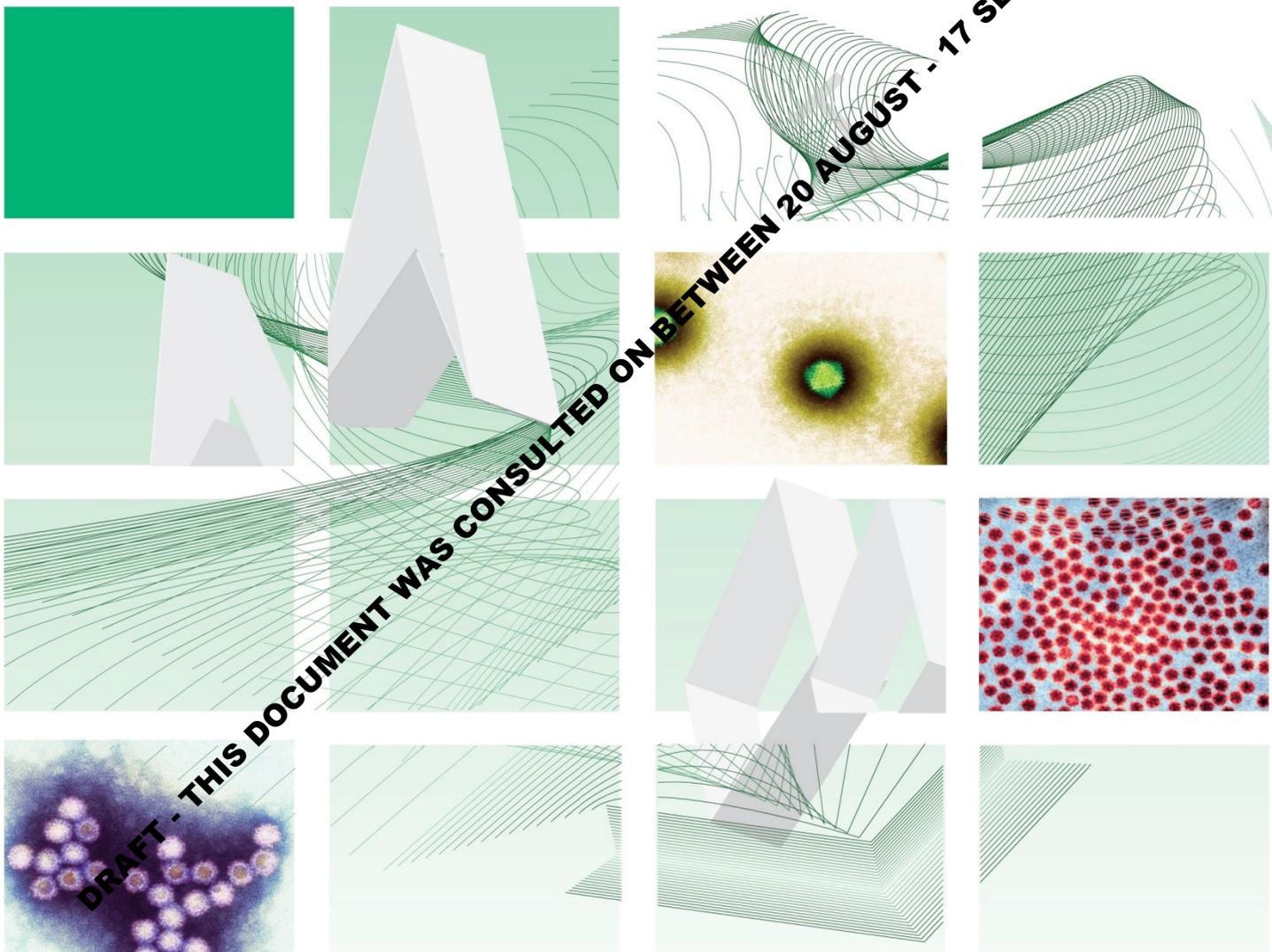




Protecting and improving the nation's health

UK Standards for Microbiology Investigations

Screening for Hepatitis E Infection



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>. 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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Logos correct at time of publishing.

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For full details on our accreditation visit: www.nice.org.uk/accreditation.

Amendment table

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

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

Amendment No/Date.	New amendment number/dd.mm.yy <tab+enter>
Issue no. discarded.	
Insert Issue no.	## <tab+enter>
Section(s) involved	Amendment

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UK Standards for Microbiology Investigations[#]: scope and purpose

Users of SMIs

- SMIs are primarily intended as a general resource for practising professionals operating in the field of laboratory medicine and infection specialties in the UK.
- SMIs 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.
- SMIs 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 SMIs

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 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

SMIs are developed in equal partnership with PHE, NHS, Royal College of Pathologists and professional societies.

The list of participating societies may be found at <https://www.gov.uk/uk-standards-for-microbiology-investigations-smi-quality-and-consistency-in-clinical-laboratories>.

Inclusion of a logo in an SMI indicates participation of the society in equal partnership and support for the objectives and process of preparing SMIs. Nominees of professional societies are members of the Steering Committee and Working Groups which develop 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.

SMIs are developed, reviewed and updated through a wide consultation process.

[#]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.

Quality assurance

NICE has accredited the process used by the SMI Working Groups to produce SMIs. The accreditation is applicable to all guidance produced since October 2009. The process for the development of SMIs is certified to ISO 9001:2008.

SMIs represent a good standard of practice to which all clinical and public health microbiology laboratories in the UK are expected to work. SMIs are NICE accredited and represent neither minimum standards of practice nor the highest level of complex laboratory investigation possible. In using SMIs, laboratories should take account of local requirements and undertake additional investigations where appropriate. SMIs help laboratories to meet accreditation requirements by promoting high quality practices which are auditable. SMIs also provide a reference point for method development.

The performance of 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 SMI Working Groups are committed to patient and public involvement in the development of SMIs. By involving the public, health professionals, scientists and voluntary organisations the resulting 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 SMIs are subject to PHE Equality objectives <https://www.gov.uk/government/organisations/public-health-england/about/equality-and-diversity>. The 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

Whilst every care has been taken in the preparation of SMIs, PHE and any supporting organisation, 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 SMI or any information contained therein. If alterations are made to an SMI, it must be made clear where and by whom such changes have been made.

The evidence base and microbial taxonomy for the SMI is as complete as possible at the time 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.

SMIs are Crown copyright which should be acknowledged where appropriate.

Suggested citation for this document

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Scope of document

Type of specimen

Whole blood, plasma, serum, faeces

Scope

This virology algorithm covers the testing of blood, plasma and serum samples for hepatitis E (HEV) using HEV antibody assays for IgM and IgG, and NAAT¹. It is recommended that IgG, IgM and NAAT testing is carried out on the same sample (ie from the original tube). For immunocompromised patients, who may have a delayed antibody response, initial screening with NAAT may be indicated. HEV RNA testing may also be undertaken on faeces.

Hepatitis E testing should be carried out as part of an initial hepatitis screen alongside hepatitis A, B and C.

The use of ALT data for limiting the number of patients tested may be considered (ie screening for HEV on patients with ALT \geq 100 IU/mL).

In cases of pregnant women who are found to be infected it is recommended that samples are referred to a reference laboratory able to genotype as a matter of urgency. There is an increased risk of more serious illness in those with a 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^{2,3}.

A diagnosis of a HEV infection may be confirmed by serology alone, by molecular testing alone or a combination of both. In accordance with national HEV infection guidelines the criteria for defining HEV infection are as follows³:

Criteria for defining an acute HEV infection in a patient with acute hepatitis – The presence of HEV RNA (with or without detectable HEV antibodies), or both anti-HEV IgG and IgM antibody.

Criteria for defining a chronic hepatitis case with acute hepatitis – The persistence of HEV RNA for at least three months (with or without detectable HEV antibodies).

These definitions may be amended in an outbreak situation.

For the investigation and management of HEV infection please refer to PHE and HSE guidelines^{3,4}.

Refer to [S 1 - Acute infective hepatitis](#) and [G 5 – Investigation of hepatitis](#) for further information regarding clinical presentations of acute infective hepatitis, treatment and associated tests.

This SMI should be used in conjunction with other SMIs.

Introduction

Hepatitis E infection is increasingly recognised in the UK, including a high proportion of cases without the traditional risk factor of travel abroad to a high incidence area. 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 screen³.

Laboratory diagnosis

The clinical presentation of acute symptomatic hepatitis E is difficult to distinguish from that of any other viral hepatitis. Whilst epidemiological features may suggest HEV infection, laboratory tests should be performed to confirm any clinical diagnosis.

Virus can be detected in stool by immune electron microscopy, and viral nucleic acid can be detected in stool and blood by RT-PCR. Some cell lines support HEV replication but virus isolation is not used as a diagnostic technique. Non-human primates are susceptible to HEV and have been used in research only; no animal model shows the spectrum of HEV infection seen in humans. A number of antibody detection formats have been developed but the commercially available systems are solid phase EIA (IgG and IgM). These assays are usually based upon antigens derived from G1 and 2 viruses and although there is probably a single HEV serotype for human infection, they may be suboptimal for G3 virus endemic in the UK.

In common with many of the other viral hepatitises, the maximal liver injury appears to coincide with development of the immune response, leading to a typical picture of the relationship between the timings of virus detection, liver injury, and antibody detection. Available data is potentially complicated by variable assay performances, in general and via genotype specific differences.

HEV is detectable in the stool from around 1 week before, and up to three weeks after, symptoms appear. There are reports of more prolonged faecal shedding of virus^{5,6}. Viraemia detectable by RT-PCR probably mirrors the period of faecal shedding, but may persist for much longer⁶.

IgM antibody becomes detectable just prior to the maximal liver injury, potentially coinciding with the onset of symptoms, and remains at detectable levels for several months. Some patients do not mount a detectable IgM response. There is a spectrum of IgM persistence but over 50% of patients will be negative six months after onset.

IgG antibody appears shortly after IgM (when present), persisting for several years in the majority.

Laboratory diagnostic criteria can be drawn up to account for the variability in natural immune responses and assay performance, particularly in the setting of low endemicity. An acute case (symptomatic presentation) is best defined by being HEV RNA positive or by showing IgG seroconversion. Other combinations of IgG and IgM results may be best interpreted according to antibody titre/ reactivity levels. IgG avidity may be useful in inconclusive cases⁷.

The histopathological appearance of acute infection occurring in hyperendemic regions is of focal hepatic necrosis, ballooned hepatocytes and a lymphocytic inflammatory infiltrate⁸. A cholestatic picture may occur but it is uncommon. The histopathological appearance of acute infection acquired in the UK may be different.

Public health management

For information regarding notification to PHE (or equivalent in the devolved administrations) refer to page 23.

For further information on public health management refer to PHE guidance³:
<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>

Definitions

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

Reactive – Initial internal-stage positive result pending confirmation.

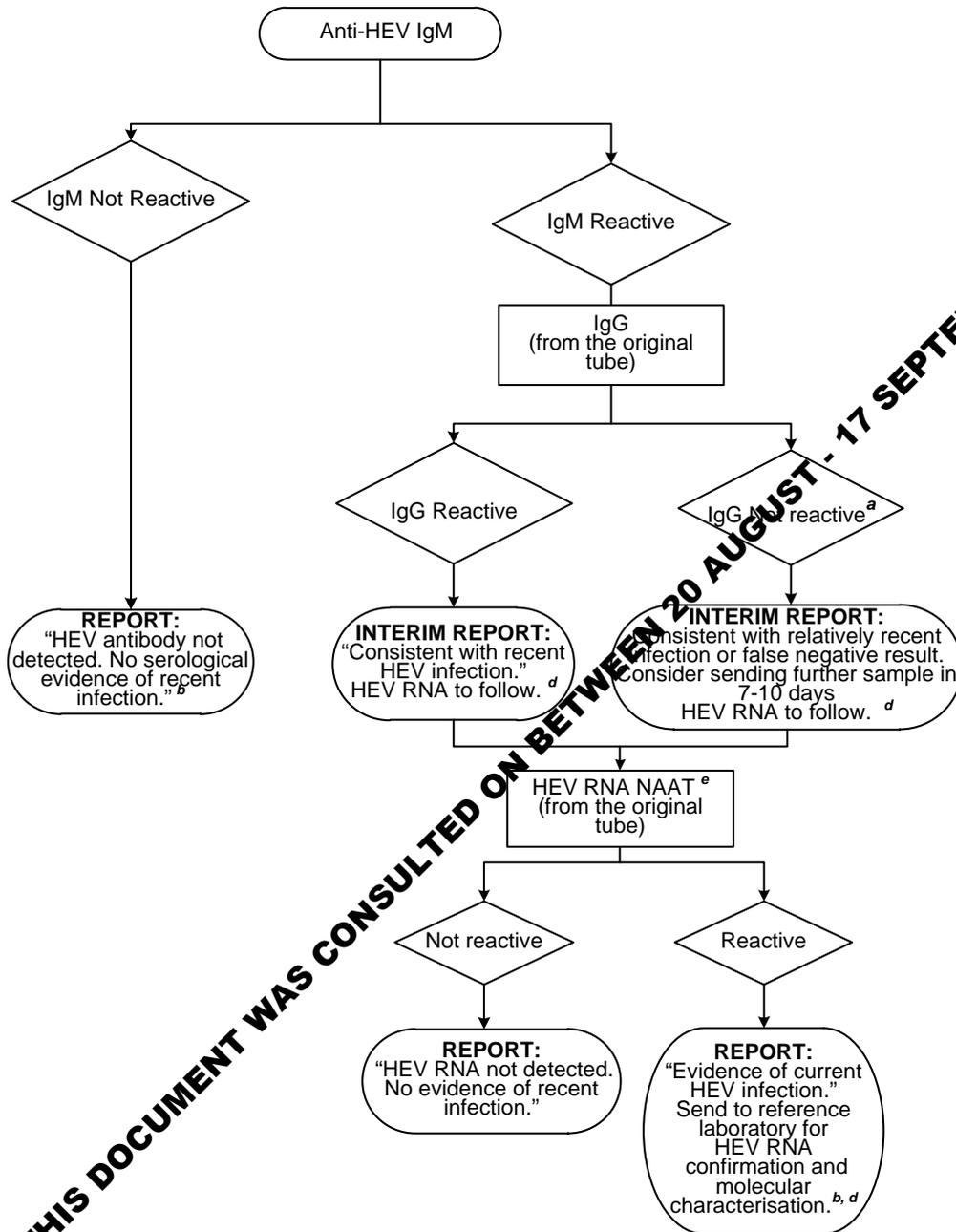
Not reactive – Initial internal-stage negative result.

Detected – Report-stage confirmed reactive result.

Not detected – Report-stage not reactive result.

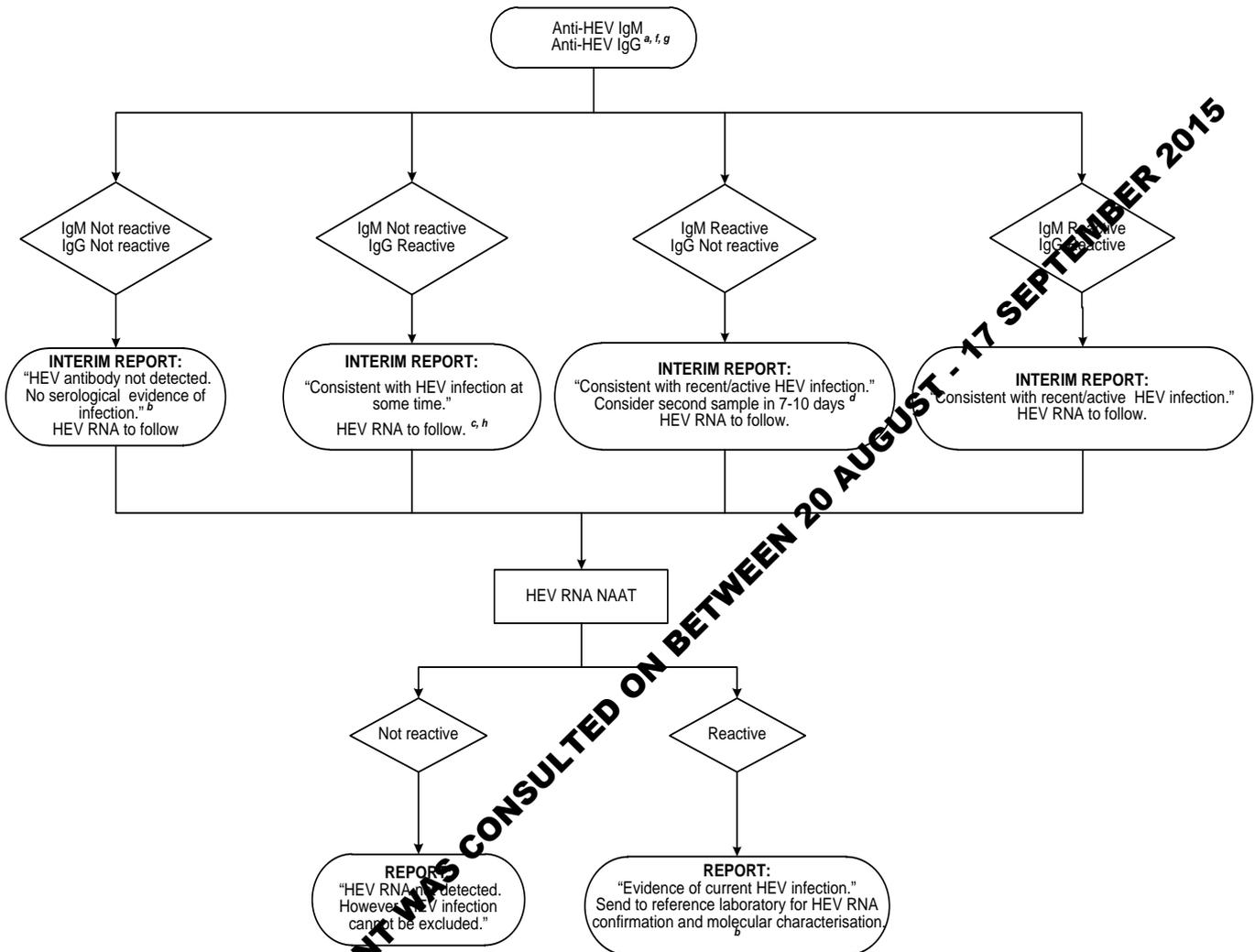
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HEV infection in the immunocompetent^{9,10}



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HEV infection in the immunocompromised⁹⁻¹¹



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Footnotes

- a) The detection of HEV IgM alone is not diagnostic of HEV infection. Send sample to referral laboratory for HEV RNA testing.
- b) Send a second sample if appropriate symptoms and LFT pattern occur within 7-10 days.
- c) Refer to reference laboratory if clinical picture and LFT pattern are consistent with acute infection.
- d) As one of the causes of acute infectious hepatitis, HEV is a notifiable disease in accordance with the Health Protection (Notification) Regulations 2010, Statutory Instruments no.659. Also ensure electronic notification via ColSurv. As HEV does not transmit readily from person to person, the public health risk is thought to be minimal from this route.
- e) Faecal antigen testing, POC tests or Biotest kits may be used as an alternative confirmation strategy to NAATs.
- f) 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 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.
- g) Faecal antigen test may be preferable in immunocompromised patients.
- h) Consider the possibility of passively acquired HEV antibody from blood, or blood products.

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Notification to PHE^{12,13} or equivalent in the devolved administrations¹⁴⁻¹⁷

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](#)^{14,15}, [Wales](#)¹⁶ and [Northern Ireland](#)¹⁷.

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