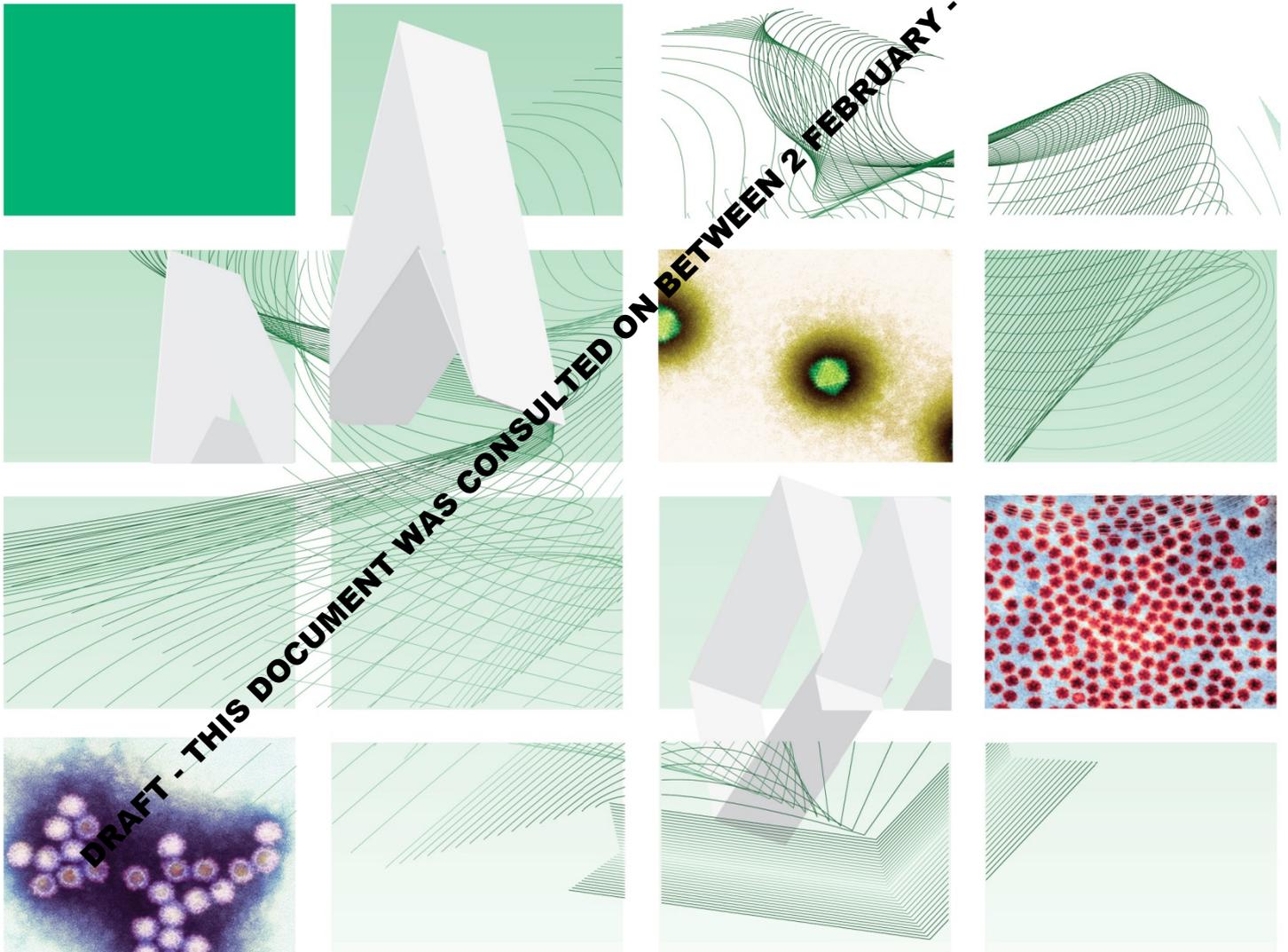




# UK Standards for Microbiology Investigations

## Screening and monitoring for hepatitis E infection

DRAFT - THIS DOCUMENT WAS CONSULTED ON BETWEEN 2 FEBRUARY - 16 FEBRUARY 2018



"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**."

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## Acknowledgments

UK Standards for Microbiology Investigations (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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# Contents

Acknowledgments .....	2
Amendment table .....	4
UK SMI: scope and purpose.....	5
Scope of document.....	8
Introduction.....	9
1 Safety considerations .....	13
2 Specimen transport, storage and retention .....	13
Public health management.....	13
HEV infection in the immunocompetent.....	14
HEV infection in the immunocompromised .....	16
Monitoring of HEV during antiviral therapy for persistent HEV infection .....	18
Report comments .....	20
Notification to PHE, or equivalent in the devolved administrations.....	22
References .....	23

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## Amendment table

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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](mailto: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.	New amendment number/dd.mm.yy <tab+enter>
Issue no. discarded.	
Insert Issue no.	d
Anticipated next review date*	
<b>Section(s) involved</b>	<b>Amendment</b>

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

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## UK SMI<sup>#</sup>: 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/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.

<sup>#</sup> 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.

UK SMIs represent a good standard of practice to which all clinical and public health 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 are 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 any 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**

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

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## Scope of document

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### Type of specimen

Whole blood, plasma, serum, faeces

This UK SMI covers the screening of blood, plasma and serum samples for Hepatitis E using HEV antibody enzyme immunoassays (EIA) screening assays. This document also covers the use of Nucleic Acid Amplification Tests (NAAT) for the detection of HEV RNA in plasma, serum and faeces samples for confirmation of HEV serology results, screening in the immunocompromised patient and monitoring of the treatment response.

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

### Definitions

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 within the manufacturer's grey zone. Further testing is required.

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

#### 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 E virus (HEV) is increasingly common in the UK with an excess of 100,000 infections estimated to occur annually in England of which a minority are associated with clinically apparent disease<sup>1,2</sup>.

HEV causes an acute infection, which may be associated with clinical hepatitis and can also result in a persistent infection in immunosuppressed hosts. Symptoms of HEV include jaundice, dark urine and pale stools and may be accompanied by tiredness, fever, nausea, vomiting, abdominal pain and loss of appetite

(<https://www.gov.uk/government/publications/hepatitis-e-symptoms-transmission-prevention-treatment/hepatitis-e-symptoms-transmission-treatment-and-prevention>).

There has been a year on year increase in case numbers since 2010 and HEV is currently the most common cause of acute viral hepatitis in England<sup>1</sup>. Indigenously acquired infections have been linked to the consumption of pork products and diet remains the major route of autochthonous HEV acquisition<sup>1</sup>.

There are four main HEV genotypes, G1-G4, which infect humans<sup>3,4</sup>. Sequence and phylogenetic analysis shows genotype 3 viruses to be associated with indigenous infections in the UK. A number of G1 (and rarely G4) infections are imported into the UK each year following travel to a high incidence area. G1 (and G2) viruses are likely to cause severe illness in pregnancy, HEV G3 does not<sup>5,6</sup>.

It is important to consider Hepatitis E as a potential cause of viral hepatitis early on in the assessment of the patient ie as part of an initial acute viral hepatitis screen<sup>7</sup> and as a cause of transaminitis in the immunosuppressed host. HEV is also an under-recognised cause of neurological presentations including brachial neuritis and peripheral neuropathy; neurological syndromes coincident with acute hepatitis E have also been reported<sup>8,9</sup>.

### Laboratory diagnosis

The clinical presentation of acute symptomatic hepatitis E cannot be distinguished from that of any other viral hepatitis. Although epidemiological features may suggest HEV infection in some cases, laboratory tests should always be performed to confirm any clinical diagnosis.

Hepatitis E testing should be carried out as part of an initial hepatitis screen in the investigation of acute clinical hepatitis alongside hepatitis A, B and C<sup>7</sup>. The use of ALT data for limiting the number of immunocompetent patients tested may be considered (ie screening for HEV infection on patients with ALT  $\geq 100$  IU/L)<sup>10</sup>. PHE advise that anyone with unexplained hepatitis, regardless of travel history be tested for HEV.

### HEV infection in the immunocompetent

Serology supported by the detection of viral nucleic acid is the principal way in which HEV infection is diagnosed in immunocompetent patients. Recombinant capsid proteins are used in assays of different format for the detection of antibody to HEV<sup>11</sup>. There is only one serotype and assays are able to detect antibody responses to G1-4 infections in animal and human hosts<sup>12</sup>. Although there are four human HEV genotypes, they elicit very similar antibody responses and appear to represent a single serotype<sup>13-15</sup>.

The serological response becomes detectable just prior to the maximal liver injury, potentially coinciding with the onset of symptoms. IgM anti-HEV precedes IgG detection, and is usually short lived but can remain detectable at decreasing levels for several months and may persist for extended periods in a small number of individuals. The significance of this is not known<sup>13</sup>.

IgG antibody appears shortly after IgM and the IgG reactivity rises rapidly in the recovery period. High level reactivity for anti-HEV IgG with low or high negative IgM is seen in samples taken after recovery from jaundice. The IgG response can persist for several years and may be lifelong in the majority of patients recovered from HEV infection<sup>16</sup>.

Laboratory diagnostic criteria can be drawn up to account for the variability in natural immune responses and assay performance. An acute case of hepatitis E with a symptomatic presentation is best defined by having HEV RNA positive serum or plasma and coincident IgM anti HEV and IgG seroconversion<sup>17</sup>. Other combinations of IgG and IgM results may be best interpreted according to antibody titre/reactivity levels but IgM reactivity on its own is not secure. The failure to seroconvert for IgG antibody in a patient sero-reactive for IgM confirms the non-specificity of the IgM reactivity<sup>17</sup>. The duration of viraemia in the immunocompetent patient is of the order of eight weeks<sup>17</sup>. In a patient presenting with hepatitis E, plasma viraemia will fall away quickly in the recovery period and it is not unusual to fail to detect HEV RNA in plasma samples taken a few weeks after the onset of jaundice.

### HEV infection in the immunocompromised

Testing for HEV may also be considered as part of the initial investigation of unexplained elevation of plasma transaminases (eg alanine transaminase, ALT), in immunocompromised individuals and in individuals with acute neurological presentations consistent with hepatitis E<sup>18</sup>. For immunocompromised patients, who may have a delayed or absent antibody response, screening for HEV RNA with NAAT is essential<sup>17</sup>.

It should be noted that detection of HEV RNA without detectable HEV antibodies in the presence of an abnormal ALT may not equate to acute HEV infection, but could be the result of persistent infection if the person is immunosuppressed<sup>19</sup>.

In those patients who are immunocompromised either through coincident infections (for example HIV) or following transplantation or chemotherapy (solid organ transplants, stem cell transplants and haematology-oncology) or systemic immunosuppressive therapy (inflammatory bowel, renal/vascular, and arthritides) the early phases of the infection will be without symptoms. In the immunosuppressed patient virus replication may persist for months or years in the absence of development of serological markers; this may occur with little elevation of serum transaminases. Up to half of all acute infections in the immunocompromised may clear spontaneously. When this clearance occurs in the face of immune recovery, for example during haematological remission it may often be associated with seroconversion, sometimes presenting as an hepatitis of recovery. Infections, which do not clear, may persist for years with or without antibody.

It is recommended that a follow up sample is taken four weeks after the first detection of HEV RNA in an immunocompromised individual. This will confirm the initial finding and help differentiate between an acute resolving infection (perhaps with seroconversion) and a possible persistent infection if viral load levels are maintained.

Where opportunity exists, previous archived samples may be used to investigate potential persistence as results may inform on the length of infection.

In monitoring of HEV RNA levels during antiviral therapy of chronic HEV infection, it is recommended that monthly HEV RNA testing is undertaken on faeces and plasma. HEV is detectable in the stool some considerable time before viraemia, and for approximately four weeks after the clearance of detectable viraemia. There are reports of more prolonged faecal shedding of virus. Infections in patients with persisting detectable viral faecal shedding at the termination of anti-viral treatment are very likely to suffer viral recrudescence and it is recommended to continue therapy until two sequential stool samples taken four weeks apart are found to be free of detectable virus<sup>20 21</sup>.

Commercial HEV 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 use.

### Established persistent hepatitis infection<sup>22</sup>

Persistent hepatitis E infection can result in chronic liver disease and rapidly progressive liver fibrosis and cirrhosis with death due to decompensated liver disease. Data from the transplant setting have shown that a reduction in levels of immune suppression led to viral clearance in 30% of cases<sup>23-25</sup>. Clearance in this setting is usually associated with sero-conversion and frequently with a transaminitis. Antiviral treatment with pegylated interferon and/or ribavirin has also been used successfully to treat persistent HEV infections where alteration of immune suppression has either been impossible or ineffective<sup>23-25</sup>.

In patients with persistent HEV infection undergoing treatment is usually ribavirin monotherapy though the usage remains unlicensed. A rapid reduction in the first week of therapy may indicate an increased likelihood of developing a sustained viral response (SVR)<sup>26</sup>. It is important to confirm stool clearance before terminating anti-viral treatment. Infections in patients with continuing detectable viral faecal shedding at the end of treatment are liable to recrudescence and it is wise to continue therapy until two sequential stool samples are found to be free of detectable virus which confirms the end of treatment response (ETR).

### HEV infection in pregnancy

In cases of pregnant women who are found to be HEV-infected, particularly in those who have travelled abroad during the incubation period, it is recommended that samples are referred to a reference laboratory for genotyping as a matter of urgency. There is an increased risk of more serious illness in those with a genotype 1 (G1) infection. Genotype G3 is the dominant virus in the UK and there is no evidence to suggest that G3 infections are associated with severe outcomes in pregnancy<sup>1,7</sup>.

## 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<sup>27,28</sup>**

UK SMLs 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 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”.

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# 1 Safety considerations

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## 1.1 Specimen collection, transport and storage<sup>28-34</sup>

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.

## 1.2 Specimen processing

Laboratory procedures that give rise to infectious aerosols must be conducted in a microbiological safety cabinet<sup>35</sup>.

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

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

# 2 Specimen transport, storage and retention<sup>27,28</sup>

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## 2.1 Optimal transport and storage conditions

Specimens should be transported and processed as soon as possible<sup>36</sup>.

If processing is delayed, refrigeration is preferable to storage at ambient temperature<sup>36</sup> and should be in accordance with manufacturers' instructions detailed in the Information for Use leaflet.

Samples should be retained in accordance with The Royal College of Pathologists guidelines 'The retention and storage of pathological records and specimens'<sup>37</sup>.

## Public health management

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For information regarding notification to PHE (or equivalent in the devolved administrations) refer to page 16.

For further information on public health management refer to PHE guidance<sup>7</sup>:

<http://www.gov.uk/government/publications/hepatitis-e-health-protection-response-to-reports-of-infection>.

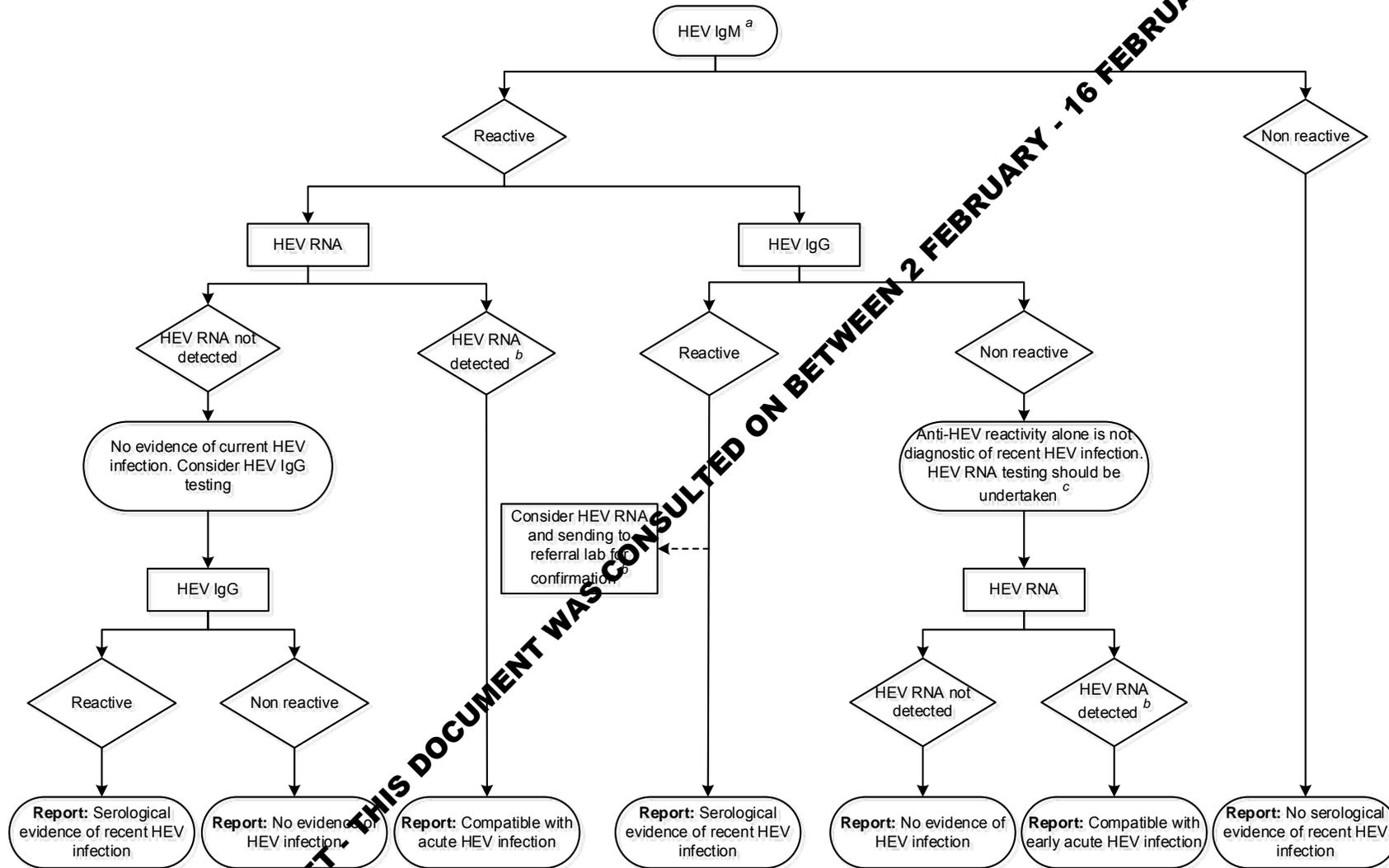
A structured enhanced surveillance questionnaire is available for laboratory confirmed cases of hepatitis E (as defined in the case definition) at:

<https://www.gov.uk/government/publications/hepatitis-e-surveillance-form>

Also refer to Health and Safety Executive guidance for employers and employees:

<http://www.hse.gov.uk/pubns/indg342.pdf>.

# HEV infection in the immunocompetent<sup>5,19</sup>



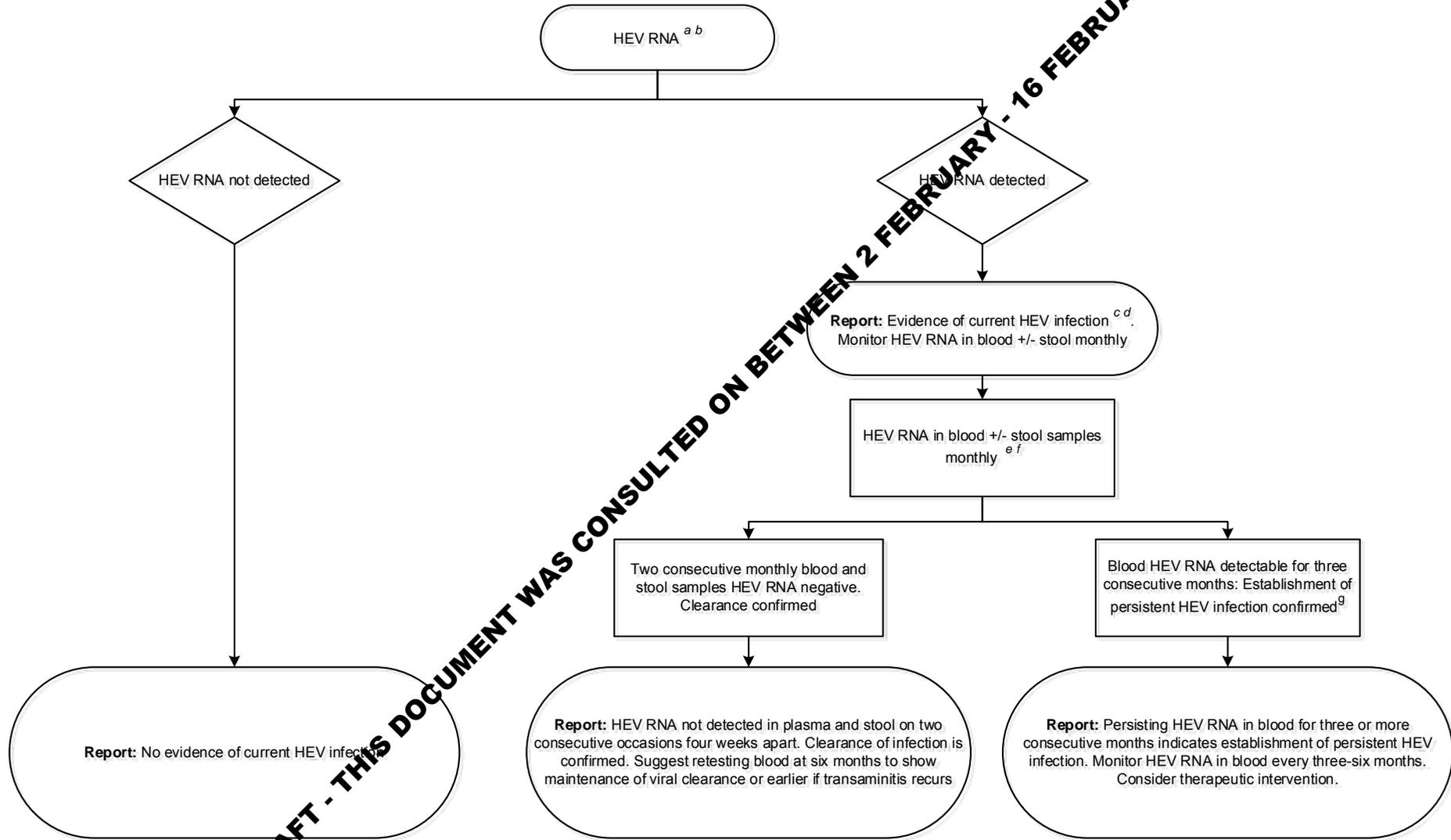
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### Footnotes - HEV infection in the immunocompetent algorithm

- a. The detection of HEV IgM alone is not diagnostic of HEV infection. A diagnosis of HEV infection following detection of IgM reactivity must be confirmed by serology (IgG reactive) or by molecular testing (HEV RNA detected). HEV RNA testing should be undertaken on all samples that are IgM reactive and IgG unreactive to confirm acute HEV infection.
- b. Consider sending to referral laboratory for genotyping and phylogenetic sequencing. Genotyping is recommended when investigating infections during pregnancy.
- c. Alternatively, request a further sample for serology within two weeks to look for evidence of seroconversion.

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# HEV infection in the immunocompromised<sup>5,19,38</sup>

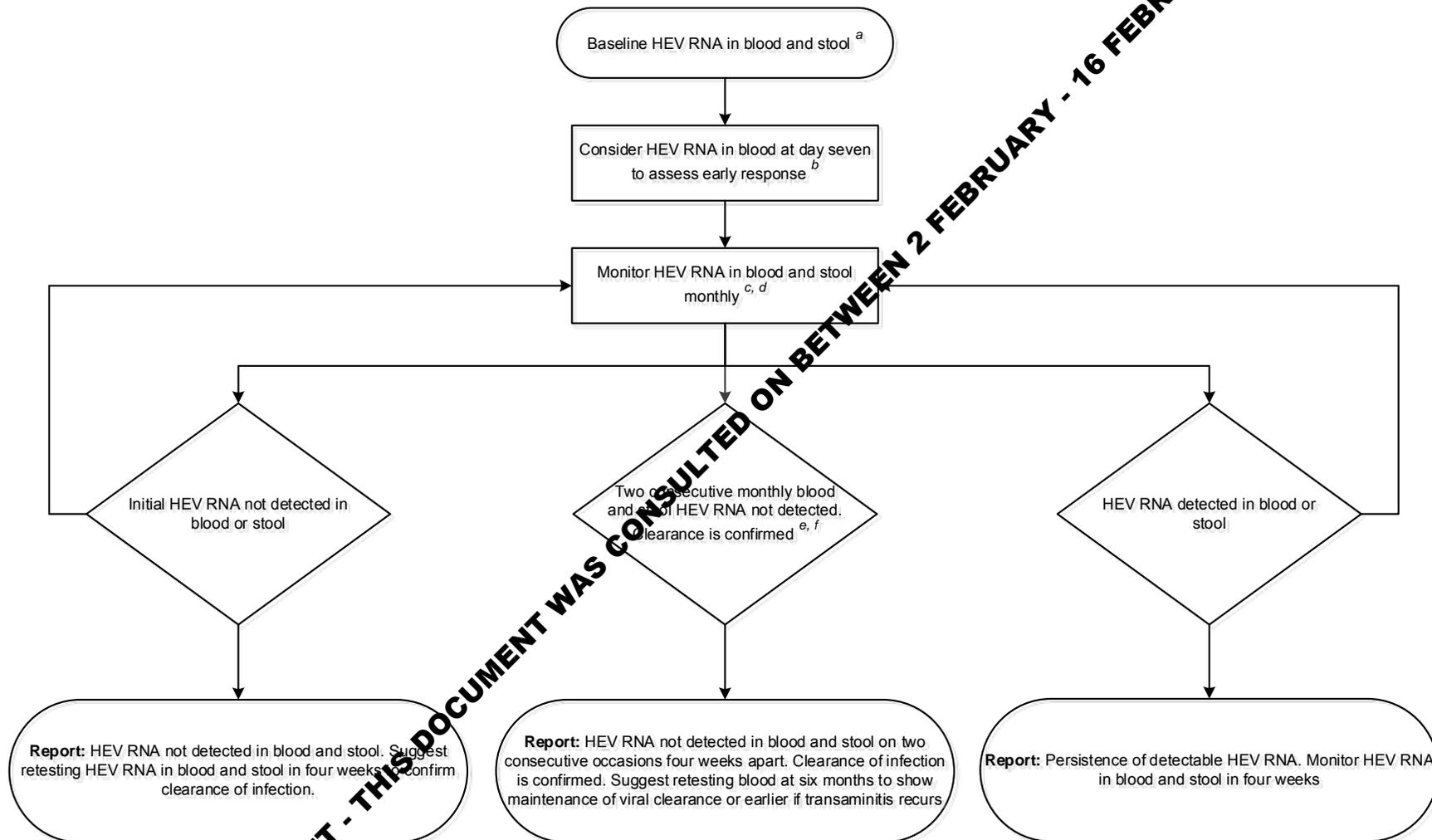


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### Footnotes - HEV infection in the immunocompromised algorithm

- a. A quantitative assay should be used in accordance with the WHO International Standard.
- b. In patients with conditions associated with immunosuppression (for example HIV infection, lymphoma and leukaemia) and in solid organ transplant recipients, HEV RNA testing is essential for the diagnosis of acute and persistent HEV infection. In these patients seroconversion is often delayed, and may not occur. If seroconversion does occur it is not necessarily associated with viral clearance.
- c. Previous archived samples may be used in the investigation of persistent infection to identify length of infection.
- d. Antibody results where available may inform patient management.
- e. Quantitative HEV RNA viral load monitoring may provide further information regarding the dynamics of the HEV infection:
  - a. Decreasing HEV RNA viral load suggests a resolving infection.
  - b. Increasing HEV RNA viral load suggests a developing recent infection.
  - c. Unchanged HEV RNA viral load suggests an established persistent infection.
- f. An alternative to monitoring HEV RNA in both blood and stool is to monitor HEV RNA in blood until it is not detected and then to monitor blood and stool until clearance is confirmed.
- g. Refer to monitoring algorithm for persistent HEV infection during antiviral therapy.

# Monitoring of HEV during antiviral therapy for persistent HEV infection



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## Footnotes - Monitoring of HEV during antiviral therapy for persistent/chronic HEV infection algorithm

- a. A quantitative assay should be used in accordance with the WHO International Standard.
- b. A rapid fall in the first week of treatment is a good predictor of an eventual sustained viral response to antiviral therapy<sup>20</sup>.
- c. A decreasing HEV RNA viral load is likely to represent resolving infection.
- d. An alternative to monitoring HEV RNA in both blood and stool is to monitor HEV RNA in blood until it is not detected and then to monitor blood and stool until clearance is confirmed.
- e. Relapse may be detected by a return of detectable HEV RNA in either, or both, blood and stool.
- f. Relapse of HEV infection following cessation of antiviral therapy is commonly associated with ongoing viral shedding in stool samples at the end of treatment. Therefore it is good practice to ensure HEV RNA stool clearance has occurred in 2 stool samples 4 weeks apart prior to stopping treatment<sup>20</sup>.

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## Report comments

### Immunocompetent patient

	HEV IgM	HEV IgG	HEV RNA in blood	Interpretative Comment	Notes
1	Negative	Not tested	Not tested	No serological evidence of HEV infection	
2	Reactive	Not Reactive	Not detected	Results probably reflect non-specific IgM reactivity. In the absence of HEV RNA and anti-HEV IgG, recent HEV infection is unlikely	Request a second sample if clinically indicated
3	Reactive	Not Reactive	Detected	Diagnostic of acute HEV infection	
4	Reactive	Reactive	Not detected	Indicative of acute HEV infection	
5	Reactive	Reactive	Detected	Compatible with current acute HEV infection	
6	Reactive	Reactive	Not tested	Compatible with acute HEV infection	

### Immunocompromised patient

	HEV RNA in blood	HEV RNA in stool (if patient is on treatment)	HEV IgM*	HEV IgG*	Interpretative Comment	Notes
1	Not detected	Not detected	Not reactive	Not reactive	No evidence of past or current HEV infection	This profile will also be seen in a previously known HEV-infected patient who has cleared their infection whilst on

						treatment but not produced an antibody response. Please note that this interpretation is only possible where previous test results are known.
2	Detected	Detected	Reactive/Not reactive	Reactive/Not reactive	Compatible with a current HEV infection. In light of this patient's immunosuppression, continued viral load monitoring	The clinical significance of a detectable serological response (any combination of IgM/IgG) in an immunocompromised patient is uncertain and does not always correlate with likelihood of clearance. In particular, the detection of anti-HEV IgM should not be used to infer a recent infection.
3	Not detected	Not detected	Reactive	Reactive	Compatible with a recent HEV infection. HEV RNA has been cleared. Please note that anti-IgM reactivity may persist in the immunocompromised patient.	
4	Not detected	Detected	Reactive	Reactive	HEV RNA remains detectable in the stool despite viral clearance from plasma. Continued viral shedding in stool has been associated with viral rebound following the cessation of therapy. Continued HEV RNA monitoring in both plasma and stool is recommended.	Relevant for patients on treatment.

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## Notification to PHE<sup>39,40</sup>, or equivalent in the devolved administrations<sup>41-44</sup>

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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](#)<sup>41,42</sup>, [Wales](#)<sup>43</sup> and [Northern Ireland](#)<sup>44</sup>

## References

### Modified GRADE table used by UK SMI's 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 SMI's 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

1. Ijaz S, Said B, Boxall E, Smit E, Morgan D, Tedder RS. Indigenous hepatitis E in England and Wales from 2003 to 2012: evidence of an emerging novel phylotype of viruses. *The Journal of infectious diseases* 2014;209:1212-8.
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