by a NAAT test. **Note:** If HCV antigen only assays are used, ensure that NAAT test is performed.

7.4 Interpreting and reporting laboratory results

The final result should be able to distinguish active HCV infection from resolved infection using a combination of antibody and NAAT tests.

It is recommended that HCV test reports include the dilution factor to aid in the interpretation of low-positive results and support clinical decision-making.

Following an initial (first sample) positive result, it is best practice to request a repeat sample.

Table 1. Investigation of hepatitis C virus infection by HCV antibody testing confirmed by NAAT.

	1st Assay	2nd Assay	Interpretative comments	Notes
	HCV Ab	**HCV NAAT**		
1	Not reactive	Not tested	HCV antibody not detected.	In the case of suspected acute hepatitis C or in immunocompromised patients, HCV RNA testing should be part of the initial evaluation.
2	Not reactive	RNA Detected [quantitative value as appropriate]	Evidence of active HCV infection. Advise referral to an appropriate specialist for further assessment/treatment. Hepatitis A and B vaccine recommended if appropriate.	Indicates either acute HCV infection or possibly a chronic infection in an immunocompromised patient. Please ensure hepatitis A and B vaccination status is known and vaccination given if needed. Consider requesting HCV genotyping and other BBV testing unless already performed.

	1st Assay	2nd Assay	Interpretative comments	Notes
	HCV Ab	**HCV NAAT**		
3	Reactive or Equivocal	RNA detected [quantitative value as appropriate]	Evidence of active HCV infection. Advise referral to an appropriate specialist for further assessment/treatment. Hepatitis A and B vaccine recommended if appropriate.	HCV antibody detected in the presence of HCV RNA allows one to infer with confidence that the HCV antibody reaction is a true positive. Please ensure hepatitis A and B status is known and vaccination given if needed. Consider requesting HCV genotyping and other BBV testing unless already performed. If initial antibody assay is equivocal and RNA detected, this may be recent infection. Consider review of clinical and results history, that is, can seroconversion to HCV antibodies be documented.
4	Reactive or Equivocal	RNA not detected	No evidence of active HCV infection.	HCV antibody positive result may indicate past HCV infection. EASL 2020 recommend that “Anti-HCV antibody-positive, HCV RNA-negative or HCV core antigen-negative patients with suspected *de novo* recently acquired HCV infection should be retested for HCV RNA 12 and 24 weeks later to confirm definitive clearance” (7).

Table 2. Investigation of hepatitis C virus infection in babies of women confirmed to have HCV infection during pregnancy using both NAAT and HCV antibody test.

	HCV NAAT at 2-3 mths	HCV NAAT at 6 mths	Interpretative comments	Notes
1	RNA detected [quantitative value as appropriate]	RNA detected [quantitative value as appropriate]	**At 2-3 months,** Evidence of HCV infection. Please send EDTA plasma for a repeat HCV NAAT at 6 months. Advise referral to Paediatric Hepatologist or Paediatric Infectious Disease Specialist for further assessment/treatment. **At 6 months,** Evidence of current HCV infection. Advise referral to Paediatric Hepatologist or Paediatric Infectious Disease Specialist for further assessment/treatment. Hepatitis A virus and B virus vaccine recommended if appropriate.	In the case of suspected acute hepatitis C virus or in immunocompromised patients, HCV RNA testing should be part of the initial evaluation. Please ensure hepatitis B virus vaccination status is known and vaccination given if needed. Consider requesting HCV genotyping and other BBV testing unless already performed (79).

2	RNA detected [quantitative value as appropriate]	RNA not detected [quantitative value as appropriate]	**At 2-3 months,** Evidence of HCV infection. Please send EDTA plasma for a repeat HCV NAAT at 6 months. Advise referral to Paediatric Hepatologist or Paediatric Infectious Disease Specialist for further assessment/treatment. **At 6 months,** No evidence of current HCV infection. Request repeat sample for retesting. Advise HCV antibody testing at 12-18 months to confirm clearance of maternal antibody.	
3	RNA not detected	Not tested	**At 2- 3 months,** Infection with HCV unlikely. Advise HCV antibody testing at 12-18 months.	

Following a negative HCV RNA result at 2-3mths of age, testing for HCV antibodies using HCV antibody test at 12-18 months			
	HCV antibody Test at 12-18mths	**Interpretative comments**	**Notes**
4	Detected	No evidence of active HCV infection. Please send EDTA plasma for a repeat HCV NAAT to confirm evidence of infection.	HCV antibody positive result may indicate past HCV infection. EASL 2020 recommend that “Anti-HCV antibody-positive, HCV RNA-negative or HCV core antigen-negative patients with suspected *de novo* recently acquired HCV infection should be retested for HCV RNA 12 and 24 weeks later to confirm definitive clearance” (7). 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 (7).
5	Not detected	No evidence of HCV infection.	

Confirmation of HCV antibody test performed at 12-18 months using HCV RNA NAAT			
	HCV NAAT at 12-18 mths	**Interpretative comments**	**Notes**
6	RNA detected [quantitative value as appropriate]	Evidence of HCV infection. Please send EDTA plasma for a repeat HCV NAAT to confirm evidence of infection. Advise referral to Paediatric Hepatologist or Paediatric Infectious Disease Specialist for further assessment/treatment.	
7	RNA not detected	No evidence of HCV infection. Likely to be resolved infection or maternal antibody if less than 18 months. Please repeat HCV antibody test after 18 months.	

8 Public health management

All confirmed cases of HCV infections should be reported to local public health authorities.

For information regarding notification refer to:

https://www.gov.uk/government/collections/notifications-of-infectious-diseases-noids

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

In addition to reporting new positive diagnosis to UKHSA 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. See link: https://www.gov.uk/guidance/bloodborne-viruses-in-healthcare-workers-report-exposures-and-reduce-risks

For the final report published on the Infected Blood Inquiry in May 2024 refer to the following link: Reports | Infected Blood Inquiry

9 Public health responsibilities of diagnostic laboratories

Diagnostic laboratories have public health responsibility as part of their duties. Amongst these are additional local testing, or referral to further characterise the organism as required, primarily for public health purposes e.g. routine cryptosporidium detection; serotyping or microbial subtyping; and a duty to refer appropriate specimens and isolates of public health importance to a reference laboratory.

Diagnostic laboratory outputs inform public health intervention, and surveillance data is required to develop policy and guidance forming an essential component of healthcare. It is recognised that additional testing and referral of samples may entail some costs that has to be borne by the laboratory but in certain jurisdictions these costs are covered centrally.

Diagnostic laboratories should be mindful of the impact of laboratory investigations on public health and consider requests from the reference laboratories for specimen referral or enhanced information.

References

An explanation of the reference assessment used is available in the scientific information section on the UK SMI website.

1. Chevaliez S. Virological tools to diagnose and monitor hepatitis C virus infection. Clinical Microbiology and Infection 2011: volume 17, issue 2, pages 116-21. https://doi.org/10.1111/j.1469-0691.2010.03418.x

2. Ramsay ME. Guidance on the investigation and management of occupational exposure to hepatitis C. Commun Dis Public Health 1999: volume 2, issue 4, pages 258-62.

3. Health and Safety Executive. 'Blood-borne viruses in the workplace: Guidance for employers and employees'.'last updated' 2024 '(viewed on' https://www.hse.gov.uk/biosafety/blood-borne-viruses/index.htm

4. UK Health Security Agency. Integrated guidance on health clearance of healthcare workers and the management of healthcare workers living with bloodborne viruses (hepatitis B, hepatitis C and HIV). 2024.

5. Public Health England. Hepatitis C clearance for healthcare workers evaluation report 2020.

6. Department of Health. Good Practice Guidelines for Renal Dialysis/Transplantation Units, Prevention and Control of Blood-borne Virus Infection - Addendum, Guidelines for dialysis away from base (DAFB). pages 1-17. October 2010.

7. European Association for Study of Liver. EASL recommendations on treatment of hepatitis C: Final update of the series(☆). J Hepatol 2020: volume 73, issue 5, pages 1170-218. 10.1016/j.jhep.2020.08.018

8. Wilkins E and others. British HIV Association guidelines for the management of hepatitis viruses in adults infected with HIV 2013. HIV Med 2013: volume 14 Suppl 4, pages 1-71. 10.1111/hiv.12106

9. UK Health Security Agency (UKHSA). Hepatitis C in England 2024: working to eliminate hepatitis C as a public health problem. Data to end of 2023 2025.

10. Public Health Scotland. Surveillance of hepatitis C in Scotland, 2024 update: progress on elimination of hepatitis C as a major public health concern 2025.

11. Public Health Wales Health protection Division. Trends in the prevention, diagnosis and treatment of blood borne viruses in Wales, Annual report 2024 (Data to end 2023). 2024.

12. Centre H-HPS. Epidemiology of hepatitis C in Ireland: Trends to Q1 2024 2024.

13. UK Health Security Agency (UKHSA). Emergency department bloodborne virus opt-out testing: 12-month interim report 2023 2023.

14. Byrne CJ and others. Mixed-methods evaluation of point-of-care hepatitis C virus RNA testing in a Scottish prison. BMJ Open 2023: volume 13, issue 4, pages e068604. 10.1136/bmjopen-2022-068604

15. Witkowska McConnell W and others. Paper microfluidic implementation of loop mediated isothermal amplification for early diagnosis of hepatitis C virus. Nature Communications 2021: volume 12, issue 1, pages 6994. 10.1038/s41467-021-27076-z

16. Radley A and others. A systematic review and meta-analysis of community and primary-care-based hepatitis C testing and treatment services that employ direct acting antiviral drug treatments. BMC Health Serv Res 2019: volume 19, issue 1, pages 765. 10.1186/s12913-019-4635-7

17. Mohamed Z and others. Time matters: Point of care screening and streamlined linkage to care dramatically improves hepatitis C treatment uptake in prisoners in England. Int J Drug Policy 2020: volume 75, pages 102608. 10.1016/j.drugpo.2019.102608

18. UK Health Security Agency. Hepatitis C in the UK 2023 report. 2023.

19. UK Health Security Agency. Hepatitis C in England 2023 report. 2023.

20. Jardim AC and others. Quasispecies of hepatitis C virus genotype 1 and treatment outcome with Peginterferon and Ribavirin. InfectGenetEvol 2009: volume 9, issue 4, pages 690-98.

21. World Health Organization. Hepatitis C 2024.

22. International Committee on Taxonomy of Viruses. Virus Taxonomy: 2018a Release. 2018.

23. Borgia SM and others. Identification of a Novel Hepatitis C Virus Genotype From Punjab, India: Expanding Classification of Hepatitis C Virus Into 8 Genotypes. The Journal of Infectious Diseases 2018: volume 218, issue 11, pages 1722-9. 10.1093/infdis/jiy401

24. Mbisa JL and others. Identification of 2 Novel Subtypes of Hepatitis C Virus Genotype 8 and a Potential New Genotype Successfully Treated With Direct Acting Antivirals. The Journal of Infectious Diseases 2024. 10.1093/infdis/jiae253

25. Murphy DG and others. Hepatitis C virus genotype 7, a new genotype originating from central Africa. J Clin Microbiol 2015: volume 53, issue 3, pages 967-72. 10.1128/jcm.02831-14

26. Smith DB and others. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assignment web resource. Hepatology 2014: volume 59, issue 1, pages 318-27. 10.1002/hep.26744

27. Buchanan R. NKL. Hepatitis C. Medicine (United Kingdom) 43 (10) (pp 607-612), 2015 Date of Publication: 01 Oct 2015 2015.

28. England PH. Hepatitis C: information for GPs 2020.

29. NHS England. Hepatitis C Clinical Network Specification 2023.

30. Ayoub HH and others. Hepatitis C virus infection spontaneous clearance: Has it been underestimated? International Journal of Infectious Diseases 2018: volume 75, pages 60-6. https://doi.org/10.1016/j.ijid.2018.07.013

31. Micallef JM and others. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. Journal of Viral Hepatitis 2006: volume 13, issue 1, pages 34-41. https://doi.org/10.1111/j.1365-2893.2005.00651.x

32. Strader DB and others. Diagnosis, management, and treatment of hepatitis C. Hepatology 2004: volume 39, issue 4, pages 1147-71.

33. Cloherty G and others. Role of Serologic and Molecular Diagnostic Assays in Identification and Management of Hepatitis C Virus Infection. J Clin Microbiol 2016: volume 54, issue 2, pages 265-73. 10.1128/JCM.02407-15

34. Marwaha N, Sachdev S. Current testing strategies for hepatitis C virus infection in blood donors and the way forward. World J Gastroenterol 2014: volume 20, issue 11, pages 2948-54. 10.3748/wjg.v20.i11.2948

35. Li HC, Lo SY. Hepatitis C virus: Virology, diagnosis and treatment. World J Hepatol 2015: volume 7, issue 10, pages 1377-89. 10.4254/wjh.v7.i10.1377

36. Brook G and others. United Kingdom National Guideline on the Management of the viral hepatitides A, B and C 2015. Int J STD AIDS 2016: volume 27, issue 7, pages 501-25. 10.1177/0956462415624250

37. Munang M and others. Outcomes and costs of single-step hepatitis C testing in primary care, Birmingham, United Kingdom. Public Health 2019: volume 166, pages 40-4. 10.1016/j.puhe.2018.09.024

38. Craine N and others. Hepatitis C testing injecting risk behaviour: the results of a uk based pilot study. International Journal of Drug Policy 2004: volume 15, pages 115-22.

39. Feng S and others. Evaluation of the Novel HISCL Chemiluminescence Enzyme Immunoassay for Laboratory Screening of Hepatitis C Virus. Clin

Vaccine Immunol 2016: volume 23, issue 7, pages 652-4. 10.1128/cvi.00078-16

40. Lauer GM, Walker BD. Hepatitis C virus infection. NEnglJMed 2001: volume 345, issue 1, pages 41-52.

41. McGibbon E and others. Half a diagnosis: gap in confirming infection among hepatitis C antibody-positive patients. Am J Med 2013: volume 126, issue 8, pages 718-22. 10.1016/j.amjmed.2013.01.031

42. Gale HB and others. Comparison of serial Hepatitis C virus detection in samples submitted through serology for reflex confirmation versus samples directly submitted for quantitation. J Clin Microbiol 2011: volume 49, issue 8, pages 3036-9. 10.1128/jcm.00577-11

43. Chapko MK and others. Cost-effectiveness of strategies for testing current hepatitis C virus infection. Hepatology 2015: volume 62, issue 5, pages 1396-404. 10.1002/hep.27966

44. Chevaliez S and others. Clinical utility of HCV core antigen detection and quantification in the diagnosis and management of patients with chronic hepatitis C receiving an all-oral, interferon-free regimen. Antivir Ther 2018: volume 23, issue 3, pages 211-7. 10.3851/imp3042

45. Heidrich B and others. Hepatitis C virus core antigen testing in liver and kidney transplant recipients. J Viral Hepat 2014: volume 21, issue 11, pages 769-79. 10.1111/jvh.12204

46. Chevaliez S and others. Clinical utility of hepatitis C virus core antigen quantification in patients with chronic hepatitis C. Journal of Clinical Virology 2014: volume 61, issue 1, pages 145-8. https://doi.org/10.1016/j.jcv.2014.05.014

47. Chevaliez S, Pawlotsky JM. Diagnosis and management of chronic viral hepatitis: antigens, antibodies and viral genomes. BestPractResClinGastroenterol 2008: volume 22, issue 6, pages 1031-48.

48. Mcmillan G and others. Evaluating the sensitivity and specificity of dried blood spots for serological testing of HIV, syphilis, hepatitis B and C Elecsys assays on the Roche Cobas system. Pathology 2023: volume 55, issue 7, pages 1000-3. https://doi.org/10.1016/j.pathol.2023.06.010

49. Villar LM and others. Usefulness of automated assays for detecting hepatitis B and C markers in dried blood spot samples. BMC Research Notes 2019: volume 12, issue 1, pages 523. 10.1186/s13104-019-4547-y

50. Lange B and others. Diagnostic accuracy of serological diagnosis of hepatitis C and B using dried blood spot samples (DBS): two systematic reviews and meta-analyses. BMC Infectious Diseases 2017: volume 17, issue 1, pages 700. 10.1186/s12879-017-2777-y

51. Nilsson SS and others. Dried blood spot: A diagnostic detection method for HBV, HCV and HIV nucleic acid using a single drop of blood. Diagn Microbiol Infect Dis 2025: volume 111, issue 3, pages 116661. https://doi.org/10.1016/j.diagmicrobio.2024.116661

52. Not A and others. Usefulness of dried blood spot samples for monitoring hepatitis C treatment outcome and reinfection among people who inject drugs in a test-and-treat program. Journal of Medical Virology 2023: volume 95, issue 2, pages e28544. https://doi.org/10.1002/jmv.28544

53. Moorman AC and others. Prevalence of false-positive hepatitis C antibody results, National Health and Nutrition Examination Study (NHANES) 2007-2012. J Clin Virol 2017: volume 89, pages 1-4. 10.1016/j.jcv.2017.01.007

54. El-Sherif A and others. High false-negative rate of anti-HCV among Egyptian patients on regular hemodialysis. Hemodialysis International 2012: volume 16, issue 3, pages 420-7. https://doi.org/10.1111/j.1542-4758.2011.00662.x

55. Kowdley KV and others. Hepatitis C virus antibodies in systemic lupus erythematosus. J Clin Gastroenterol 1997: volume 25, issue 2, pages 437-9. 10.1097/00004836-199709000-00008

56. Advisory Committee on Dangerous Pathogens. The Approved List of Biological Agents. Health and Safety Executive 2023. pages 1-39. **++**

57. British Standards Institution (BSI). BS EN12469 - Biotechnology - performance criteria for microbiological safety cabinets 2000. **++**

58. 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. pages 1-14. **++**

59. Centers for Disease Control and Prevention. Guidelines for Safe Work Practices in Human and Animal Medical Diagnostic Laboratories. MMWR Surveill Summ 2012: volume 61, pages 1-102. **+**

60. Department for Transport and others. Transport of infectious substances UN2814, UN2900 and UN3373 Guidance note number 17/2012 (revision 7). 2013. **++**

61. Department of Health. Health Protection Legislation (England) Guidance. pages 1-112. 2010. **++**

62. Health and Safety Executive. Blood-borne viruses in the workplace. Guidance for employers and employees. HSE. 2001. **++**

63. 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. **++**

64. Health and Safety Executive. Risk assessment: A brief guide to controlling risks in the workplace. HSE. 2014. **++**

65. Health and Safety Executive, Advisory Committee on Dangerous Pathogens. Management and operation of microbiological containment laboratories. HSE. 2019. **++**

66. Health Services Advisory Committee. Safe working and the prevention of infection in clinical laboratories and similar facilities. Books. H 2003. **++**

67. Scottish Government. Public Health (Scotland) Act. 2008. **++**

68. UK Health Security Agency (UKHSA). Laboratory reporting to UKHSA: a guide for diagnostic laboratories. UKHSA 2023. pages 1-31. **++**

69. World Health Organization. Guidance on regulations for the transport of infectious substances 2021-2022. WHO. 2021. **++**

70. Home Office. Public Health Act (Northern Ireland) 1967 Chapter 36. 1967. **++**

71. Home Office. Anti-terrorism, Crime and Security Act. 2001. **++**

72. 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. pages 1-37. **++**

73. The Royal College of Pathologists. The retention and storage of pathological records and specimens (5th edition). pages 1-59. 2015. **++**

74. The Welsh Assembly Government. Health Protection Legislation (Wales) Guidance. 2010. **++**

75. 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). Clin Infect Dis 2013: volume 57, pages e22-e121.

76. Baleriola C and others. 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: volume 49, issue 9, pages 3163-7. 10.1128/JCM.02447-10

77. Society for Maternal-Fetal Medicine and others. Hepatitis C in pregnancy: screening, treatment, and management. Am J Obstet Gynecol 2017: volume 217, issue 5, pages B2-B12. 10.1016/j.ajog.2017.07.039

78. National Institute for Health and Care Excellence. Who should I test for hepatitis C? 2022.

79. World Health Organization. Guidelines on hepatitis B and C testing 2017.

80. Resti M and others. 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: volume 317, issue 7156, pages 437-41.

81. Tovo PA and others. Persistence rate and progression of vertically acquired hepatitis C infection. European Paediatric Hepatitis C Virus Infection. JInfectDis 2000: volume 181, issue 2, pages 419-24. JID990852 [pii];10.1086/315264 [doi]

82. Thomas SL and others. 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: volume 27, issue 1, pages 108-17.

83. Scottish Intercollegiate Guidelines Network. SIGN 133: Management of Hepatitis C. 2013.

84. Polywka S and others. Accuracy of HCV-RNA PCR tests for diagnosis or exclusion of vertically acquired HCV infection. J Med Virol 2006: volume 78, issue 2, pages 305-10.

85. England K and others. Excluding hepatitis C virus (HCV) infection by serology in young infants of HCV-infected mothers. Acta Paediatr 2005: volume 94, pages 444-50.

86. Jarasvaraparn C and others. Updated Clinical Guidelines on the Management of Hepatitis C Infection in Children. Pathogens 2024: volume 13, issue 2. 10.3390/pathogens13020180

87. Getchell J and others. Testing for HCV infection: an update of guidance for clinicians and laboratorians. MMWR MorbMortalWklyRep 2013: volume 62, issue 18, pages 362-5. mm6218a5 [pii]

88. Davison SM and others. Perinatal hepatitis C virus infection: diagnosis and management. ArchDisChild 2006: volume 91, issue 9, pages 781-5.

89. Resti M and others. Guidelines for the screening and follow-up of infants born to anti-HCV positive mothers. DigLiver Dis 2003: volume 35, issue 7, pages 453-7.

90. Dunn DT and others. Timing and interpretation of tests for diagnosing perinatally acquired hepatitis C virus infection. PediatrInfectDisJ 2001: volume 20, issue 7, pages 715-6.