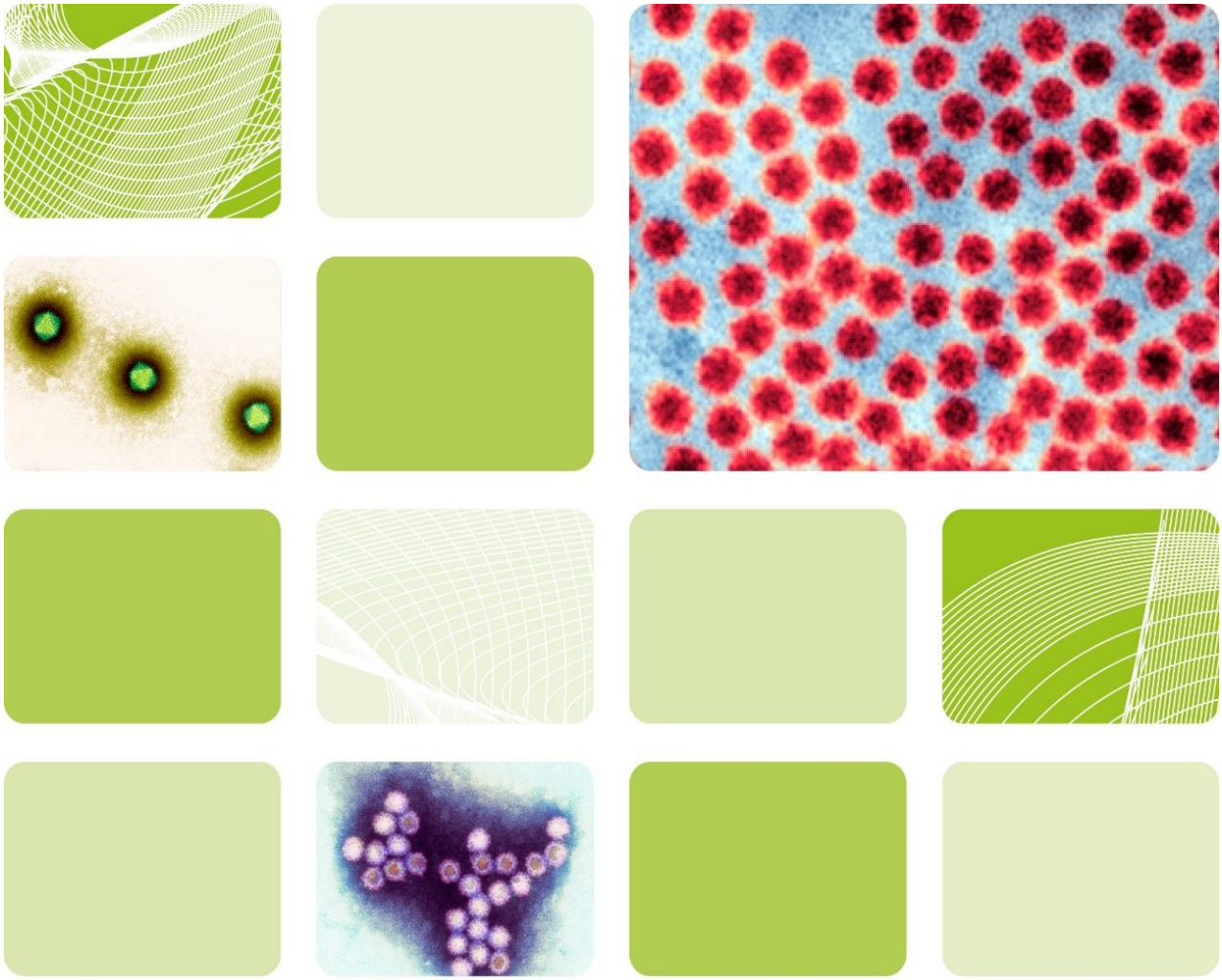
UK Health Security Agency

UK Standards for Microbiology Investigations

Screening and monitoring for hepatitis E infection



Issued by the Standards Unit, UK Standards for Microbiology Investigations, UKHSA

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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	1/23.05.25
Issue number discarded	1
Insert issue number	1.1
Section(s) involved	**Amendment**
Whole document.	**This is an administrative point change.** **The content of this UK SMI document has not changed.** **The last scientific and clinical review was conducted on 05/11/2018.** Hyperlinks throughout document updated to Royal College of Pathologists website. Public Health England replaced with UK Health Security Agency throughout the document, including the updated Royal Coat of Arms Partner organisation logos updated. Broken links to devolved administrations replaced. References to NICE accreditation removed. Scope and Purpose replaced with General and Scientific information to align with current UK SMI template.
Section 10: Public health responsibilities of diagnostic laboratories	This section has been added to UK SMI templates to highlight the public health responsibilities that diagnostic laboratories have as part of their duties.

Amendment number/date	-/05.11.18
Issue number discarded	-
Insert issue number	1
Anticipated next review date*	05.11.21

Section(s) involved	Amendment

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

1 General information

View general information related to UK SMIs.

2 Scientific information

View scientific information related to UK SMIs.

3 Scope of document

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 immunoassay (EIA) screening. 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. For information on treatment refer to European Association for the Study of the Liver (EASL) and for information on transplant patients refer to The Advisory Committee on the Safety of Blood, Tissues and Organs (SABTO) guidance.

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'.

4 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, less than 1% are associated with clinically apparent disease[1,2].

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 (Hepatitis E: symptoms, transmission, treatment and prevention - GOV.UK). 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[1]. Indigenously acquired infections have been linked to the consumption of pork products and diet remains the major route of autochthonous HEV acquisition[1].

There are four main HEV genotypes, G1-G4, which infect humans[3,4]. 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[5,6].

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 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[7-9].

4.1 Laboratory diagnosis

The clinical presentation of acute symptomatic hepatitis E infection 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[7]. It might also be useful to do serology for CMV and EBV infection. The use of alanine transaminase (ALT) data for limiting the number of immunocompetent patients tested may be considered (ie screening for HEV infection on patients with ALT ≥100 IU/L) although in many infections, such as in blood donors, the elevation of ALT may be slight or even absent[10]. UKHSA advise that anyone with unexplained clinical hepatitis, regardless of travel history be tested for HEV.

4.2 HEV symptomatic and non-symptomatic infection in the immunocompetent

Serology supported by the detection of viral nucleic acid is the principal way in which hepatitis E is diagnosed in immunocompetent patients. Asymptomatic HEV infection is sought in donors of blood, tissue and organs by nucleic acid testing alone. Recombinant capsid proteins are used in assays of different format for the detection of antibody to HEV[11]. Although there are four human HEV genotypes, they elicit very

similar antibody responses and appear to represent a single serotype[12-15]. For symptomatic infections, 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[13].

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 viral clearance and following recovery from jaundice in the symptomatic patients. The IgG response can persist for several years and may be lifelong in the majority of patients recovered from HEV infection[16].

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 infection with or without symptomatic presentation is best defined by having HEV RNA positive serum or plasma and coincident IgM and IgG anti-HEV reactivity[17]. 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 of IgG antibody seroconversion in a patient previously sero-reactive soley for IgM confirms the non-specificity of the initial IgM reactivity[17]. The duration of viraemia in the immunocompetent patient is of the order of eight weeks[17]. In a patient presenting with hepatitis E, plasma viraemia and antigenaemia 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.

4.3 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 ALT) in immunocompromised individuals and in individuals with acute neurological presentations consistent with hepatitis E infection[18]. For immunocompromised patients, who may have a delayed or absent antibody response, screening for HEV viraemia by RNA with NAAT is essential[17].

Detection of HEV viraemia without detectable HEV antibodies in the presence of an abnormal ALT may not equate to acute HEV infection, but could be the result of previously undiagnosed persistent infection in the immunosuppressed patient[19].

In those patients who are immunocompromised either through coincident infections (for example HIV) and immune-diatheses (loss of immune function for a variety of systematic diseases) or following transplantation or chemotherapy (solid organ transplants, stem cell transplants and haematology-oncology) or systemic immunosuppressive therapy (inflammatory bowel, renal/vascular, and arthridites), the early phases of the infection may 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. Minimal elevation of LFTs may be a surrogate marker for persistent HEV infection and an indicator for testing for viraemia in immunocompromised patients[17]. Up to half of all initially diagnosed 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 hepatitis recovery. Infections, which do not clear, may persist for years with or without antibody.

For this reason it is recommended that a follow up sample is taken four weeks after the first detection of HEV viraemia in an immunocompromised individual and tested both for antibody and viraemia. 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 and results may inform on the length of infection.

In monitoring of HEV RNA levels during antiviral therapy of persistent chronic HEV infection, it is recommended that monthly HEV RNA testing is undertaken on faeces and plasma. HEV RNA 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[20,21].

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.

4.4 Established persistent hepatitis infection[22]

Persistent hepatitis E infection can result in chronic liver disease and rapidly progressive liver fibrosis and cirrhosis with death due to decompensated liver disease. Persistence is defined as remaining viraemic for at least 3 months. Persistence of an unchanged viral load over a period of one month suggests that a persistent infection is very likely. Data from the transplant setting have shown that a reduction in levels of immune suppression led to viral clearance in 30% of cases[23-25]. Clearance in this setting is usually associated with sero-conversion and frequently with a transaminitis.

In patients with persistent HEV infection treatment is usually ribavirin monotherapy though this usage remains unlicensed. A rapid reduction in viral load during the first week of therapy may indicate an increased likelihood of developing a sustained viral response (SVR)[26]. 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[23-25].

4.5 Confirmation of viral clearance

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 recrudesce and it is wise to continue therapy until two sequential stool samples one month apart are found to be free of detectable virus. This confirms the end of treatment response (ETR). A significant proportion of patients achieving ETR clearance will suffer viral recrudescence of the original infection, confirmable by viral phylogeny, usually associated with a return of ALT elevation. For this reason it is recommended to consider retesting for viraemia at 6 months, or earlier

at any sign of a return of transaminitis, in order to confirm a standard virological response (SVR) for viral clearance.

4.6 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. 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[1,7].

5 Technical information/limitations

5.1 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.

5.2 Specimen containers[27,28]

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”.

6 Safety considerations[27-44]

6.1 Specimen collection, transport, and storage[27-32,45]

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.

6.2 Specimen processing

Laboratory procedures that give rise to infectious aerosols must be conducted in a microbiological safety cabinet[35].

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 Specimen transport, storage, and retention[27,28]

7.1 Optimal transport and storage conditions

Specimens should be transported and processed as soon as possible[46].

If processing is delayed, refrigeration is preferable to storage at ambient temperature[46] and should be in accordance with manufacturers' instructions.

Samples should be retained in accordance with The Royal College of Pathologists guidelines 'The retention and storage of pathological records and specimens'[47].

8 Public health management

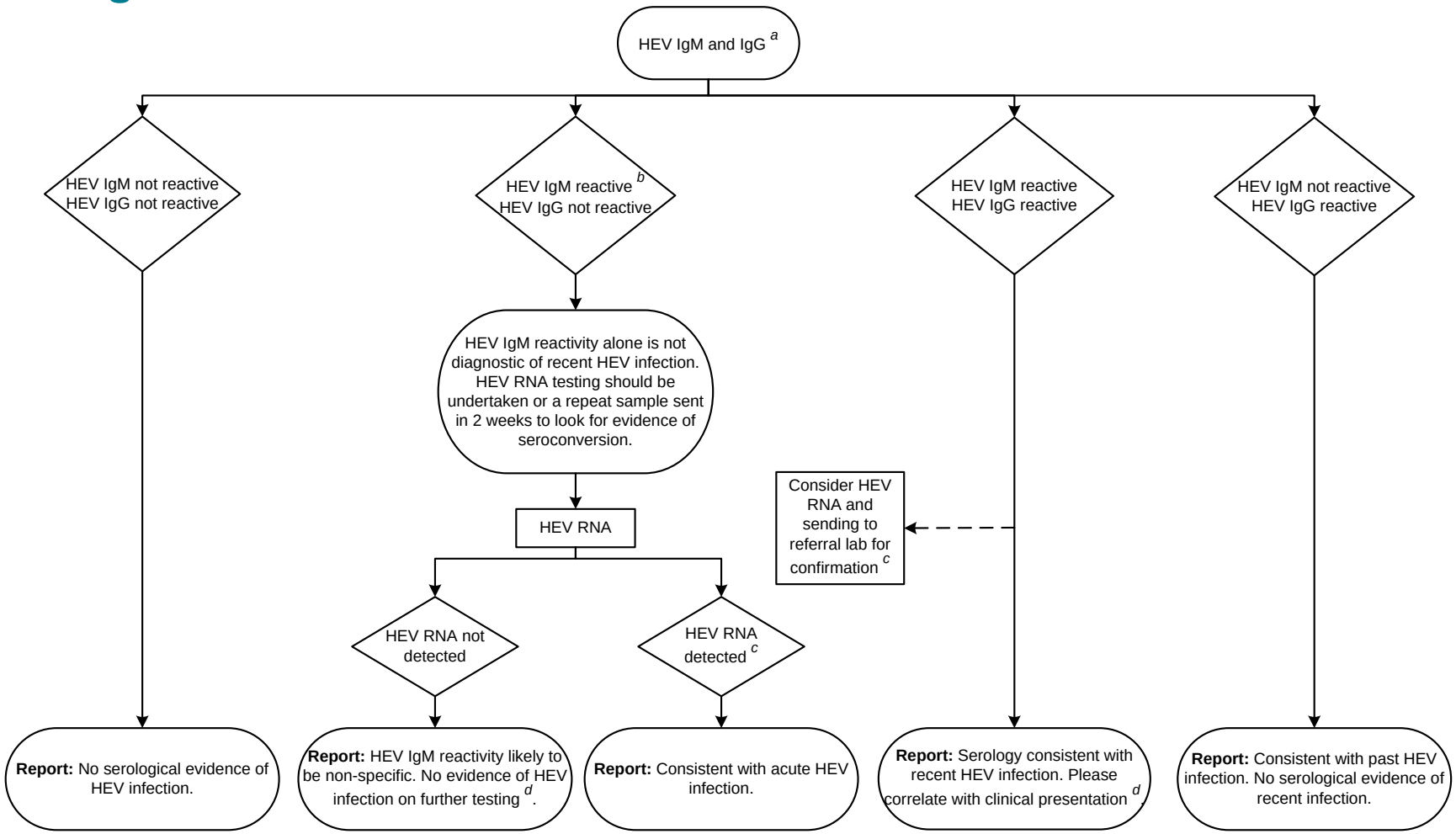
For information regarding notification to UKHSA (or equivalent in the devolved administrations) refer to page 16.

For further information on public health management refer to UKHSA guidance[7]: http://www.gov.uk/government/publications/hepatitis-e-health-protection-response-to-reports-of-infection .

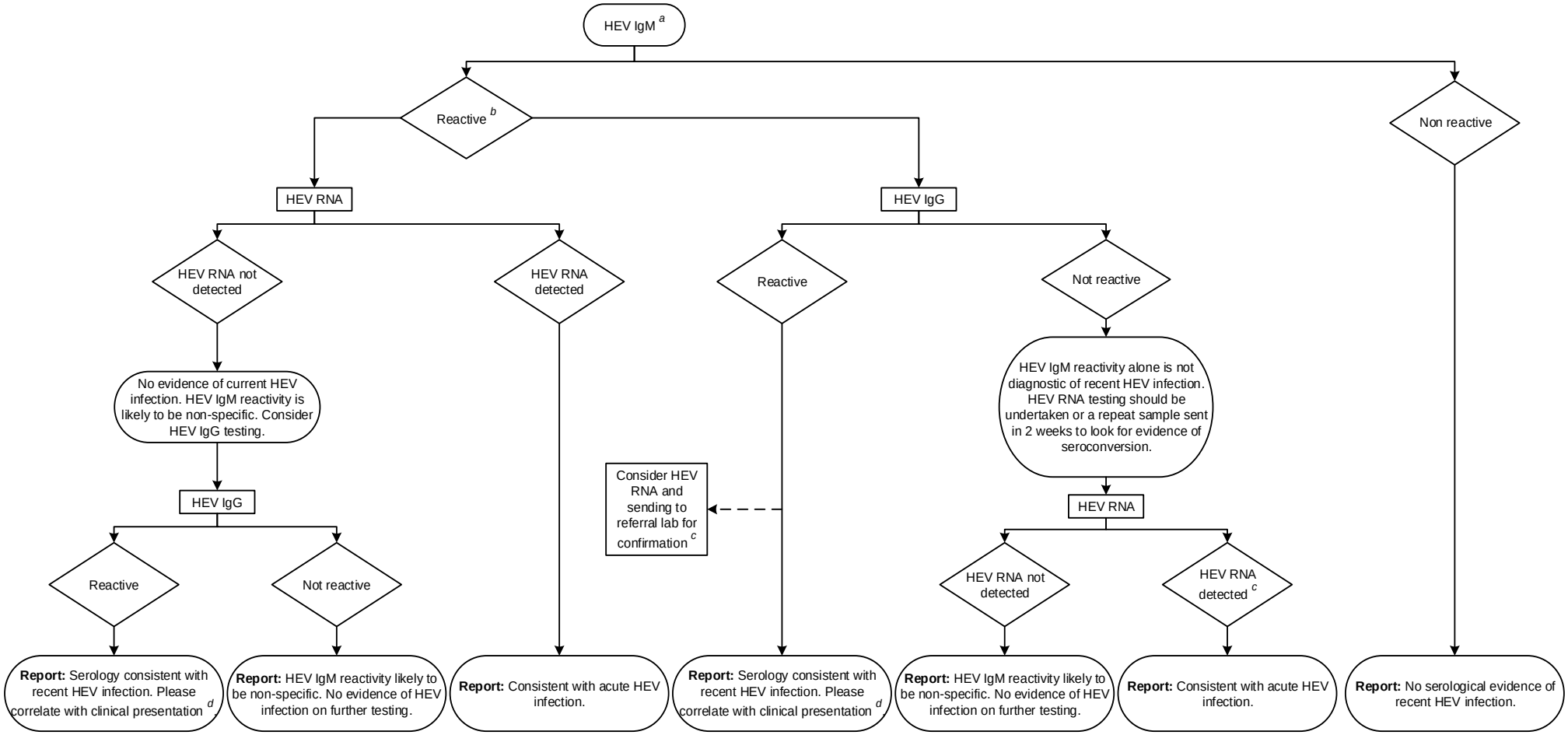
A structured enhanced surveillance questionnaire is available for laboratory confirmed cases of hepatitis E (as defined in the case definition) at: https://www.gov.uk/government/publications/hepatitis-e-surveillance-form

Also refer to Health and Safety Executive guidance for employers and employees: http://www.hse.gov.uk/pubns/

9 HEV infection in the immunocompetent – Screening with HEV IgM and IgG[5,19]



10 HEV Infection in the immunocompetent - Screening with HEV IgM



Footnotes - HEV infection in the immunocompetent algorithm

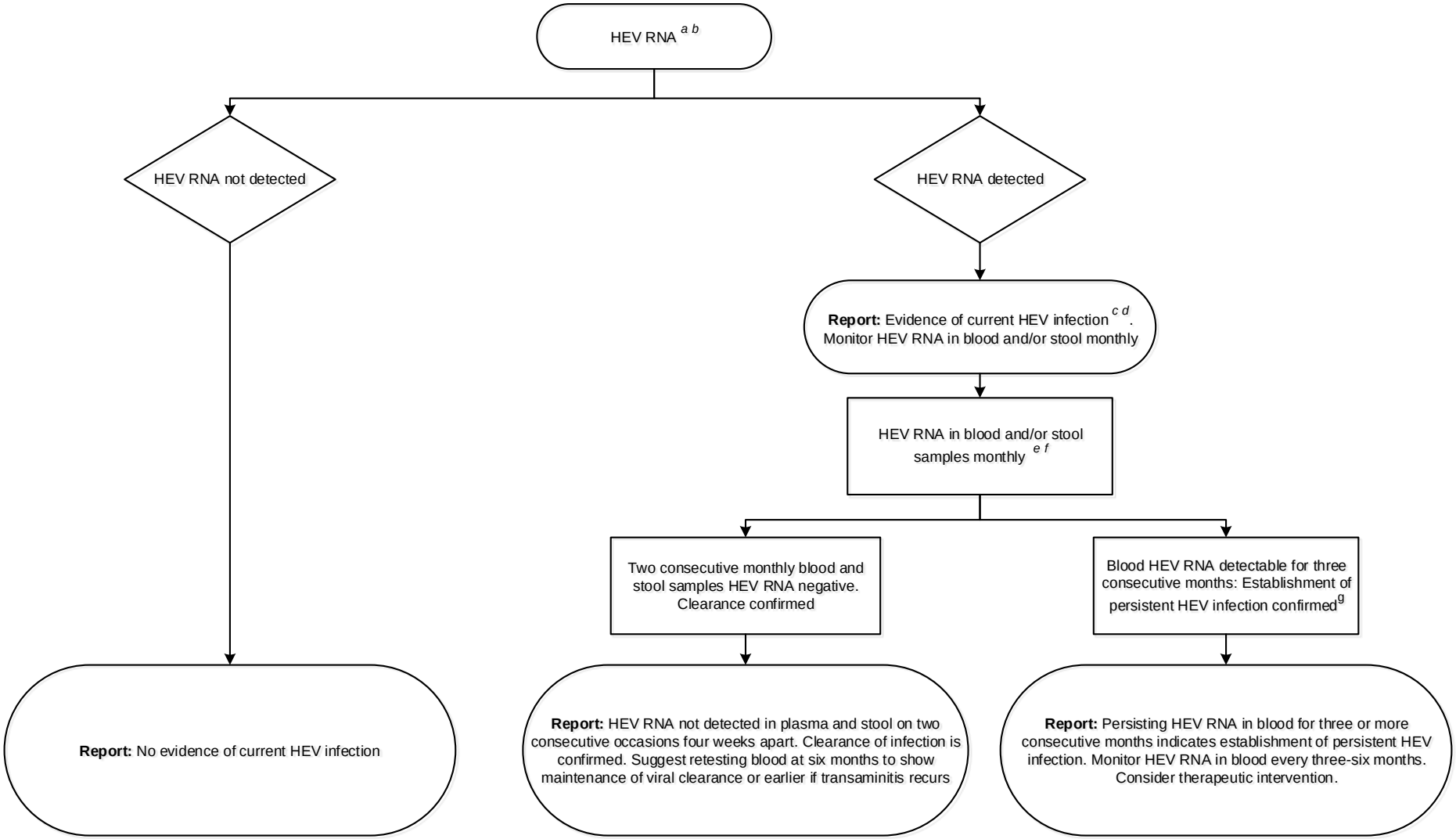
a. Initial screening may be undertaken with HEV IgM or a combination of HEV IgM and IgG depending on local laboratory requirements.

b. The detection of HEV IgM alone is not diagnostic of HEV infection as the specificity of the assays is often low. In laboratories where initial screening is undertaken with HEV IgM only further testing with HEV RNA or HEV IgG is recommended where the IgM is reactive.

c. Consider sending to referral laboratory for genotyping and phylogenetic sequencing. Genotyping is recommended when investigating infections during pregnancy.

d. The significance of a reactive HEV IgM result needs to be interpreted after careful consideration of the clinical presentation, IgM index and the exclusion of other possible causes.

11 HEV infection in the immunocompromised[5,19,48]



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 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:

   i. Decreasing HEV RNA viral load suggests a resolving infection.

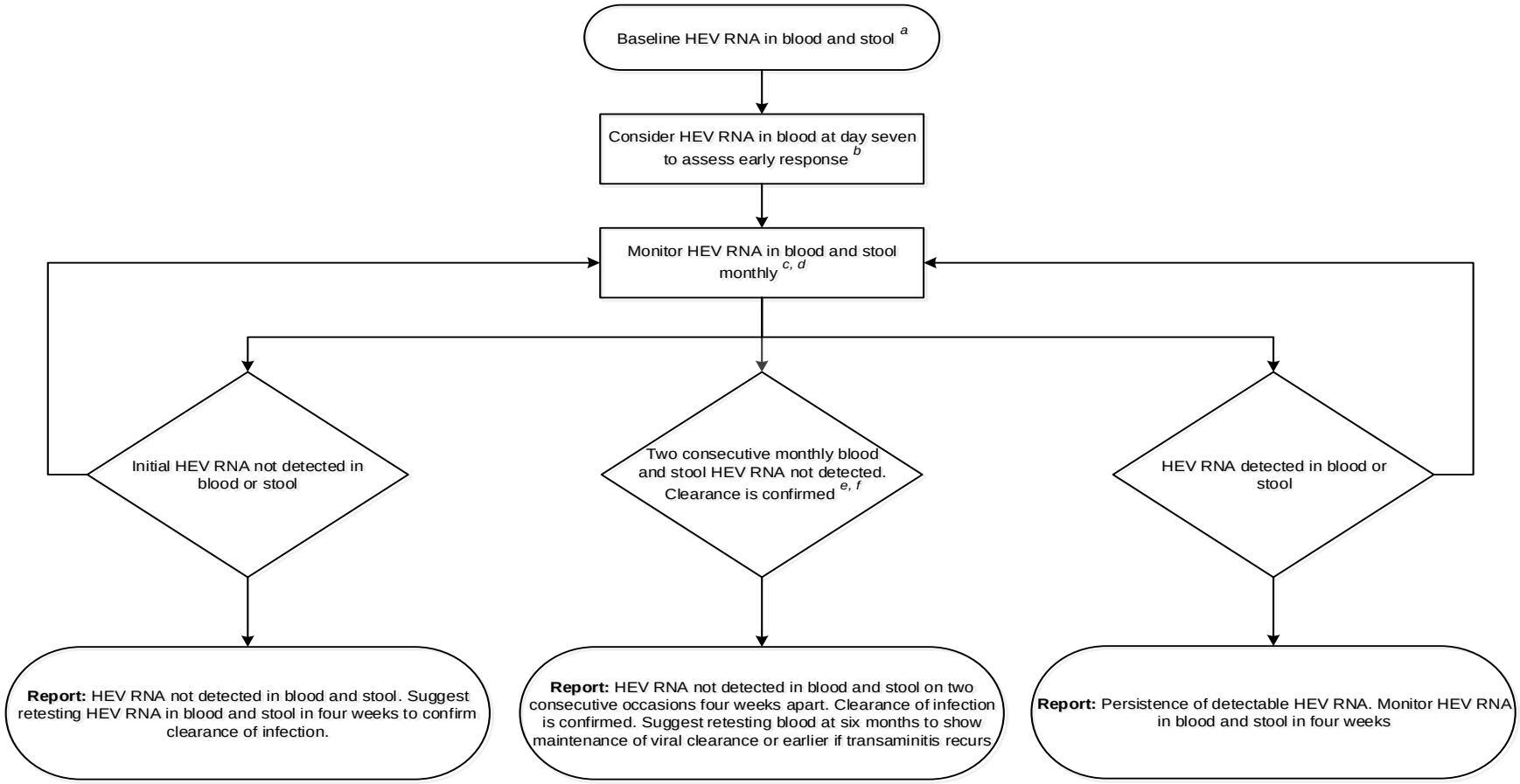
   ii. Increasing HEV RNA viral load suggests a developing recent infection.

   iii. 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.

12 Monitoring of HEV during antiviral therapy for persistent HEV infection



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 virological response to antiviral therapy[20].

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[20].

13 Report comments

Immunocompetent patient

	HEV IgM	HEV IgG	HEV RNA in blood	Interpretative Comment	Notes
1	Not Reactive	Not tested	Not tested	No serological evidence of recent HEV infection	
2	Not Reactive	Not Reactive	Not tested	No serological evidence of HEV infection.	
3	Not Reactive	Reactive	Not tested	Consistent with past HEV infection. No serological evidence of recent infection.	
4	Reactive	Not tested	Not Detected	No evidence of current HEV infection. HEV IgM reactivity is likely to be non-specific. Consider HEV IgG testing.	
5	Reactive	Not tested	Detected	Consistent with acute HEV infection.	
6	Reactive	Not Reactive	Not tested	HEV IgM reactivity alone is not diagnostic of recent HEV infection. HEV RNA testing should be undertaken or a repeat sample sent in 2 weeks to look for evidence of seroconversion.	The detection of HEV IgM alone is not diagnostic of HEV infection as the specificity of the assays is often low.
7	Reactive	Not Reactive	Not Detected	HEV IgM reactivity likely to be non-specific. No evidence of HEV infection on further testing.	
8	Reactive	Not Reactive	Detected	Consistent with acute HEV infection.	
9	Reactive	Reactive	Not detected	Serology consistent with recent HEV infection or non-specific IgM reactivity. HEV RNA not detected.	The significance of a reactive HEV IgM result needs to be interpreted after careful consideration of the clinical

					presentation, IgM index and the exclusion of other possible causes.
10	Reactive	Reactive	Detected	Consistent with acute HEV infection.	
11	Reactive	Reactive	Not tested	Serology consistent with recent HEV infection. Please correlate with clinical presentation and consider HEV RNA testing.	The significance of a reactive HEV IgM result needs to be interpreted after careful consideration of the clinical presentation, IgM index and the exclusion of other possible causes. HEV RNA testing should be considered for confirmation.

Immunocompromised patient*

	HEV RNA in blood	HEV RNA in stool	Interpretative Comments	Notes
1	Not detected	Not tested	No evidence of current HEV infection	
Base line sample				
2	Detected	Not tested	Evidence of current HEV infection. Monitor HEV RNA in blood and/or stool monthly.	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. Previous archived samples may be used in the investigation of persistent infection to identify length of infection.
Monitoring samples				
3	Detected	Detected or Not tested	*Detectable for ≥3 consecutive months:* Persisting HEV RNA in blood for three or more consecutive months indicated establishment of persistent HEV infection. Monitor HEV RNA in blood every three-six months. Consider therapeutic intervention.	Quantitative HEV RNA viral load monitoring may provide further information regarding the dynamics of the HEV infection: • Decreasing HEV RNA viral load suggests a resolving infection. • Increasing HEV RNA viral load suggests a developing recent infection. • Unchanged HEV RNA viral load suggests an established persistent infection. 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.

				Refer to monitoring algorithm for persistent HEV infection during antiviral therapy.
4	Not detected	Not detected	*Two consecutive monthly blood and stool samples HEV RNA negative.* HEV RNA not detected in plasma and stool on two consecutive occasions 4 weeks apart. Clearance of infection is confirmed. Suggest retesting blood at six months to show maintenance of viral clearance or earlier if transaminitis recurs.	

*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 and the use of HEV serology is not part of the routine diagnostic algorithm.

13 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.

14 Notification to UKHSA[49,50,] or equivalent in the devolved administrations[51-54]

The Health Protection (Notification) regulations 2010 require diagnostic laboratories to notify UK Health Security Agency (UKHSA) 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 UKHSA 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 UKHSA. The vast majority of NHS laboratories voluntarily report a wide range of laboratory diagnoses of causative agents to UKHSA and many UKHSA Health Protection Teams have agreements with local laboratories for urgent reporting of some infections. This should continue.

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

https://www.gov.uk/guidance/specialist-and-reference-microbiology-laboratory-tests-and-services
Other arrangements exist in Scotland[51,52], Wales[53] and Northern Ireland[54].

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An explanation of the reference assessment used is available in the scientific information.

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