

TECHNICAL REPORT



Options for national testing and surveillance for hepatitis E virus in the EU/EEA

Operational guidance

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Conflict of interest declarations were provided and are available on request.

Representatives of the European Food Safety Authority (EFSA, Valentina Rizzi and Michaela Hempen) and the World Health Organization Regional Office for Europe (Antons Mozalevskis) were observers in this group and received documents for review.

The work was supported by two service contracts No. ECD.7600 (HEV epidemiological support – P/2017/OCS/253) and No. ID 5132 (Hepatitis B, C, and E in the EU/EEA: monitoring and testing activities). The following staff were involved on the contractor's side: Esther Aspinall (Glasgow Caledonian University and Health Protection Scotland), Andrew Rideout (NHS Dumfries and Galloway) and Chris Biggam (Glasgow Caledonian University).

ECDC would also like to acknowledge the following ECDC staff for supporting the project and providing critical review of the documents: Mike Catchpole, Johanna Takkinen and Phillip Zucs.

Suggested citation: European Centre for Disease Prevention and Control. Options for national testing and surveillance for hepatitis E virus in the EU/EEA – Operational guidance. Stockholm: ECDC; 2019.

Stockholm, September 2019

ISBN: 978-92-9498-375-6

DOI: 10.2900/417723

Catalogue number: TQ-04-19-540-EN-N

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Abbreviations and acronyms

ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AP	Alkaline phosphatase
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EASL	European Association for the Study of the Liver
EFSA	European Food Safety Authority
EU	European Union
HEV	Hepatitis E virus
LFT	Liver function test
NAT	Nucleic acid test
PT	Prothrombin time
SoHO	Substances of human origin
WHO	World Health Organization

Executive summary

Hepatitis E virus (HEV) is one of the leading causes of acute viral hepatitis worldwide, with genotype 3 predominating in high-income countries, such as in the European Union/European Economic Area (EU/EEA) [1,2]. HEV infection is an endemic zoonosis in EU/EEA countries. Human hepatitis E infection is not included in the list of infectious diseases and special health issues to be reported at the EU level [3]. Populations under surveillance, case definitions and reporting systems are decided by each country individually. Twenty of the 31 EU/EEA countries reported having HEV-specific surveillance systems and more than 20 000 cases have been reported from 2005–2015, the vast majority locally acquired. A national case definition for acute cases was available for 12 countries.

In 2017, the WHO Regional Office for Europe published the 'Action plan for the health sector response to viral hepatitis in the WHO European Region' [4]. It mentions several milestones, including 'harmonized surveillance objectives...and case definitions'. ECDC has identified the need to support EU/EEA countries in implementing the WHO European action plan, particularly in relation to hepatitis E [4]. ECDC, together with its HEV expert group, has therefore developed this operational guidance on hepatitis E testing and surveillance at country level to provide assistance to Member States and harmonise practices across the EU/EEA. The document provides options for the aspects considered most relevant for surveillance of HEV infections and it is for each Member State to decide which of these suggestions are appropriate for their situation. Many EU/EEA countries have stable and long-standing surveillance systems for hepatitis E. Information from these countries, as well as clinical guidelines from the European Association for the Study of the Liver (EASL), were used in the preparation of this guidance [5].

The ECDC HEV expert group agreed that one of the primary objectives of national HEV surveillance should be to describe the epidemiology of the infection in a country based on the incidence of acute cases. As the majority of infections are asymptomatic, it is necessary to be able to distinguish asymptomatic cases identified through screening or case finding, especially those identified through blood donor screening, from acute symptomatic cases. Chronic hepatitis E infections show a different clinical presentation, affect specific groups of patients and can cause severe and fatal disease progression. The report presents options intended to support the description of the epidemiology of acute and chronic infections over time. All experts but one agreed with the inclusion of chronic infections in national surveillance and emphasised the need to monitor persistent HEV infections. This will enable a better understanding of the impact and severity of HEV infections and support efforts, particularly with regard to blood safety and transplants, to prevent infections with severe and fatal outcomes. In addition, more robust data will provide further evidence regarding the case for control measures in the agriculture and food industries. The surveillance of HEV phylogenotypes or subtypes, as well as the identification of potential clusters/outbreaks and collection of information on suspected routes of transmission, were considered secondary objectives for national surveillance. Information on risk factors for infection, food exposure history, clinical complications or other parameters was thought to be outside the scope of routine surveillance systems and best collected through enhanced studies.

Taking into consideration the complexity, cost and epidemiological benefits, the minimal requirements for national HEV surveillance to meet the primary objective were assessed to be annual laboratory reporting of confirmed cases with a basic epidemiological data set (i.e. date of diagnosis, age, sex and place of residence). The best option to meet all the objectives was considered to be monthly comprehensive or at least representative reporting of laboratory-confirmed cases with individual information on the laboratory method used, the viral geno- or subtype, source of notification or laboratory diagnosis, travel history, case status (acute or chronic) and clinical presentation (asymptomatic, hepatic or extra-hepatic).

The ECDC expert group noted that it is crucial for public health authorities to understand the populations targeted by laboratory testing algorithms, especially when developing surveillance systems. Therefore, the development and implementation of clinical recommendations and guidelines for testing should involve and inform national or local public health authorities. The ECDC expert group agreed with EASL recommendations that patients with signs of viral hepatitis and certain other groups (even without clinical symptoms) should be considered a priority for HEV testing.

The ECDC expert group considered that the minimum laboratory criterion for confirming an acute case is detection of both HEV-IgM and IgG antibodies in serum or plasma. Detection of HEV RNA by PCR alone or in addition to serology was also considered an option. The presence of HEV RNA in blood and/or stool samples for at least three months with a confirmation based on persistent PCR positivity alone was assessed as essential for confirming a chronic case. In order to monitor the circulating HEV genotypes/subtypes, the ECDC expert panel concluded that a subset of HEV RNA-positive samples should be sequenced.

As most human cases are likely related to the consumption of contaminated food, it is considered important to also provide evidence of the number of (clinical) cases related to viruses from animal (particularly pig) populations in order to support control efforts in farming and food processing and ultimately reduce the risk of infection.

1 Background

Hepatitis E virus (HEV) is one of the leading causes of acute viral hepatitis worldwide [2]. In the European Union/European Economic Area (EU/EEA), cases of hepatitis E have been increasingly reported over the last decade [6]. Genotype 3 infections predominate in high-income countries [1]. Unlike HEV genotypes 1 and 2 that are restricted to humans and have caused large epidemics, genotype 3 infection is a zoonosis and has been linked to the consumption of contaminated pork or shellfish products [1,7–9]. In the EU/EEA, large outbreaks are uncommon, but family clusters associated with the consumption of undercooked pork products or raw pork liver sausage have been documented [7,10]. In several cases, infections have been traced back to contaminated blood products or infected organs [11–13]. HEV infection may be asymptomatic or cause an acute self-limiting hepatitis [14]. The majority (up to 95%) of infections occur without or with only mild clinical symptoms. Symptomatic patients mostly show signs and symptoms of viral hepatitis, although in the initial phase, patients may also experience non-specific symptoms such as flu-like myalgia, arthralgia, weakness and vomiting, which are followed by liver-specific jaundice, itching, light stool and dark urine [15] as well as an increase of liver-related markers (e.g. alanine transaminase (ALT) and aspartate transaminase; AST) [16]. Different clinical presentations are not uncommon, particularly neurological manifestations such as small fibre neuropathy, Parsonage Turner syndrome or Guillain-Barré syndrome. HEV infection can also cause other extrahepatic manifestations, renal and haematological disorders. Risk factors for symptomatic or complicated infection include male sex, older age and pre-existing liver disease [17]. Persistent chronic HEV infection has been reported particularly among those who are immunosuppressed or who have pre-existing liver disease [14]. Chronic HEV infection may rapidly lead to cirrhosis and is characterised by a prolonged viraemia without necessarily clear signs of viral hepatitis and IgM or IgG antibodies may be absent [18–20]. The burden of disease due to HEV in Europe is unclear given a lack of published information and the considerable differences in awareness, testing and surveillance efforts across EU/EEA Member States. However, there is emerging evidence that HEV is an under-recognised pathogen in high-income countries and the overall notification rate has increased over the last decade [21].

Situation in the EU/EEA Member States

Hepatitis E is not notifiable at the EU level. ECDC has therefore compiled information on the national situation relating to HEV testing, diagnosis, surveillance and the availability of epidemiological data in EU/EEA Member States covering 2005–2015 [6,22]. The number of confirmed cases of HEV infection in Europe increased year on year, with a particularly sharp increase after 2011 and more than 20 000 nationally notified cases in total from 2005–2015, most of them locally acquired. The rising numbers were assessed to be partly due to increased awareness and testing, as well as the availability of more accurate tests (NAT and serology). The state of implementation of routine HEV testing and surveillance was found to be heterogeneous across EU/EEA Member States: more than half of them have well established testing protocols and surveillance systems, a small proportion have more recent or evolving systems and a third have no surveillance for HEV in place. A national case definition requiring laboratory confirmation for acute cases was available for 12 countries. Eight countries used clinical criteria and three used epidemiological criteria. Surveillance systems in Ireland and the United Kingdom differentiate between acute and chronic HEV infection, with RNA persistence for at least three months defining chronicity of infection. Most of the 20 EU/EEA Member States with HEV surveillance collected case-based data and more than 70% of the systems collected the following basic information: unique patient identifier, date of notification, source of notification, date of birth, sex, and date of onset of disease (Table 2).

ECDC conducted an expert consultation meeting (Lisbon, 2016) to assess the risk and prevention of HEV transmission through substances of human origin (SoHO). A publication summarised the epidemiology of HEV infections among blood donors, strategies to prevent transfusion-transmitted HEV in 11 European countries and listed blood donation screening programmes that have been implemented locally or nationally based on risk assessments [13].

Action plan of World Health Organization

In 2017, the WHO Regional Office for Europe published the 'Action plan for the health sector response to viral hepatitis in the WHO European Region' [4], which adapts the WHO 'Global health sector strategy on viral hepatitis, 2016–2021' [23]. The action plan, together with resolution EUR/RC66/R10, was endorsed and signed on 14 September 2016. The action plan aims at 'elimination of viral hepatitis as a public health threat in the WHO European Region by 2030' [4]. One of the milestones is to have 'harmonized surveillance objectives...and case definitions' by 2018. The target for 2020 for the Member States is 'to have a national hepatitis infection surveillance programme...that can detect outbreaks in a timely manner, assess trends in incidence, inform disease burden estimates, and do effective real-time tracking of viral hepatitis diagnosis, treatment and care cascade, including vulnerable populations' [4]. The WHO document underlines that national laboratory systems should be strengthened to ensure availability of diagnostics and perform high-quality diagnosis for both acute and chronic

infections. Related priority actions include the assessment and strengthening of surveillance systems and case definitions as well as developing and rolling out national viral hepatitis testing and diagnostic guidelines. The recommended actions in the Member States also include the establishment or maintenance of effective surveillance systems for hepatitis E. WHO commits to providing 'guidance on viral hepatitis testing' and doing their best 'in collaboration with ECDC, to optimize data collection, harmonize case definitions, improve data collection and analysis' [4].

Purpose and scope

ECDC has identified a need to support EU/EEA countries in implementing the WHO European action plan to enhance or adapt their capacity for HEV surveillance and control. As the disease is not under EU-wide surveillance, there is no harmonised case definition or reporting system. The specific surveillance systems for HEV that are in place differ across the 20 countries. This document offers options on the implementation or adjustment of national HEV surveillance and covers criteria derived from the European Association for the Study of the Liver (EASL) for clinical testing, case definitions for acute and chronic HEV infections and reporting schemes. Its aim is to help countries in fulfilling WHO's 2018 milestones and 2020 targets [4]. Harmonised criteria for testing and reporting of hepatitis E should also foster data comparability across EU/EEA countries. Comparable data will in turn improve knowledge on the epidemiology of HEV infections in the EU/EEA, provide evidence for risk assessment and the implementation of public health measures and inform animal health and food safety authorities. Ultimately, this will support preventive and control measures to reduce the risk of transmission to humans.

2 Methods

ECDC's HEV expert group

In 2015, ECDC initiated activities to assess the risk of HEV as an emerging pathogen in the EU/EEA Member States. To support these activities, ECDC asked Member States to nominate experts for ECDC's HEV expert group. In addition to nominated Member State experts, scientists working on hepatitis E in relation to blood safety, clinical science and vaccine/WHO reference material (proven by peer-reviewed publications) were included as members. A representative each from the WHO Regional Office for Europe and the European Food Safety Authority were invited as observers.

Data collection

For the development of this operational guidance, information from different sources was used:

- In 2016, ECDC published a report on 'Hepatitis E in the EU/EEA, 2005–2015' [22]. It was based on a survey on HEV testing, diagnostic practices, surveillance and epidemiological data that was sent to the national focal points of food- and waterborne diseases in the ECDC Programme for Food- and Waterborne Diseases and Zoonoses. Thirty of the 31 Member States responded to the survey. Country-level responses were detailed and informative, providing a rich dataset to inform this subsequent work (Annex 1).
- An online survey was developed to collect information, as well as rank priorities and identify common objectives for national HEV surveillance, data requirements and case definitions for acute and chronic cases and clinical testing (Annex 3). The questionnaire was piloted with experts at the HEVnet meeting in 2017 [24] and ECDC staff. All members of ECDC's HEV expert group were then invited to participate in November 2017. Eleven of 22 members from 10 countries responded to the survey (Annex 2).
- EASL published clinical practice guidelines on HEV infection with graded (1 strong/ 2 weak) recommendations to clinicians on whom to test for hepatitis E based on the level of evidence (levels A–C) [5].
- Peer-reviewed publications were non-systematically searched for additional information on clinical testing guidelines, blood donor screening or other relevant data useful for this document.

Data synthesis

- A draft document was shared with the ECDC HEV expert group in October 2018 for review and comments. Comments were included for discussion and final agreement.
- A meeting with the ECDC HEV expert group was conducted in November 2018 to discuss the content and agree on the next version of the document. Discussion points and dissenting opinions were added to the respective chapters.
- This version was shared with all members of ECDC's HEV expert group and ECDC staff for final revisions and approval.

3 Results

Objectives for national surveillance

The group considered that harmonised surveillance approaches and comparable data provide the necessary information and best evidence for developing public health guidance, as well as informing animal health and food safety authorities to support preventive and control measures in the animal population and food production.

The expert group considered the following primary surveillance objectives as the most relevant:

- monitoring the incidence of acute HEV cases*
- monitoring chronic HEV infections**; and
- describing the epidemiology of acute and chronic HEV infections.

**: Surveillance data should enable distinguishing between cases detected through blood donor screening and cases derived from diagnostic laboratory testing. Surveillance data should also allow distinguishing between symptomatic and asymptomatic cases.*

***Note: One expert disagreed with monitoring of chronic infections as a primary objective and suggested that the incidence of chronic infections could be a secondary objective if the surveillance system allows for it. Otherwise, chronic infections may be addressed through specific studies (on risk factors or immunopathogenesis).*

The secondary surveillance objectives are:

- monitoring HEV phylotypes/subtypes
- identifying potential clusters/outbreaks; and
- collecting information on possible routes of transmission.

Possible surveillance systems

The clinical presentation of an HEV infection can vary substantially from asymptomatic or self-limiting symptomatic hepatitis to severe chronic disease. Extrahepatic manifestations, e.g. neurological syndromes, can also occur. The fact that up to 95% of HEV infections are asymptomatic was considered when discussing the surveillance objectives.

The ECDC expert group keenly debated whether national HEV surveillance systems should include only symptomatic cases or all HEV infections with or without clinical symptoms. The group finally agreed that systematic and continuous surveillance of acute and chronic cases allows for a more complete assessment of the epidemiology, severity and mortality associated with HEV. Nevertheless, it was considered important for a national surveillance system to collect information on symptomatic cases to better understand the epidemiology of acute clinical cases. Information on the source of notification would enable the differentiation of acute asymptomatic HEV cases identified through blood donor screening programmes from acute symptomatic HEV cases reported by laboratories or physicians. Information on chronic cases may also support decisions on the implementation/discontinuation of blood donor screening programmes.

The group further agreed that prevalence and incidence data from a representative blood donor screening programme would fulfil the objective of monitoring HEV infections in a population, but such universal screening programmes are currently only implemented in a few Member States. In addition, comprehensive blood donor screening is cost-intensive and may not be feasible or reasonable (based on the national risk assessment) in each country.

Sentinel surveillance and blood donor screening represent alternative ways of collecting information relevant to some of the outlined objectives. For any non-comprehensive systems, denominator data, e.g. on the number of tested patients or specimens for HEV, are necessary to understand the data and should be considered.

Best options for national surveillance: minimal and optimal requirements

For national surveillance of HEV, the ECDC expert group favoured a comprehensive or stable representative sentinel surveillance system collecting a minimum set of clinical and epidemiological data on each laboratory-confirmed case. Monthly reporting at a minimum was suggested to be the best option for the detection, investigation of and response to possible outbreaks. Annual data collection was considered a minimum requirement. The most important variables to collect in national surveillance were considered to be date of diagnosis, patient age, sex, place of residence and the laboratory method applied for case confirmation (serology – IgM/IgG – or PCR). Where available, the genotype/subgenotype should be collected. In addition, information on case status (acute or chronic), hospitalisation and travel history was considered valuable.

The group discussed that information on outcome (recovery/death) and clinical presentation (asymptomatic, hepatic or extrahepatic) would be useful, but very challenging to obtain within the surveillance structures in all countries and for all cases. This may also be true for information on the source of notification or laboratory diagnosis. The group noted that data on patient risk factors, food and other exposure history and clinical complications should be collected through supplementary research studies because routine surveillance will not provide sufficiently valid data. Relevant risk factors may include reduced immunity, receipt of substances of human origin (SoHO), chronic liver disease or pregnancy.

Testing for HEV

Testing methodology: certain considerations

The best point in time for a specimen to be taken during the course of HEV infection was considered to be at the time of ALT elevation, but in general as soon as possible after disease onset. Plasma and serum can both be used to detect or confirm HEV infection by serological assays or PCR, but the experts considered plasma the more stable analyte for RNA testing. HEV RNA can also be detected in faeces, which is less invasive than drawing blood and is essential in monitoring response to antiviral treatment. HEV RNA in faeces can persist for prolonged periods after clearance of detectable viraemia.

In a substantial number of immunosuppressed patients, including transplant and haematological patients, with persistent HEV infection, both the IgG and IgM antibody response may be absent for several years. Organ and haematological transplant recipients should therefore be tested using HEV PCR instead of HEV serological markers.

Antigen tests could replace PCR as a surrogate test during HEV viraemia, but have a lower sensitivity than PCR and cannot replace serological testing. Antigen tests can be used for chronically immunosuppressed patients and are predictive for chronicity in acute infection [25]. The expert group noted that the experience with antigen tests in this context is limited.

Clinical practice guidelines for HEV testing

When implementing a surveillance system for a disease, it is important to understand not only the underlying population, but also the clinical criteria for testing. They help to interpret the reported case-based data and changes over time when new testing systems are introduced or additional patient groups are included.

The European Association for the Study of the Liver (EASL) published clinical practice guidelines and recommendations on HEV infection testing in 2018 (Table 1) [5].

Table 1. Recommendations and suggestions for HEV testing in clinical patients according to the European Association for the Study of the Liver [5]

Manifestation	HEV testing	Level of evidence
Acute	Recommended: All patients with symptoms consistent with acute hepatitis irrespective of travel history	A1
Acute	Recommended: Travellers with hepatitis returning from areas endemic for HEV gt1 or 2	A1
Acute	Recommended: Patients presenting with drug-induced liver injury	A1
Acute	Recommended: Patients with unexplained flares of chronic liver disease	C2
Chronic	Recommended: All immunosuppressed patients with unexplained abnormal LFTs	A1
Extrahepatic	Recommended: Patients presenting with neuralgic amyotrophy irrespective of LFT results	B1
Extrahepatic	Recommended: Patients presenting with Guillain-Barré syndrome irrespective of LFT results	B1
Extrahepatic	Suggested: Patients with encephalitis/myelitis	C2
SoHO	Recommended: Patients with abnormal LFTs after receiving blood products	A1
SoHO	Recommended: blood donor services screen blood donors for HEV by NAT, informed by local risk assessment and cost-effectiveness studies	A1

LFT: liver function testⁱ

NAT: nucleic acid amplification test

SoHO: substances of human origin

Level of evidence A: data derived from meta-analyses or systematic reviews or from (multiple) randomised controlled trials (RCTs) with high quality

Level of evidence B: data derived from a single RCT or multiple non-randomised studies

Level of evidence C: small studies, retrospective observational studies, registries

Recommendations grade 1: strong

Recommendations grade 2: weak.

Criteria to initiate testing for HEV in all patients

For acute cases, EASL recommends with a high level of evidence (A1) that 'all patients with symptoms consistent with acute hepatitis should be tested for hepatitis E virus'. The suggestion to test patients with unexplained flares of chronic liver disease is based on a low level of evidence and graded weak (C2). Immunocompetent patients with biochemical evidence of hepatitis, suspected drug-induced liver injury or encephalitis and patients with unexplained acute neurology and a raised ALT are also recommended to be tested. For patients with decompensated chronic liver disease, neuralgic amyotrophy or Guillain-Barré syndrome, the recommendation is that testing should be done at disease onset irrespective of ALT results. EASL recommends with high confidence that travel history alone without the clinical picture of hepatitis should not be used as criterion for HEV first-line testing (A1; Table 1).

The ECDC expert group concurred with the EASL recommendations that all patients with symptoms consistent with viral hepatitis should be tested for HEV. This is already in place in many EU/EEA countries.

Criteria to initiate testing for HEV in risk groups and other relevant patients

In general, EASL recommends the same testing scheme for immunocompromised and immunocompetent patients but considers a persistently abnormal ALT level an additional criterion in an immunocompromised patient. With a high level of evidence, EASL recommends that all immunosuppressed patients with unexplained abnormal LFTs are tested for HEV by PCR (A1) [5]. In addition, patients with suspected drug-induced liver injury are strongly recommended for HEV testing (A1). For patients presenting with extra-hepatic manifestations, irrespective of LFT results, EASL recommends HEV testing in case of neuralgic amyotrophy (B1), Guillain-Barré syndrome (B1) and encephalitis/myelitis (C2). In addition, patients with unexplained acute neurological symptoms and a raised ALT should be included (Table 1).

The ECDC expert group agreed with the EASL guidelines. The group acknowledged that SoHO recipients are at risk for chronic HEV infection and that systematic testing and monitoring in this cohort is essential for a robust national surveillance system.

ⁱ Group of tests to detect, evaluate and monitor liver disease or damage. The tests include prothrombin time, activated partial thromboplastin time, albumin, bilirubin (direct and indirect), alanine transaminase and aspartate aminotransferase, alkaline phosphatase and others.

The group also emphasised that genotype 1 or 2 infections during pregnancy have a higher risk of severe clinical complications.

Routine testing for HEV in blood donors and recipients

EASL recommends testing for patients with abnormal LFTs after receiving blood products (A1) and screening of blood donors for HEV by NAT for blood donor services, informed by local risk assessment and cost-effectiveness studies (A1; Table 1) [5].

The ECDC expert group emphasised that testing of donations should be implemented according to the national situation and based on a risk assessment within each Member State.

Acute case confirmation

EASL strongly recommends using a combination of serological testing and NAT to diagnose acute HEV infection (A1). EASL lists as positive markers for an acute infection HEV antigen presence based on RNA positivity alone or together with IgM or/and IgG positivity. If only serological testing is used, a rising IgG titre and IgM positivity are required [5].

The ECDC expert group suggested positivity of both IgM and IgG as minimum criteria for the confirmation of acute HEV infection. Although a positive PCR alone (in the absence of serological test results) can be considered sufficient to confirm an acute case, PCR testing may not be available in all laboratories and countries. PCR diagnosis is considered optional in acute cases. IgM positivity indicates a recent infection and specimens with a low level of IgM are often PCR negative. In a minority of cases, IgM may persist for 6–12 months, while virus RNA is only detectable by PCR for 1–2 months [5,26].

Clinical symptoms used for hepatitis E confirmation

The ECDC expert group considered signs of viral hepatitis based on laboratory parameters, such as elevated liver enzymes, most relevant. The group discussed that the clinical presentation may vary among acute cases and that patients with extrahepatic manifestations of HEV may present with different symptoms. The group concluded that whether and which symptoms should be included for the confirmation of an acute case should be at each country's discretion.

Chronic case confirmation

EASL strongly recommends NAT testing to diagnose a chronic HEV infection (A1) and lists HEV RNA positivity with or without anti-HEV antibodies for three or more months, as well as the detection of viral antigen, as markers [5].

The ECDC expert group considered PCR positivity, i.e. the presence of HEV RNA for at least three months, sufficient for labelling a case as chronic (Annex 2).

Molecular epidemiology, sequencing of HEV isolates

It was considered that viral isolates should be sequenced by national/regional reference laboratories within defined studies, but also related to routine surveillance. Certain countries have already established criteria to select isolates for sequencing based on clinical criteria, geographical distribution, specimens with low Ct values, chronic cases or patients under treatment (Figure 1). The generation of full-length sequences should be left to specific studies addressing research questions by analysing representative samples. It was noted that the availability of whole genome sequencing in laboratories will increase the availability of full-length sequences, but the definition of reference sequences and the viral load in the specimens remains critical for reliable analysis.

Epidemiological case definition

The ECDC expert group considered an outbreak (91%), food-related exposure (73%) and occupational exposure (55%) to constitute possible epidemiological links (Annex 2). However, an epidemiological link to a confirmed case was not accepted as a strong indication for testing. This criterion may be useful and relevant in an outbreak setting, but not for regular surveillance purposes. The ECDC expert group did not consider an epidemiological or 'probable' case definition a requirement for national surveillance.

4 Synthesis: options for national surveillance

ECDC and the ECDC HEV expert group concluded that taking into account the EASL recommendations and the situation in EU/EEA Member States, the adoption of the following objectives and options (minimal or optional) by national surveillance systems for HEV would facilitate achievement of the WHO Action Plan and deliver more consistent and robust evidence for policy.

Objectives

Primary:

- to monitor the incidence of acute HEV casesⁱⁱ
- to monitor chronic HEV infectionsⁱⁱⁱ; and
- to describe the epidemiology of acute and chronic HEV infections.

Secondary:

- to monitor HEV phylotypes/subtypes
- to identify potential clusters/outbreaks; and
- to collect information on possible routes of transmission.

Coverage: national or representative for the country (sentinel surveillance or blood donor screening)

Frequency of reporting

- minimal – annual; and
- optimal – at least monthly.

Data source^{iv}

- minimal – laboratory reporting; and
- optimal – comprehensive reporting (e.g. laboratory, clinical service providers, SoHO donor services).

Data format^{iv}

- minimal – aggregated number of laboratory-confirmed cases; and
- optimal – laboratory-confirmed cases with case-based data including clinical information.

Data to be collected

- minimal – date of diagnosis, age, sex and place of residence
- optimal – laboratory confirmation (method used); viral geno- or subtype; source of notification or laboratory diagnosis; travel history; hospitalisation; case status (acute, chronic); clinical presentation (asymptomatic, hepatic or extra-hepatic); outcome (recovery/death)
- suggested for additional studies - patient risk factors, food and other exposure history, complications; and
- denominator data in non-comprehensive systems.

Clinical criteria for testing

- all patients with symptoms consistent with viral hepatitis and special groups following EASL guidelines [5] (Table 1).

Requirement for laboratory confirmation of an acute case

- minimal – detection of IgM and IgG antibodies or HEV nucleic acid in serum or plasma; and
- optimal – detection of IgM and IgG antibodies and HEV nucleic acid in serum or plasma.

Requirement for laboratory confirmation of a chronic case

- presence of HEV RNA for at least three months and confirmation based on persistent PCR positivity.

ⁱⁱ Surveillance data should enable to distinguish between cases detected through blood donor screening and cases deriving from diagnostic laboratory testing. Surveillance data should also allow to distinguish between symptomatic and asymptomatic cases.

ⁱⁱⁱ Note: One expert disagreed with the proposal to include the monitoring of chronic infections as a primary objective and suggested that the incidence of chronic infections could be a secondary objective if the surveillance system implemented allows for it. Otherwise, the chronic infections issue may be addressed through specific studies (on risk factors or immunopathogenesis).

^{iv} According to structure and decision by each country.

5 Suggested case definitions for national surveillance

Acute hepatitis E virus infection (hepatitis E virus, HEV)

Clinical criteria*

Any person with a discrete onset of symptoms clinically compatible with acute viral hepatitis or consistent with known extrahepatic manifestations of HEV

**: decision to be taken by each Member States whether and which clinical criteria should be included.*

Laboratory criteria

- HEV-specific antibody response (IgM and IgG)
- AND/OR
- detection of HEV nucleic acid in serum/plasma or stool.

Case classification

- A. Possible case: Not applicable
- B. Probable case: Not applicable; and
- C. Confirmed case: Any person meeting the laboratory criteria with or without clinical criteria

Chronic hepatitis E virus infection (hepatitis E virus, HEV)

Laboratory criteria

- persistent detection of HEV nucleic acid in plasma, serum or stool for more than 3 months.

Case classification

- A. Possible case: Not applicable
- B. Probable case: Not applicable; and
- C. Confirmed case: Any person meeting the laboratory criteria.

6 Discussion and conclusions

A structured and harmonised approach to collect comparable surveillance data over time will provide more consistent information on the epidemiology of HEV, including disease severity and more robust evidence to develop public health guidance for prevention measures. The objectives of national HEV surveillance focus on the basic trends and distribution of the infection and additional epidemiological studies may be better suited to assess more detailed questions such as route of transmission, burden or identification of particular risk factors. Enhanced studies can address specific research questions in depth, but do not require continuous collection of data from the same population.

Although surveillance systems could enable the early detection of outbreaks for public health response, the long incubation period and delay of reporting may make this difficult for HEV. The group suggested as a minimal requirement for any national surveillance system to monitor the annual number of acute laboratory-confirmed cases accompanied by a minimum dataset, such as date of diagnosis, age, sex and place of residence. The minimum dataset is already collected in 19 EU/EEA countries as of 2015. The best option, in place in 12 countries, is a comprehensive or at least representative monthly reporting of case-based data, including information on laboratory confirmation (method used), viral geno- or subtype, source of notification, travel history, hospitalisation, case status (acute, chronic) and clinical presentation (asymptomatic, hepatic or extrahepatic). Real-time surveillance of HEV infections is already established in 12 countries.

The suggestions for national surveillance of HEV infection overlap with previous recommendations regarding the surveillance of hepatitis A virus infection in terms of surveillance systems and minimum dataset [27]. The surveillance objectives for hepatitis B and C virus infections are more advanced and have been developed and refined over time, but they still include monitoring the incidence of acute and chronic infections as well as molecular surveillance of the viral genotypes [28]. EU case definitions for hepatitis B and C are only based on laboratory confirmation.

Surveillance data with molecular information on circulating hepatitis E viruses in humans across EU/EEA countries will inform animal health and food safety authorities responsible for preventive and control measures in the animal population and food production. ECDC and the ECDC HEV expert group reflected on clinical guidelines available in the countries and on EASL recommendations and assessed their relevance for surveillance purposes. This document does not aim to provide suggestions or recommendations on testing or case management, which are the responsibility of the individual clinician and the national public health authority. Reporting of cases with HEV infection needs to be embedded in and adjusted to the existing systems and structures. Most of the EU/EEA countries with surveillance systems for HEV already share many of the suggested features and would not need to revise their approaches substantially in order to adopt the options proposed in this report.

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Annex 1. Survey on surveillance of hepatitis E in EU/EEA, 2005–2015

This work builds on previous work conducted by ECDC: 'Hepatitis E in the EU/EEA, 2005–2015' [22], which comprised of a survey of the ECDC National Focal Points and Operational Contact Points for Food- and Waterborne Diseases and Zoonoses Disease Programme in January 2016. The survey covered HEV testing, diagnosis, surveillance and epidemiological data. Thirty of the 31 Member States responded to the survey. Country-level responses were detailed and informative, providing a rich dataset on which to base subsequent work. The raw dataset was used for this report. The questionnaire, as well as the summarised data, was published in the surveillance report 'Hepatitis E in the EU/EEA, 2005–2015 – Baseline assessment of testing, diagnosis, surveillance and epidemiology'. Unpublished relevant information used in this guidance document is included below.

National surveillance implementation, data collection and testing

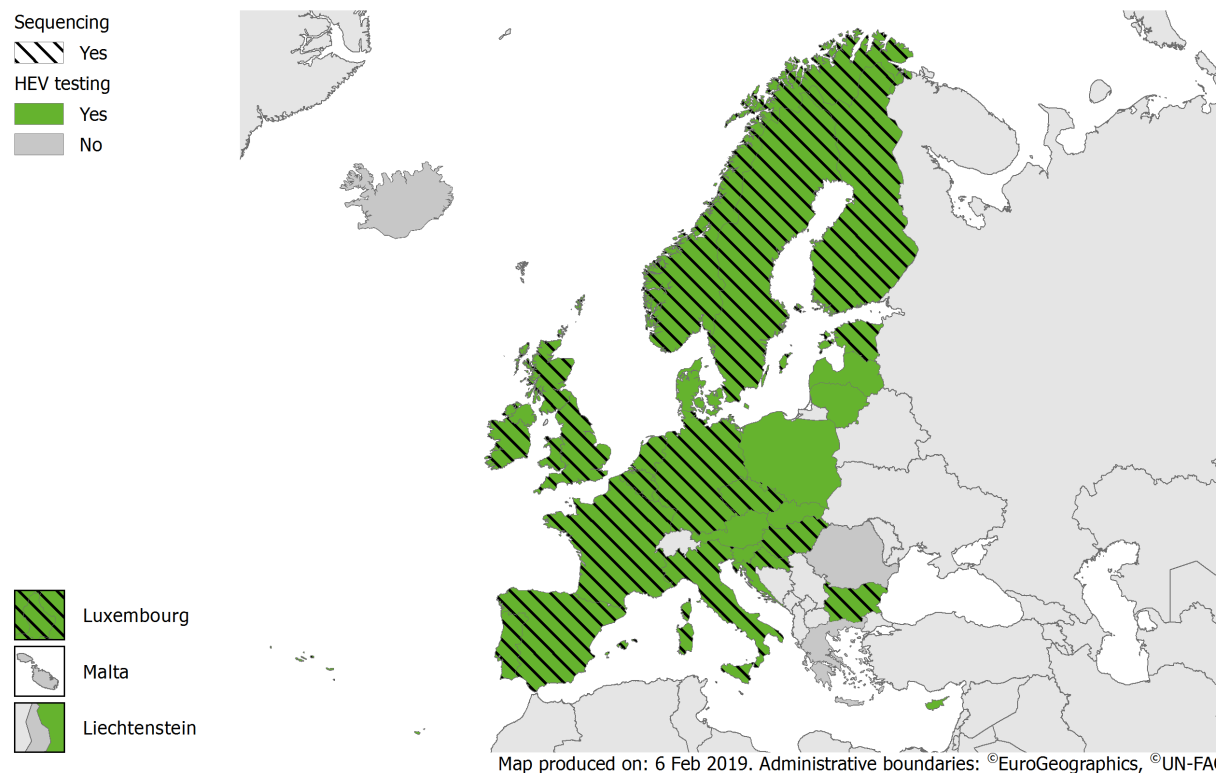
Fifteen of the 30 participating countries reported having national surveillance systems specific for hepatitis E, including 12 with compulsory reporting, 16 with case-based reporting and 11 with real-time or daily reporting [22]. For data transfer to the national level, a variety of systems were mentioned and systems in certain countries collect more specific information on HEV cases. The majority of countries reported that their systems collect case-based epidemiological and clinical information, outcome after 12 months and exposure data (Table 2). Few countries collect information on ethnicity, migration status, alcohol consumption, medication, immunosuppression, other medical conditions or recent transfusion/transplantation.

Table 2. Case-based hepatitis E surveillance data by number of collecting EU/EEA countries, 2005–2015

Case information collected	Number of countries
Date of notification to surveillance organisation	20
Sex	20
Age or date of birth	19
Date of clinical onset	19
Source of notification	19
Travel history within EU/EEA	17
Unique patient identifier	17
Travel history outside EU/EEA	16
Date of diagnosis	15
Hospitalisation	15
Occupation	15
HEV-related death	14
Clinical symptoms	13
Cluster link	10
Environmental contact with livestock/farm animals	9
Pregnancy	9
Food consumption history – groups of foods	8
Food consumption history – detailed food items	7
Ethnicity	6
Immunosuppressive medication or condition	6
Recent transfusion of blood components or blood products	6
Alcohol consumption	5
Medication	5
Other underlying medical conditions	5
Other	5
Recent transplantation	5
Migration background/refugee status	2

Data from the ECDC surveillance study in EU/EEA countries [6,22].

For the diagnosis of an acute case of hepatitis E, 24 countries reported using IgM detection (ELISA or Western blot), 23 used IgG (ELISA, Western blot) in addition and 20 used PCR. In the surveillance study in EU/EEA countries, 26 of the 30 participating countries reported to have testing for HEV available and 18 also perform sequencing of virus isolates (Figure 1) [22].

Figure 1. HEV testing and sequencing of isolates performed in EU/EEA countries as of 2015

Experts provided some information on why HEV testing is initiated or performed. The data showed a great variability across but also within countries. The list below details the reasons provided from the Member States for requesting HEV testing:

- requested by clinician or blood service
- related to clinical illness, generally when tests for other aetiological agents are negative
- on request of a physician when hepatitis symptoms are clinically diagnosed in an acute case and results for hepatitis A virus, hepatitis B virus and hepatitis C virus infections are negative
- Laboratories initiate HEV testing on clinician's request in patients with elevated liver transaminases, contacts of patients with hepatitis E, patients with exposure history.
- acute hepatitis and chronic non-A/B hepatitis
- acute cases of hepatitis with no other cause, foreign travel or immunosuppressed patients. Specific request for HEV antibodies and PCR
- Samples are sent abroad for testing on an individual basis.
- ALT \geq 100 U/L or jaundice. Immunosuppressed patients tested on request with no criteria.
- suspected cases according to clinical symptoms, such as contacts of ill persons or those carrying out 'epidemiologically serious activity' – those working with ducting devices or purifying water, in a facility for human body care, in the area of food production, manipulation and supply or in the area of cosmetic products production
- increased liver enzymes, signs of acute hepatitis and negative test for HAV and differential diagnosis of viral hepatitis
- HEV testing is usually initiated by physicians for patients presenting with symptomatic hepatitis of unknown cause, with elevated liver enzymes alone or for patients under immunosuppression (e.g. HEV screening once per year). Further specialised testing (HEV genotyping, confirmation) in the reference lab is initiated at the request of official health authorities or by infectious disease laboratory specialists.
- specific request from a clinician as part of a viral hepatitis screen at the national virus reference laboratory, all specimens submitted for hepatitis A testing are now also routinely tested for HEV in patients with graft-versus-host disease; and
- yearly routine HEV PCR testing of transplant recipients.

Testing guidelines were available in Slovenia and Slovakia, as well as the following countries that provided additional information:

- Croatia – Testing of HEV is performed in the process of differential diagnosis in patients with elevated transaminases. First, anti-HEV IgM and IgG antibodies are determined using a screening test (immunoenzyme assay) and in all reactive results confirmatory testing (Western blot) is performed. Sera with anti-HEV IgM confirmed by Western blot are further processed for HEV RNA determination;
- France – immunocompetent: anti-HEV IgM; immunocompromised: anti-HEV IgM if negative HEV RNA
- UK (England and Wales) – There are brief recommendations for testing in the public health operational guidelines that state virological testing for HEV infection is recommended in the following:
 - Any individual, regardless of travel history, displaying signs and symptoms of acute hepatitis (including jaundice and raised liver transaminases). It is recommended that HEV testing is included as part of the initial acute viral hepatitis screen, as today it is a far more common cause of acute viral hepatitis than hepatitis A virus.
 - Immunocompromised individuals (see Green Book Chapter 6^v for examples) with persistently deranged liver transaminases (note that in these individuals, liver enzymes may be only mildly deranged). There is value in considering that such individuals should have regular testing for HEV infection in the absence of elevated liver enzymes.

Clinical symptoms used for hepatitis E confirmation

Thirteen countries provided a case definition. In five countries, clinical criteria were not relevant for surveillance purposes. The others included the following clinical definitions of a confirmed case of hepatitis E:

- clinical picture of an acute hepatitis, defined as a minimum of one of the four following criteria: fever, jaundice, elevated transaminases, and upper abdominal pain
- symptoms of hepatitis (elevated liver enzymes)
- acute hepatitis
- at least one of fever, elevated liver enzymes, icterus, upper abdominal pain
- general symptoms (fatigue, abdominal pain, loss of appetite, intermittent nausea and vomiting), fever/mild fever and at least one of the following three: jaundice, dark urine, elevated serum aminotransferase levels.
- acute illness compatible with hepatitis, and ALT >10 times the upper limit of the normal range
- clinical symptoms of hepatitis; and
- any person with the first symptoms of acute viral hepatitis (e.g. fatigue, abdominal pain, anorexia, nausea and vomiting). At least one of the following three: fever, jaundice and/or elevated serum aminotransferase levels.

^v Public Health England. Contraindications and special considerations: the green book, chapter 6. London: PHE; 2017. Available from: <http://www.gov.uk/government/publications/contraindications-and-special-considerations-the-green-book-chapter-6>

Annex 2. Survey to ECDC's expert group

Data collection

A comprehensive survey was developed by experts from Glasgow Caledonian University and Health Protection Scotland in consultation with ECDC that included the following sections/topic areas:

- Section A: Respondent details
- Section B: Objectives for national surveillance
- Section C: Undertaking national surveillance
- Section D: Data requirements for national surveillance
- Section E: Case definitions for surveillance – acute and chronic cases
- Section F: Clinical testing for HEV; and
- Section G: Any other comments.

The survey comprised mainly of closed (i.e. 'tick box') questions in order to maximise clarity and reduce survey completion time for members of the group. Certain questions used a numbered or adapted Likert scale (e.g. Very/Somewhat/Not important) in order to draw out preferences more effectively. A small number of free text questions were used to enhance understanding of the survey responses and better capture input from the expert group. The draft survey was revised following feedback from participants at the HEVnet meeting [24], the deputy unit head of the Blood borne virus unit at Public Health England and the ECDC project manager. The survey was also piloted with a small number of ECDC staff in November 2017 and revisions made accordingly. The final survey document is included in Annex 3 and was uploaded to the EUSurvey website [29]. A link to the survey (<http://ec.europa.eu/eusurvey/runner/HepEVirusSurvey201718>) was circulated to all members of ECDC's HEV expert group by ECDC in November 2017, as well as a downloadable PDF version of the survey. A number of reminder emails were sent in order to maximise uptake of the survey.

Data analysis

Data from the survey was extracted electronically to a CSV file for analysis. Quantitative data were summarised using numbers and percentages and qualitative data were summarised using thematic analysis.

Data synthesis

The contracted experts from Glasgow Caledonian University and Health Protection Scotland shared the draft results with the ECDC project manager by email.

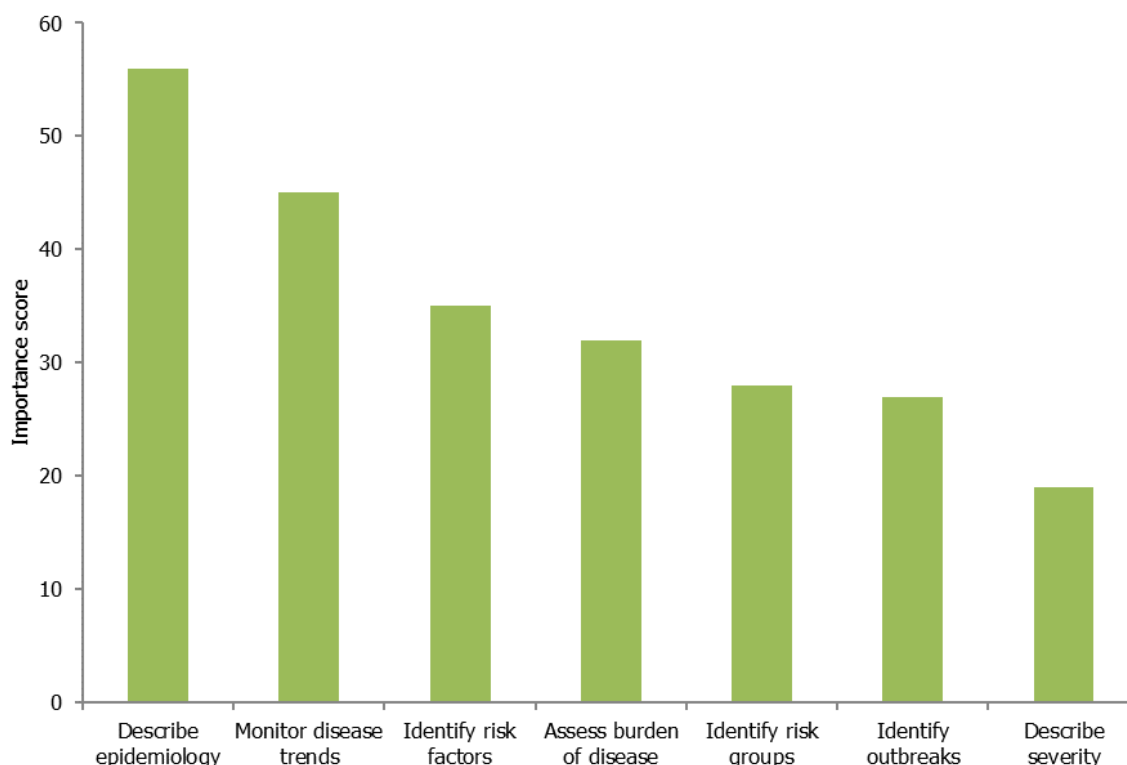
Results and discussion

Section A: Respondent details

Eleven of 22 members of the group responded to the survey. Ten respondents were based in national surveillance organisations and one was based at a national blood transfusion organisation. Respondents were from the following Member States: Denmark, Estonia, Germany, Ireland, Italy (two responses), Latvia, the Netherlands, Norway, Spain, Sweden and the UK (England and Wales).

Section B: Objectives for national surveillance

Respondents were asked to rank seven potential objectives of national surveillance in order of importance (most important=7 to least important=1; Figure 2). Six (55%) respondents thought that 'describing the epidemiology of the disease in a country' was the most important objective and three respondents (27%) thought that 'monitoring disease trends' was the most important. The importance score for each category was calculated by using the maximum possible score (7 points x 11 responses=77) minus the sum of the individual scores. Figure 1 shows the composite scores for all potential objectives for all respondents.

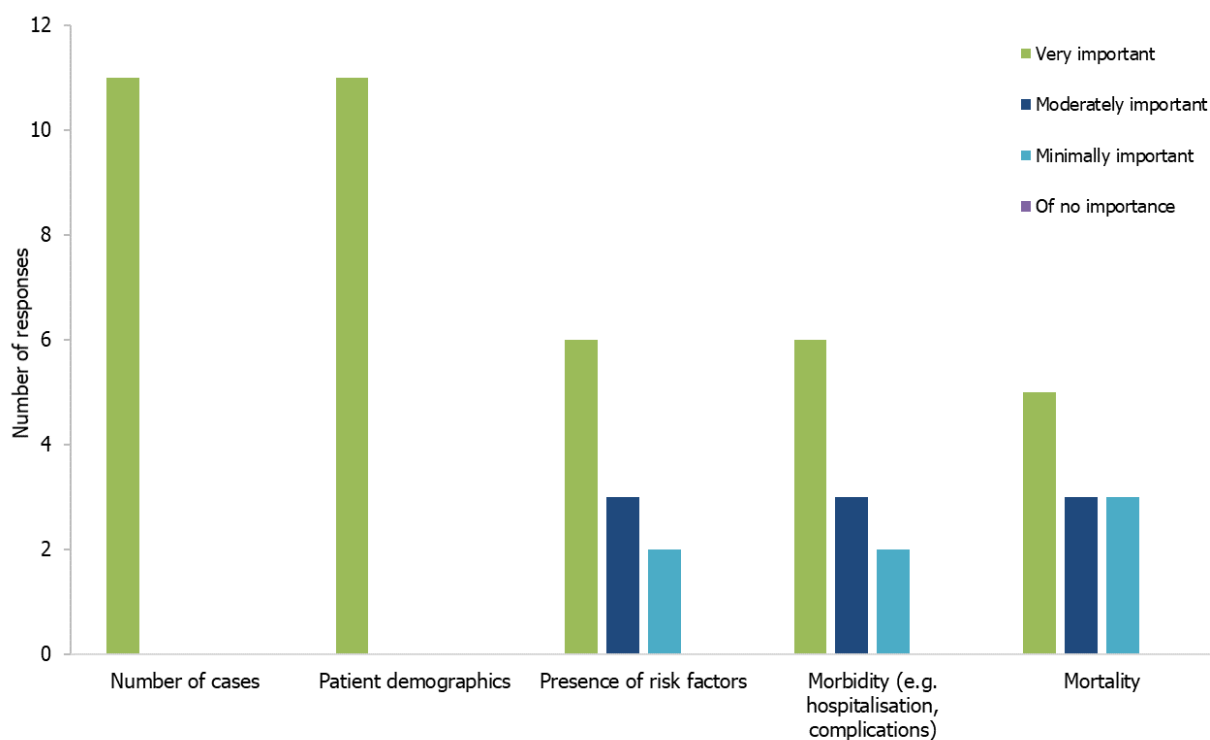
Figure 2. Purpose of national hepatitis E surveillance

Importance score=maximum possible score (7 points x 11 responses=77) - sum of individual scores.

Section C: Undertaking national surveillance

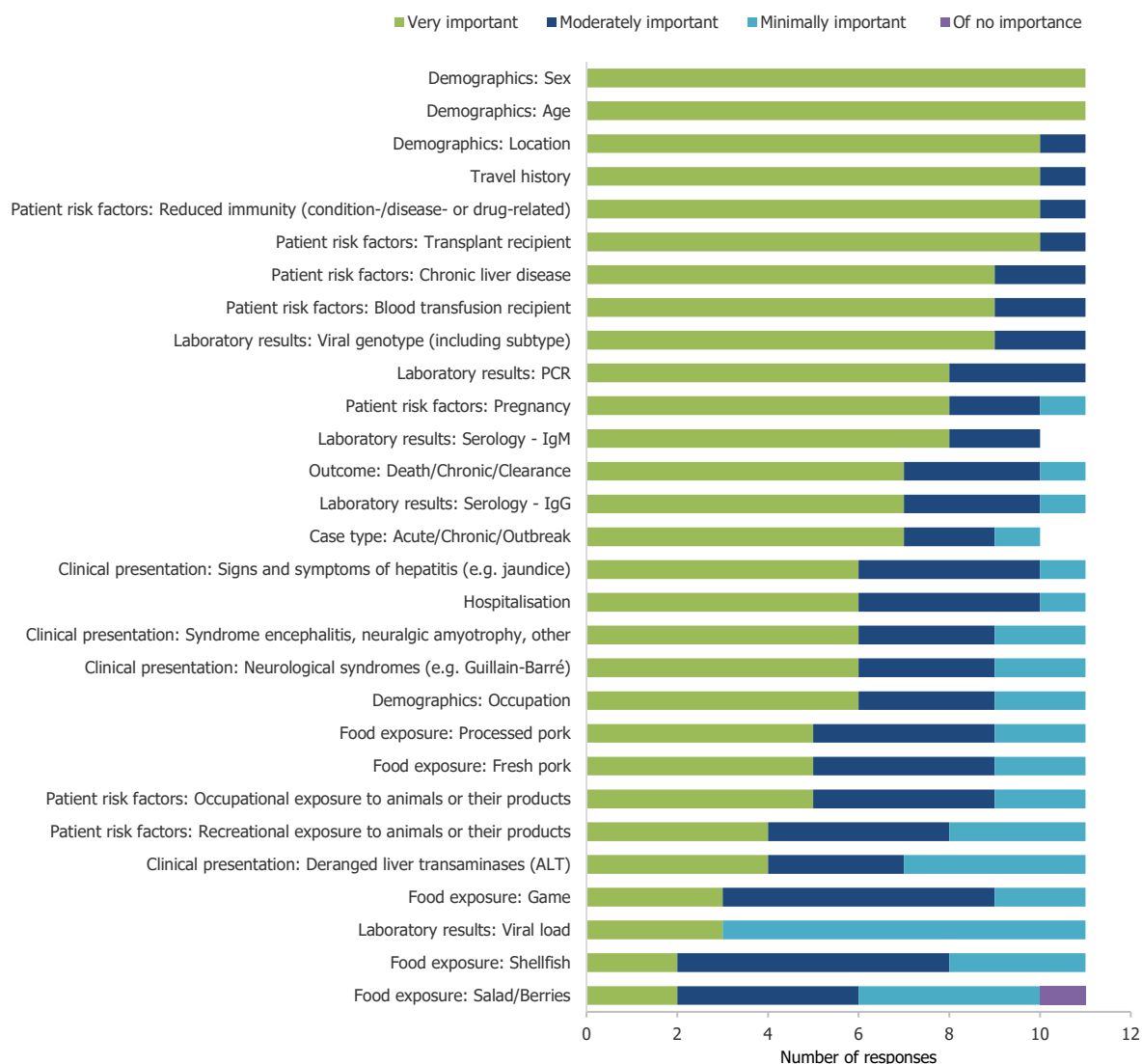
Based on their answers to the question on the purpose of national surveillance, respondents were asked to rate the importance of collecting the number of cases, morbidity, mortality, patient demographics and presence of risk factors from 'very important' to 'of no importance'. The responses are shown in Figure 3. All 11 respondents thought that while considering complexity, cost and epidemiological benefits, HEV surveillance should be comprehensive, with mandatory reporting of laboratory-confirmed results together with clinical and epidemiological data. Seven (64%) respondents thought that reporting to the national level should be conducted weekly, three (27%) monthly and one (9%) on a quarterly basis.

Two respondents thought that laboratories should be responsible for reporting, two thought general practitioners should be responsible and two thought local departments of public health should be responsible. The remaining five respondents thought that it would depend on existing systems and infrastructure in each Member State. All 11 respondents thought that reporting should be conducted electronically.

Figure 3. Importance of collecting and monitoring data on HEV

Section D: Data requirements for national surveillance

Respondents were asked, considering their stated objectives for hepatitis E surveillance, the importance of various items of data collection. The responses are shown in Figure 4. The items considered to be the most important were age, sex, location, travel history and patient risk factors (reduced immunity, history of organ transplant or blood transfusion, chronic viral disease, pregnancy). Relevant information to know was the type of test performed for case confirmation (IgM, IgG, PCR) and viral genotype or subtype. The least important information was about blood tests (biochemistry, haematology) and viral load. In addition, data on clinical presentation and information about exposure or food exposure history were considered of minor importance for national surveillance.

Figure 4. Importance of collecting individual case data for surveillance purposes

Section E: Epidemiological case definition for probable cases

The majority of respondents (8; 73%) thought that there was no requirement for an epidemiological 'probable' case definition. Three thought that there should be an epidemiological case definition. There was one suggested definition: 'Symptoms suggestive of viral hepatitis; Epidemiological link to outbreak or a confirmed case of Hepatitis E; Consumption of suspected risk food (e.g. containing raw pork liver) in context of outbreak'.

Section F: Clinical testing for HEV

Respondents were asked about a number of clinical scenarios and whether a test for HEV should be offered (as first- or second-line or not at all) to a patient not in a risk group and a patient in a risk group for HEV infection or for complicated HEV infection.

The scenarios were as follows:

- Scenario 1 – presentation with symptoms of viral hepatitis, no other information known
- Scenario 2 – presentation with deranged (LFTs, but no symptoms of viral hepatitis
- Scenario 3 – presentation with deranged LFTs and non-specific symptoms
- Scenario 4 – presentation with deranged LFTs and symptoms of viral hepatitis
- Scenario 5 – presentation with epidemiological link but no symptoms
- Scenario 6 – presentation with epidemiological link and non-specific symptoms; and
- Scenario 7 – presentation with epidemiological link and symptoms of viral hepatitis.

Risk group

Respondents were asked which groups they would consider as high risk. Risk groups were considered to be the immunosuppressed, including transplant (100%) and chronic liver disease patients (82%) and pregnant women (64%).

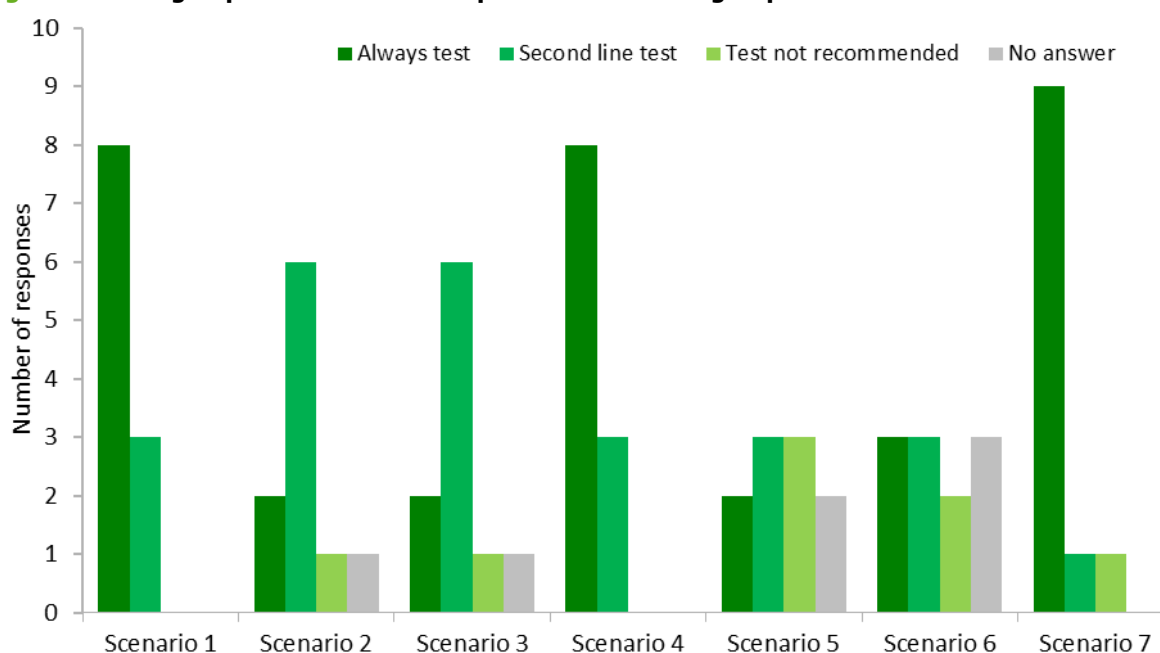
Epidemiological link

Respondents were asked what would constitute an epidemiological link. Possible epidemiological links were considered to be an outbreak (91%) and food-related (73%) and occupational exposure (55%).

Testing of patient not in risk group

Respondents considered that for patients not in a risk group, testing should always be undertaken where there are symptoms consistent with viral hepatitis and that other factors such as deranged LFTs, non-specific symptoms, and epidemiological links are less important (Figure 5). However, it was noted that scenarios 5 and 6 are relevant during an epidemiological or outbreak investigation to identify a possible source infection, for active case finding or if there are cases belonging to risk groups (e.g. pregnant women).

Figure 5. Testing requirement for HEV in patients not in risk group



Scenario 1: presentation with symptoms of viral hepatitis, no other information known

Scenario 2: presentation with deranged liver function tests (LFTs), but no symptoms of viral hepatitis

Scenario 3: presentation with deranged LFTs and non-specific symptoms

Scenario 4: presentation with deranged LFTs and symptoms of viral hepatitis

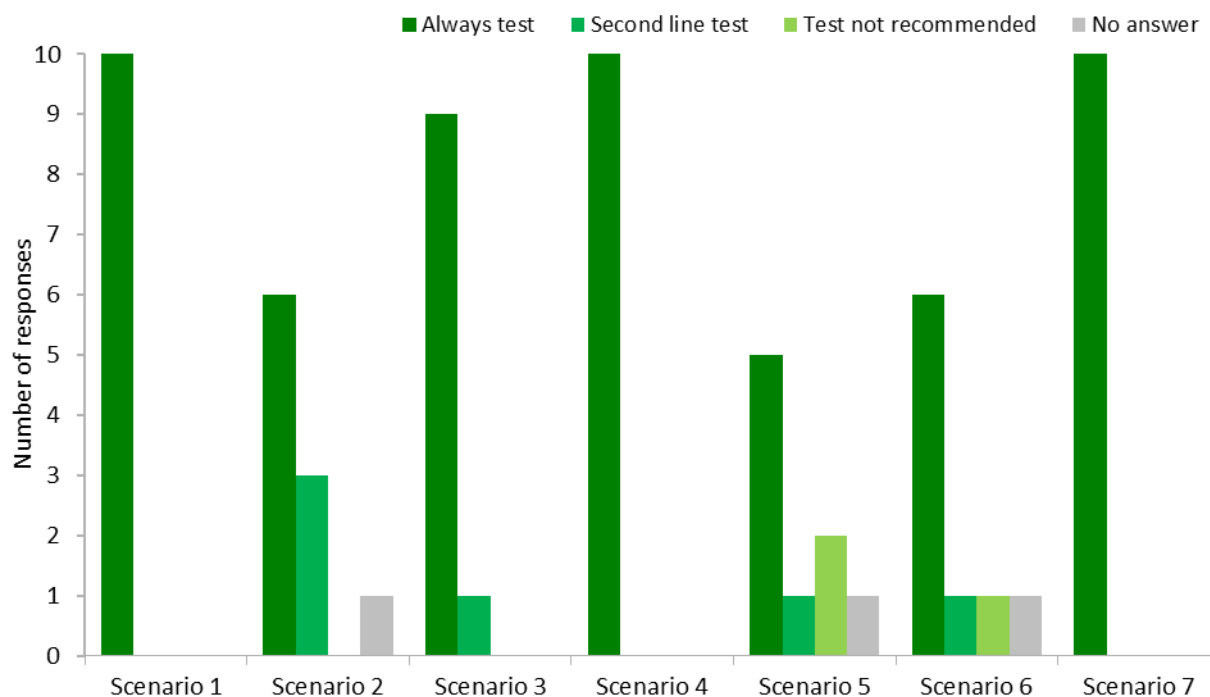
Scenario 5: presentation with epidemiological link but no symptoms

Scenario 6: presentation with epidemiological link and non-specific symptoms

Scenario 7: presentation with epidemiological link and symptoms of viral hepatitis.

Testing of patient in risk group or at risk for complicated infection

Responses regarding scenarios 1–7 among patients in a risk group are shown in Figure 6. Among patients in a risk group, nearly all respondents recommended always testing for scenarios 1, 3, 4 and 7, showing a preference for hepatic-related signs and symptoms. Testing was not always recommended for scenarios 2, 5, and 6, which involved combinations of deranged LFTs or epidemiological links with no or non-specific symptoms.

Figure 6. Need for HEV testing in high-risk patients

Scenario 1: presentation with symptoms of viral hepatitis, no other information known

Scenario 2: presentation with deranged liver function tests (LFTs) but no symptoms of viral hepatitis

Scenario 3: presentation with deranged LFTs and non-specific symptoms

Scenario 4: presentation with deranged LFTs and symptoms of viral hepatitis

Scenario 5: presentation with epidemiological link but no symptoms

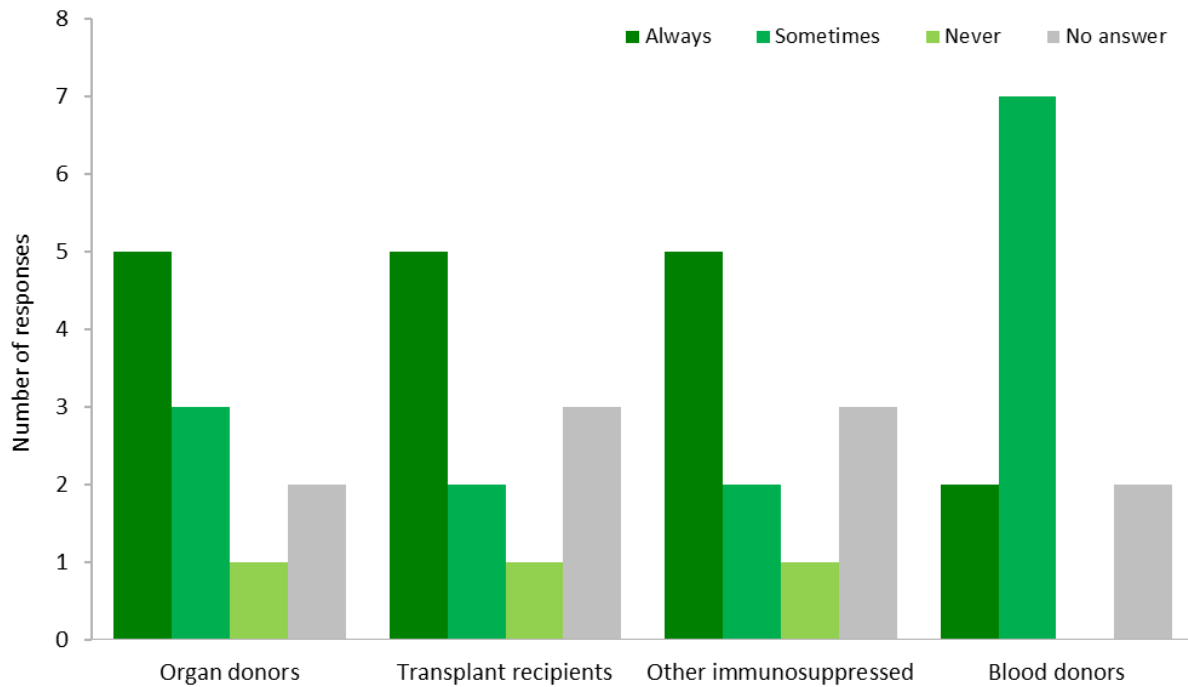
Scenario 6: presentation with epidemiological link and non-specific symptoms

Scenario 7: presentation with epidemiological link and symptoms of viral hepatitis.

Routine testing for HEV

Respondents were also asked which groups require routine testing for HEV. Five (45%) respondents thought that routine testing for HEV should be conducted for organ donors, transplant recipients and other people with other causes of immunosuppression (Figure 7). Two respondents suggested that there should be special measures (additional screening) for blood transfused to immunocompromised patients. Another three commented that blood donations, not blood donors, should be tested and also taking local and national blood safety policies into account. Testing of donations should particularly be conducted for products and organs used for immunocompromised people. Only two of the 11 respondents reported having a national screening programme already in place.

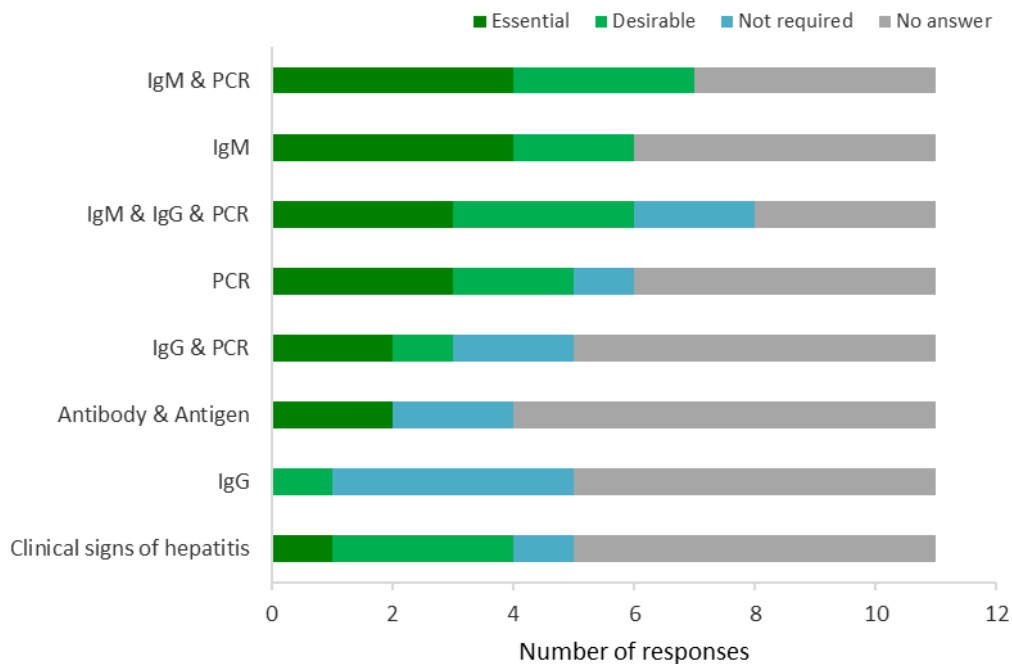
Figure 7. Routine testing for HEV in risk groups



Acute case confirmation

Respondents were asked about the type of test that should be used to confirm an acute case for surveillance purposes. The most common response was that a combination of IgM and PCR positivity should be required to confirm an acute case (Figure 8). Two experts commented that IgM and IgG positivity are used to notify an acute case using PCR as an additional, but not obligatory, test. It was also noted that serological tests should not be conducted without symptoms (they are not validated for this purpose and will yield a high number of false positives).

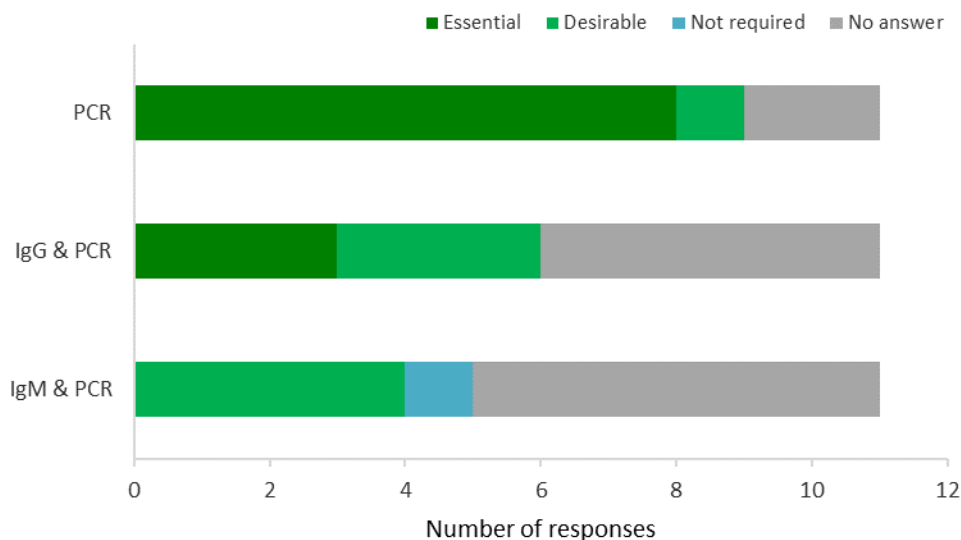
Figure 8. Laboratory tests required to confirm acute case



Chronic case confirmation

Respondents were asked about the types of tests that should be used to confirm a chronic hepatitis E case for surveillance purposes. The majority of respondents thought that PCR alone was sufficient to confirm a chronic case (Figure 9). Eight respondents felt that PCR positivity alone was essential and sufficient to confirm a chronic case, while six considered IgG and PCR positivity as desirable (3) or essential (3). Only four thought IgM and PCR were desirable tests to be useful for chronic case confirmation.

Figure 9. Laboratory tests required to confirm a chronic case



Chronic case minimum time period

There were eight responses to the question about minimum time period of infection to diagnose a chronic case:

- 3 months (four responses)
- 3–6 months (two responses); and
- 6 months (two responses).

Certain respondents noted at least three months' and others six months' presence of HEV RNA as the minimum duration of infection before labelling a case as having chronic hepatitis E. When defining the status of a chronic case, there was a certain lack of clarity in the number of required tests to confirm chronic status. Certain experts mentioned only one test was necessary, while others requested 1–2 positive tests with a minimum of three months apart.

Some commented that the duration of infection is unclear and it is also unclear when a case should be considered chronic. Knowledge gaps exist regarding the duration of viraemia in chronic patients. Even experts in the field do not agree on the definition of chronic hepatitis E, so the answers are subjective. Questions regarding chronic hepatitis E would be better directed toward clinical experts in the field.

Chronic case clearance

There were seven responses to the question about when an individual should be considered to have cleared chronic HEV infection:

- PCR negative (three responses)
- PCR negative in two plasma samples six months apart
- undetectable serum HEV RNA level at least six months after therapy
- negative RNA in serum and faeces, in two samples; and
- HEV RNA negative at follow-up.

The understanding of the clearance of a chronic infection also showed certain variations: having either two PCR negative samples (serum and plasma) six months apart or an undetectable serum HEV RNA level at least six months after therapy, according to published literature [30].

Section G: Other comments

Significant knowledge gaps/need for review of evidence in relation to any questions asked?

- The routes of HEV genotype 3 infections in Europe have still not been fully elucidated.
- The role of contaminated drinking water and vegetables is unclear.
- The use of hidden pig plasma proteins in various food items.

Other comments

'Raw pig meat' is not popular everywhere and must be considered a rare source in some countries.

Very good questions. But I would have to talk to a clinician to answer those on indication for testing.

For many of the questions, it was difficult to know whether the responses should indicate what is ideal for surveillance of HEV or what would be the best feasible approach for HEV surveillance. For example, while it would be ideal to have information regarding occupation and patient risk groups, it would not be possible to collect this information within the current surveillance structure. It was therefore difficult to answer questions on 'how important' it is to collect this information in the context of surveillance.

Annex 3. Survey document

(Available from: <http://ec.europa.eu/eusurvey/runner/HepEVirusSurvey201718>)

ECDC Hepatitis E Virus Survey (2017-18)

Welcome to the European Centre for Disease Prevention and Control (ECDC) Hepatitis E Virus Survey 2017-18.

ECDC has identified a need to more closely assess the emerging threat of Hepatitis E (HEV) to humans in the EU/EEA, and has therefore initiated a number of different activities to better understand the epidemiological situation and different surveillance systems in place for HEV infections in Member States.

By completing this survey you are helping develop an expert opinion on the implementation or adjustment of HEV surveillance, minimum criteria for clinical testing, case definitions for acute and chronic HEV and reporting requirements for this infection.

Section A: Respondent information

[Start]

- Name
- Role
- Affiliation

Section B: Objectives for National Surveillance

Q1. What should be the purpose of national Hepatitis E surveillance?

Please rank the following options in order of importance by placing a number next to each - i.e. place a 1 next to the option you consider to be the most important purpose of national Hep E surveillance; place a 2 next to the option you think is the second most important purpose; and so on until you have ranked all of the options in your preferred order of importance.

- 1a) Describe the epidemiology of the disease in the country
- 1b) Monitor disease trends
- 1c) Assess the burden of disease in population
- 1d) Identify risk factors* for infection to tailor prevention strategies
- 1e) Identify risk groups* for infection to tailor prevention strategies
- 1f) Identify outbreaks
- 1g) Describe severity (hospitalisation and mortality related to HEV) to tailor intervention strategies

** For examples of risk factors and risk groups please see Q7 below*

Q2. How important is it to collect and monitor the following data, based on your answer above?

	Very important	Moderately important	Minimally important	Of no importance
Number of cases				
Morbidity (e.g. hospitalisation, complications)				
Mortality				
Patient demographics				
Presence of risk factors				

Section C: Undertaking National Surveillance

Q3. Whilst considering complexity, cost, and epidemiological benefits, which form of surveillance do you think would be the most appropriate for reporting at national level?

- Laboratory-based (only lab-confirmed to be reported directly from all labs)
- Comprehensive (mandatory reporting of lab-confirmed together with clinical and epidemiological data)?
- Sentinel (e.g. via selected reference labs / hospitals / GPs)
- Based only on serostudies or epidemiological studies
- Not required at all

Q4. How often should reporting to the national level be conducted?

- Weekly
- Monthly
- Quarterly
- Annual

Q5. Who should be responsible for reporting to the national authority?

- Laboratories
- GPs / Primary care physicians
- Local departments of Public Health
- Other

Q6. What mode of reporting to the national authority should be used? (considering complexity / ease / confidentiality / current infrastructure)

Please select the most appropriate response.

- Electronically
- Via paper
- Fax
- Phone
- Laboratory data exchange system

Section D: Data requirements for National Surveillance

Q7. How important would it be to collect the following items of data, in order to meet the surveillance objectives you outlined in Q1 above?

	Very important	Moderately important	Minimally important	Of no importance
Demographics - Age				
Demographics - Sex				
Demographics - Occupation				
Demographics - Location				
Case type - Acute / Chronic / Outbreak				
Outcome - Death / Chronic / Clearance				
Hospitalisation				
Travel history				
Food exposure - Fresh pork				
Food exposure - Processed pork				
Food exposure - Game				
Food exposure - Shellfish				
Food exposure - Salad/Berries				
Other (please state below)				

If 'Other' please state below

Patient risk factors

	Very important	Moderately important	Minimally important	Of no importance
Pregnancy				
Reduced immunity (condition/disease related or drug related)				
Chronic liver disease				
Transplant recipient				
Blood transfusion recipient				
Occupational exposure to animals or their products				
Recreational exposure to animals or their products				
Others, please state				

If 'Other' please state below

Clinical Presentation

	Very important	Moderately important	Minimally important	Of no importance
Signs and symptoms of hepatitis (e.g. jaundice)				
Deranged liver transaminases (ALT)				
Neurological syndromes (e.g. Guillain-Barré syndrome, encephalitis, neuralgic amyotrophy, other)				
Other				

If 'Other' please state below

Laboratory results

	Very important	Moderately important	Minimally important	Of no importance
Viral load				
PCR				
Viral genotype (incl. subtype)				
Serology – IgM				
Serology – IgG				
Haematology				
Biochemistry				

Section E: Case definitions for surveillance - acute and chronic cases**Q8a: Should there be an epidemiological 'probable case' definition?**

- Yes (proceed to Q8b)
- No (proceed to Q9)

Q8b: If 'Yes', should it be similar to the EU case definition for Hepatitis A (i.e. Any person meeting the clinical criteria and with an epidemiological link)?

- Yes (proceed to Q9)
- No (proceed to Q8c)

Q8c. If 'No', what should it be? (please tick all necessary additional criteria or leave blank if none required)

- Symptoms suggestive of viral hepatitis and/or
- Epidemiologic link to outbreak or a confirmed case of hepatitis E
- Consumption of suspected risk food (e.g. containing raw pork liver) in context of outbreak
- Other

If 'Other' please state below

Section F: Clinical testing for HEV

Question 9: When should a test for HEV be conducted?

Please tick one box only for each clinical presentation

SCENARIO A: PATIENT IS NOT IN A RISK GROUP

	Always test	Test only as second line (other viral screen negative)	Test not recommended	Test recommended in specific circumstances (please state)
(9A1) Present with symptoms of viral hepatitis, no other information known				
(9A2) Present with deranged LFTs but no symptoms of viral hepatitis				
(9A3) Present with deranged LFTs AND non-specific symptoms				
(9A4) Present with deranged LFTs AND symptoms of viral hepatitis				
(9A5) Present with epidemiological link* but no symptoms				
(9A6) Present with epidemiological link* and non-specific symptoms				
(9A7) Present with epidemiological link* AND symptoms of viral hepatitis				

If you've recommended a test in specific circumstances, please expand on your response in the box below (you can use the presentation reference codes (e.g. "9A1", "9A5", etc) to help you reference your response).

SCENARIO B: PATIENT IS IN RISK GROUP FOR HEV, OR COMPLICATED / CHRONIC HEV

	Always test	Test only as second line (other viral screen negative)	Test not recommended	Test recommended in specific circumstances (please state)
(9B1) Present with symptoms of viral hepatitis, no other information known				
(9B2) Present with deranged LFTs but no symptoms of viral hepatitis				
(9B3) Present with deranged LFTs AND non-specific symptoms				
(9B4) Present with deranged LFTs AND symptoms of viral hepatitis				
(9B5) Present with epidemiological link* but no symptoms				
(9B6) Present with epidemiological link* and non-specific symptoms				
(9B7) Present with epidemiological link* AND symptoms of viral hepatitis				

If you've recommended a test in specific circumstances, please expand on your response in the box below (you can use the presentation reference codes (e.g. "9B2", "9B6", etc) to help you reference your response).

Which groups should be considered as risk groups in scenario B?

	Yes	No
Pregnancy		
Chronic liver disease		
Reduced immunity		
Other		

If 'Other' please state below

*** What would constitute an epidemiological link in scenarios A and B?**

	Yes	No
Occupational exposure		
Consumption of foodstuff suspected to be infected		
Outbreak scenario		
Other		

If 'Other' please state below

Q10. Which groups, in your view, requires testing for HEV?

(Tick one box only for each group)

	Always	Sometimes (please give details below)	Never
Blood donors prior to donation			
Organ / HSCT donors prior to donation			
Transplant recipients			
Other immunosuppressed groups			

If you've responded 'sometimes' to any of the groups, please expand on your response in the box below.

Do you already have national guidelines for HEV testing?

- Yes
- No

If so, please provide a weblink here _____

Case definitions**Q11. Which test(s) should be used to confirm an acute case for surveillance purposes?**

	Essential	Desirable	Not required
IgM only			
IgM and PCR			
IgG only			
IgG and PCR			
IgM and IgG and PCR			
PCR only			
Antibody and antigen			
Clinical signs of hepatitis			
Other (please state)			

If 'Other' please state below

Q12. What is required in order to diagnose a chronic case for surveillance purposes?

	Essential	Desirable	Not required
IgM and PCR			
IgG and PCR			
PCR			
Other (please state)			

Q13. What should be the minimum duration of infection before labelling a case as having chronic Hepatitis E?

(Please label your response 'weeks' / 'months' / 'years')

Q14. How many tests should be required to confirm chronic status?**Q15. When should someone with chronic infection be considered to have cleared HEV infection?**

Section G: Other comments

Q16. Are there any significant knowledge gaps / need for review of evidence in relation to any of the questions asked?

If so, please expand below

Q17. Do you have any other comments to make regarding HEV testing, case definition, or surveillance?

If so, please expand below

[End]

Thank you – please click 'Submit' to finalise and submit your responses.

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