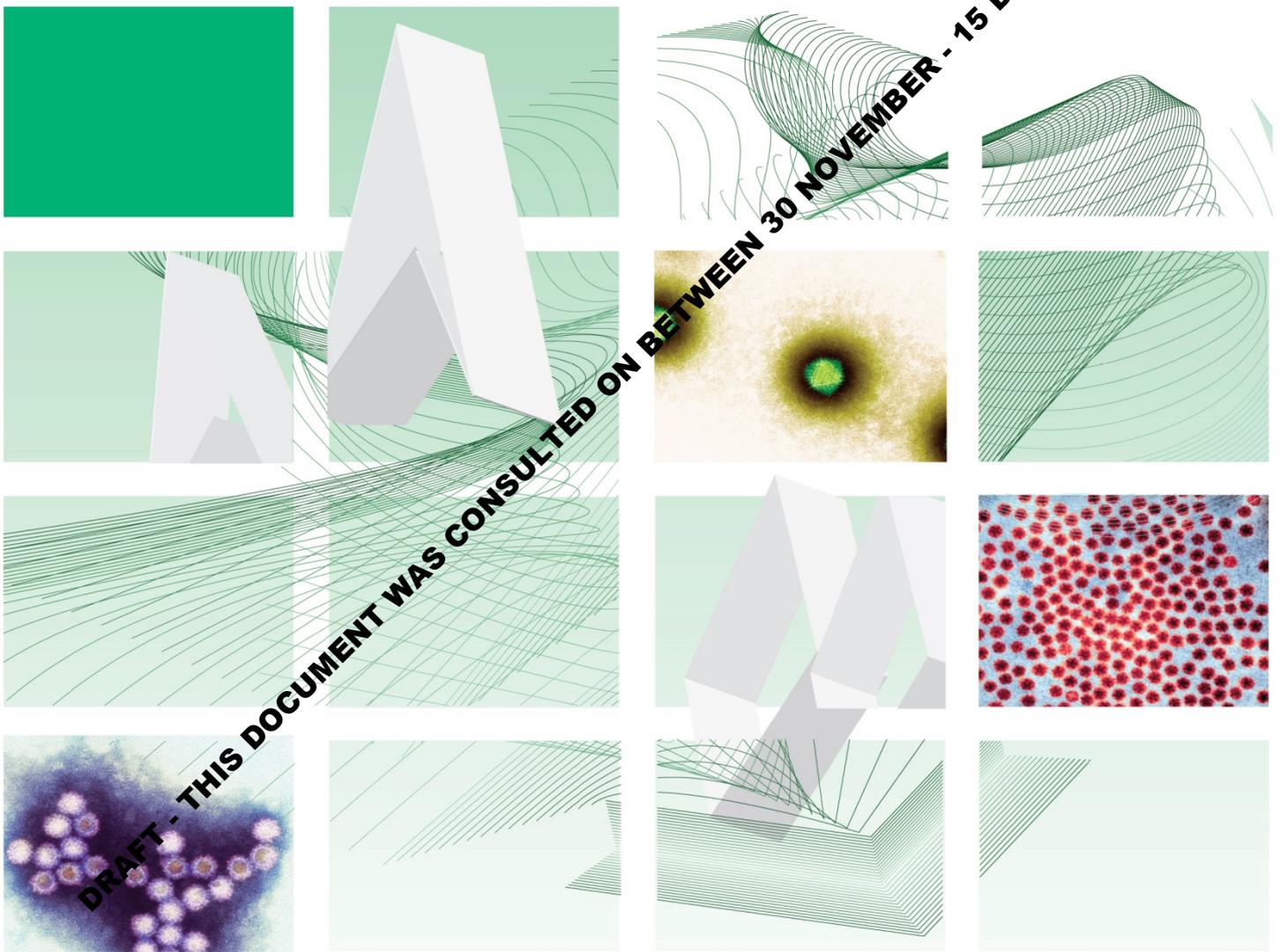




UK Standards for Microbiology Investigations

Screening for hepatitis C infection



"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**."

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.

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PHE publications gateway number: 2616472

UK Standards for Microbiology Investigations are produced in association with:



Logos correct at time of publishing.

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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 number/date	9/dd.mm.yy<tab+enter>
Issue number discarded	6.2
Insert issue number	
Anticipated next review date*	
Section(s) involved	Amendment
Whole document.	<p>Introduction updated to include background information on Hepatitis C virus.</p> <p>Document updated to include sections: Technical limitations, Safety considerations, public health management and report comments.</p> <p>References updated.</p>

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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. Guidance notes cover the clinical background, differential diagnosis, and appropriate investigation of particular clinical conditions. 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/government/uploads/system/uploads/attachment_data/file/54112/uk-standards-for-microbiology-investigations-smi-quality-and-consistency-in-clinical-laboratories.pdf. 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 organisation 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.

UK SMIs are Crown copyright which should be acknowledged where appropriate.

Suggested citation for this document

Public Health England. (YYYY <tab+enter>). Screening for hepatitis C infection. UK Standards for Microbiology Investigations. V 5 Issue. <https://www.gov.uk/uk-standards-for-microbiology-investigations-smi-quality-and-consistency-in-clinical-laboratories>

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Scope of document

Type of specimen

EDTA whole blood, EDTA plasma, serum

This UK SMI covers the screening of blood, plasma and serum samples for hepatitis C (HCV) using HCV antibody EIA screening assays as well as confirmation using Nucleic Acid Amplification Tests (NAAT)/immunoblots and HCV antigen EIA screening assays.

Reflex testing is recommended; HCV RNA NAAT should be performed on the same sample as the original antibody assay. This decreases the turnaround time for referral, benefits patient care and increases cost effectiveness^{1,2}.

Combined antigen/antibody assays may be used; however, further studies are required to determine their relative sensitivities and specificities^{3,4}.

Commercial RNA assays may not be validated for all sample types listed above. Manufacturers' recommendations should be followed and all kits should be validated, verified and deemed fit for purpose prior to use⁵.

For the investigation and management of occupational exposure please refer to PHE and HSE guidelines^{6,7}.

Refer to SaBTO guidance for information regarding screening for HCV in the case of blood and organ donation and transplantation⁸.

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

Abbreviations

Abbreviation	Definition
HCV	hepatitis C virus (complete infectious virion)
HCV Ag	hepatitis C antigen
Anti-HCV HCV Ab	Antibody to HCV

Definition

For all antigen, antibody and 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 virus (HCV) is a blood-borne virus of the *Flaviviridae* family and the only member of the Hepacivirus genus^{9,10}. It is a single-stranded, positive sense enveloped RNA virus with a genome of approximately 9600 bases⁹. According to the World Health Organization (WHO), more than 185 million people worldwide are infected with hepatitis C virus and, of these, 700,000 die every year¹¹. In the UK, 214,000 people are estimated to be living with chronic Hepatitis C¹². There is also an estimated 10 million people worldwide believed to be co-infected with HIV, possibly linked to high-risk traumatic sexual practices and drug use in men who have sex with men (MSM)¹³. Due to the high disease prevalence and the existence of effective (and expensive) medical treatments able to dramatically change the prognosis, early detection programs can potentially prevent the development of serious chronic conditions, improve health, and save resources.

In HCV, the relationship between neutralising antibodies and the control of viraemia is more complex due to the enormous genetic variability of the virus (much greater than the variability seen with HIV), particularly in the E2 envelope glycoprotein region where many antibodies are targeted¹⁴. This variability leads to HCV being regarded as existing in an individual as a ‘quasispecies’, as essentially HCV is likened to a horde of closely-related variants circulating in the one infected host⁹. The window between detection of HCV RNA and antibodies to HCV can be months, with an average of 60 days¹⁵. There are six genotypes of HCV (1-6) with multiple subtypes, although a new genotype has been proposed as genotype 7¹⁶⁻¹⁹. Subtypes are labelled a, b, c and so on in order of their discovery. The HCV genotypes 1, 2, and 3 appear to have a worldwide distribution, their relative prevalence varies from one geographic area to another. The HCV genotype 4 appears to be prevalent in North Africa, Central Africa and the Middle East while genotypes 5 and 6 seem to be confined to South Africa and Hong Kong, respectively. The most common genotypes in the UK are 1 and 3^{20,21}.

Hepatitis C is a liver infection caused by hepatitis C virus. Its main complications are cirrhosis and liver cancer. Transmission of hepatitis C virus is through contact with blood or blood derived products. Therefore, the main risk factors are contaminated blood supply, injecting drug use, unsafe therapeutic needle use, or medical procedures²². There is a clear divide between the modes of transmission depending on whether in the developed or developing world²². In the developed world, the primary mode of transmission is through injecting drug use, particularly since blood and blood derived products are so thoroughly screened for HCV²³. In the UK, data shows that HCV remains common in the injecting drug use population, with 10% and 70% antibody positivity prevalence for those injecting for 2 years and 15 years respectively²⁴. In developing countries, where supplies of sterile syringes are short or non-existent, unsafe therapeutic needle use is much higher than in the developed world, where a person may receive multiple injections adding a cumulative risk of acquiring HCV²². Other transmission sources are body modification (tattooing and

body piercing), occupational, perinatal and sexual exposures, but these occur very infrequently²⁵. Prevalence of HCV infection is higher in persons having received blood transfusions, tissue/organ transplants or blood products such as haemophiliacs, prior to 1992 before sensitive screening tests were available²⁶.

HCV is often asymptomatic (85-90% of cases) and therefore is rarely diagnosed during the acute phase of infection^{16,23,27}. Symptoms may include jaundice, nausea and malaise; however, although fulminant hepatitis is extremely rare, it has been described during the first 8 weeks of infection¹⁶. A majority of acute cases go on to become chronic and, without treatment, the majority of chronic cases do not clear the virus¹⁶. HCV RNA detectable for longer than 6 months is considered chronic infection with sequelae including end-stage cirrhosis and hepatocellular carcinoma (HCC) although the length of time this may take can vary from less than 20 years to greater than 30 years¹⁶. Co-infection with HIV displays accelerated disease progression as HCV behaves as an opportunistic infection²². Co-infection with hepatitis B virus displays more severe liver disease progression than either single infection²². Increased alcohol intake also accelerates the progression of chronic HCV towards end-stage cirrhosis and HCC²². Transplantation is often necessary due to HCV infection related liver failure, leading to further complications with progression towards cirrhosis in over 25% of patients within 5 years of transplantation²⁸.

HCV screening in people who may be at increased risk of infection has been strongly recommended by WHO guidelines as well as guidelines from the UK – Public Health England (PHE), British HIV Association (BHIVA) and the British Association of Sexual Health and HIV (BASHH) to address the need to improve rates of earlier diagnosis^{11,12,29,30}.

Laboratory diagnosis

Laboratory diagnosis is based upon the detection of antibodies for the virus using serological methods followed by the detection of the presence of virus using nucleic acid amplification testing, or antigen testing to confirm viraemia^{9,26,30-33}. Antibodies to HCV are detected using Enzyme Linked Immunosorbent Assays (ELISA) and Chemiluminescent Immunoassays (CLIA)/ immunoblots³⁴. Assays have progressed in development to second generation (core proteins and non-structural proteins 3 and 4) and third generation (inclusion of antigen non-structural protein 5)¹⁶. Assays that detect free HCV antigen are about 97% as sensitive as HCV NAAT³⁵.

A sensitive NAAT is preferable to an EIA antigen test for confirmation. HCV antigen EIA is less sensitive than NAAT, with a sensitivity equivalent to NAAT values of 500-3000 IU/mL. The HCV antigen test is reported to have a 100% positive specificity and 96.3% sensitivity in confirming HCV infection, when compared with the HCV NAAT tests³⁶. HCV antigen testing therefore should not be used to confirm infection in sera with low levels of antibody, as false negatives are more likely^{36,37}. Laboratories should be aware that if antigen negative, patients who are infected may be missed and NAAT should be considered. If an antigen test is used, the sensitivity IU/ml cut off of the assay should be stated on the report.

Some platforms require samples for NAAT to be split within 6hrs to comply with their CE marking which may not be easily achievable by all laboratories. However, management of HCV infection is dependent on whether active hepatitis C infection is present and therefore a positive HCV antigen or NAAT result, which indicates active infection, is required for identifying appropriate treatment regimens. In addition, where

infections are common in groups who may be difficult to re-bleed, requesting an additional repeat sample to confirm active infection is not ideal. The presence of RNA and antibodies to HCV do not confirm whether infection is acute or chronic¹⁵. However, antibodies do take a long time to develop and are therefore only detectable in 50-70% of symptomatic acute infections²⁷.

The presence of HCV RNA in blood is a good marker of replicating virus¹⁵. Detection is possible 1-3 weeks after infection with the use of molecular methods to detect HCV RNA. Molecular methods can also be used to distinguish between the genotypes and subtypes, of particular importance as some genotypes are more prevalent than others in different global regions and knowledge of the genotype may be relevant in treatment selection and in the differentiation of relapse from reinfection¹⁶.

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^{38,39}

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”.

Safety considerations

Laboratory procedures that give rise to infectious aerosols must be conducted in a microbiological safety cabinet⁴⁰.

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.

1 Specimen transport, storage and retention^{38,39}

1.1 Optimal transport and storage conditions

Specimens should be transported and processed as soon as possible⁴¹.

If processing is delayed, refrigeration is preferable to storage at ambient temperature⁴¹.

Samples should be retained in accordance with The Royal College of Pathologists guidelines 'The retention and storage of pathological records and specimens'⁴².

Public health management

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 page 19.

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 diagnosis to PHE Health Protection Teams, participating laboratories should also report into sentinel surveillance programmes for HCV.

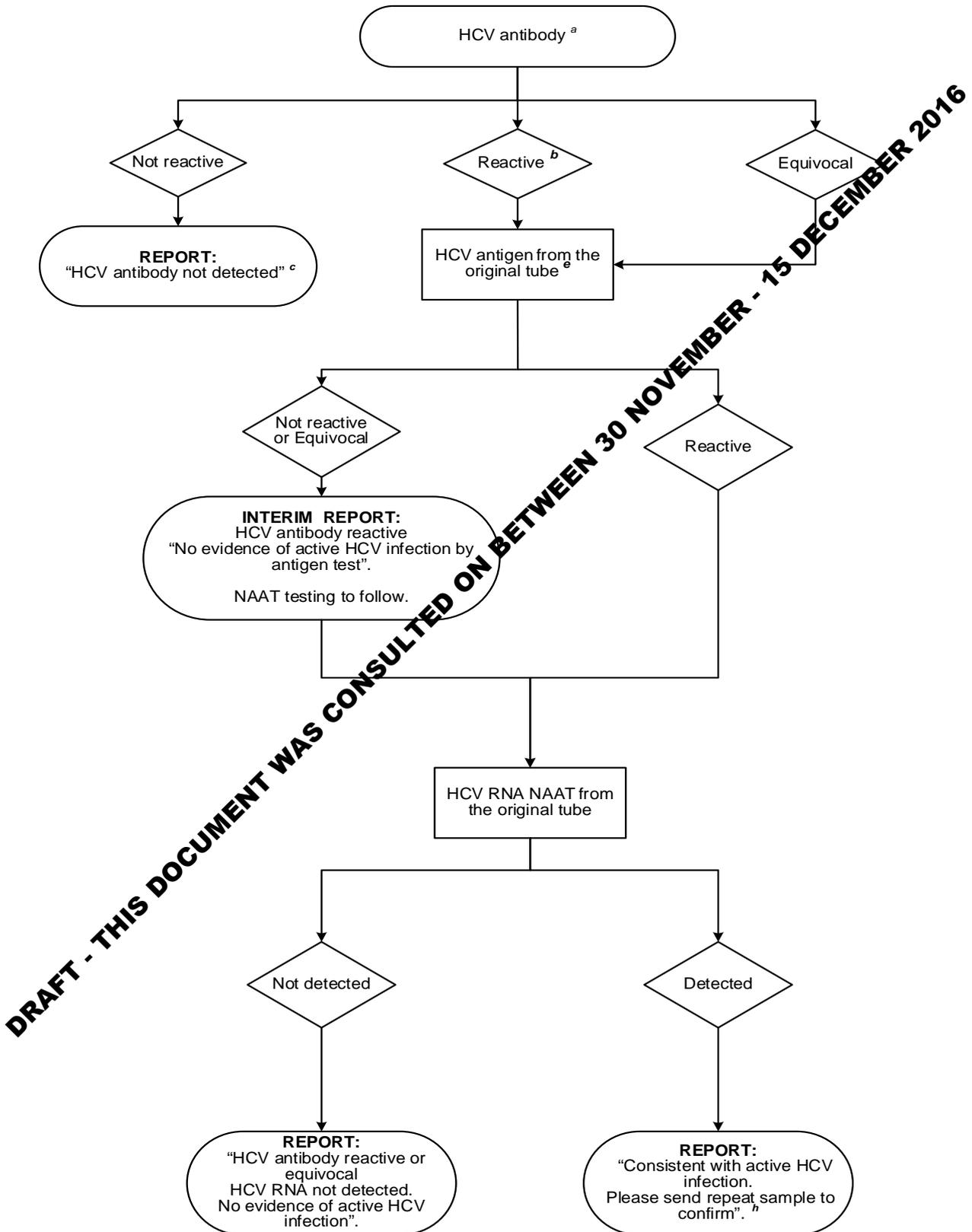
In the UK, guidance for hepatitis C infected health care workers (HCW) is available⁴³. See link: <https://www.gov.uk/guidance/bloodborne-viruses-in-healthcare-workers-report-exposures-and-reduce-risk>

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Investigation of hepatitis C infection by HCV antibody testing confirmed by NAAT ^{31,44,45}



Investigation of hepatitis C infection by antibody testing confirmed by antigen ³¹



Footnotes for algorithms

For immunocompromised patients, who may have a delayed antibody response or cases strongly suspected to be due to acute HCV or where re-infection or re-activation is suspected, immediate screening with NAAT or HCV antigen may be indicated. Screening using HCV antigen or NAAT testing is increasingly used for renal dialysis units⁴⁶.

- a) Report at this stage as an interim report if confirmation will be delayed and the result may have immediate significance for patient management; suggested wording 'Initial HCV antibody. Presumptive positive, awaiting confirmation'.
- b) If occupational exposure risk, request a repeat sample at an appropriate interval, usually a sample after 6 weeks for NAAT⁴³. Most people will be NAAT positive by 4 weeks post exposure and antibody positive by 12 weeks post exposure. Follow local guidelines when dealing with occupational health.
- c) Qualitative HCV NAAT or quantitative NAAT can be used. High levels of sensitivity can only be achieved with optimal sample volume; if less than the recommended volume is used (perhaps diluted) this must be reported and a repeat sample requested. All assays should include appropriate controls including an inhibition control.
- d) A sensitive NAAT is preferable to an EIA antigen test for confirmation. Laboratories should be aware that if antigen negative, patients who are infected may be missed and NAAT should be considered. If an antigen test is used the sensitivity of the assay should be stated in the report.
- e) HCV antibody positive result may indicate past HCV infection. Some laboratories may like to do a second antibody test to confirm. Refer to report table for interpretation of results.
- f) Refer to report table for final interpretation for combinations of additional tests.
- g) Advise referral to an appropriate specialist for further assessment/treatment.

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Report comments ⁴⁵

The final result should be able to distinguish active infection from resolved infection and acute 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 by HCV antibody testing confirmed by NAAT					
	1 st Assay	2 nd Assay	3 rd Assay Optional if needed	Interpretative comments	Notes
	HCV Ab	HCV NAAT	HCV Ab		
1	Unreactive	Not tested	Not tested	HCV antibody not detected.	
2	Reactive or Equivocal	RNA Detected	Not tested	<p>HCV antibody reactive HCV RNA detected Evidence of active HCV infection.</p> <p>Consider requesting HCV genotyping and other BBV testing unless already performed.</p> <p>Refer to hepatitis service. Hepatitis A and B vaccine recommended if appropriate".</p>	<p>HCV antibody detected on the basis that the presence of HCV RNA allows one to infer with confidence that the HCV IgG reaction is a true positive.</p> <p>Advise referral to an appropriate specialist for further treatment.</p> <p>Please ensure hepatitis A and B immunity status is known and vaccination given if needed.</p>

Investigation of hepatitis C infection by HCV antibody testing confirmed by NAAT					
	1 st Assay	2 nd Assay	3 rd Assay Optional if needed	Interpretative comments	Notes
	HCV Ab	HCV NAAT	HCV Ab		
3	Reactive or Equivocal	RNA not detected	Not tested	No evidence of active HCV infection.	Second antibody test may be performed according to local policy.
4	Reactive or Equivocal	RNA not detected	Reactive or equivocal	No evidence of active HCV infection.	HCV antibody positive result may indicate past HCV infection. Some laboratories may like to do a second antibody test to confirm. Suggest a repeat sample to confirm HCV antibody status. Please note that an undetectable HCV NAAT does not exclude current infection because viraemia may be intermittent. Suggest testing a follow-up blood for HCV NAAT to investigate possible fluctuating viraemia. Refer to EASL guidelines 2015 ⁴⁴ .
5	Reactive or Equivocal	RNA not detected	Not reactive	No evidence of active HCV infection.	Consider reporting initial HCV Ab reactivity according to local policy.
6	Unreactive	RNA detected	Not tested	Evidence of active HCV infection	Indicates either acute HCV infection or possibly a chronic infection in an immunocompromised patient.

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Investigation of hepatitis C infection by antibody testing confirmed by antigen						
	1 st Assay HCV Ab	2 nd Assay HCV Ag	3rd assay HCV Ab	4 th assay HCV NAAT	Interpretative comments	Notes
7	Unreactive	Not tested	Not tested	Not tested	HCV antibody not detected.	
8	Reactive or Equivocal	Reactive	Not tested	Not tested	Consistent with active HCV infection. Advise referral to an appropriate specialist for further assessment/treatment. Consider requesting HCV genotyping and recommend other BBV testing unless already performed. Refer to hepatitis service. Hepatitis A and B vaccine recommended if appropriate.	
9	Reactive or Equivocal	Unreactive	Unreactive	Not tested	No evidence of active HCV infection	Consider reporting initial HCV Ab reactivity according to local policy.
10	Reactive or Equivocal	Equivocal	Unreactive	Not detected	No evidence of active HCV infection	Consider reporting initial HCV Ab reactivity according to local policy.
11	Reactive or Equivocal	Equivocal	Unreactive	Detected	Consistent with active HCV infection. Advise referral to an appropriate specialist for further assessment/treatment.	

Investigation of hepatitis C infection by antibody testing confirmed by antigen						
	1 st Assay HCV Ab	2 nd Assay HCV Ag	3rd assay HCV Ab	4 th assay HCV NAAT	Interpretative comments	Notes
					Consider requesting HCV genotyping and recommend other BBV testing unless already performed. Refer to hepatitis service. Hepatitis A and B vaccine recommended if appropriate.	
12	Reactive	Unreactive or Equivocal	Reactive or Equivocal	Not tested	HCV antibody detected.	If negative, request a further sample.
13	Equivocal	Unreactive or Equivocal	Reactive or Equivocal or Unreactive	Not tested	Indeterminate HCV status	Please send a repeat sample to confirm including by NAAT.

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Notification to PHE^{47,48}, or equivalent in the devolved administrations⁴⁹⁻⁵²

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 (HCAs) 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](#)^{49,50}, [Wales](#)⁵¹ and [Northern Ireland](#)⁵².

References

Modified GRADE table used by UK SMI 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-VI). A summary table which defines the grade is listed below and should be used in conjunction with the reference list.

Strength of recommendation	Quality 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
C Weakly recommended: seek alternatives	III Non-analytical studies, for example, case reports, reviews, case series
D Never recommended	IV Expert opinion and wide acceptance as good practice but with no study evidence
	V Required by legislation, code of practice or national standard
	VI Letter or other

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DRAFT - THIS DOCUMENT WAS CONSULTED ON BETWEEN 30 NOVEMBER - 15 DECEMBER 2016