Standardising surveillance of hepatitis E virus infection in the EU/EEA: A review of national practices and suggestions for the way forward

Cornelia Adlhoch⁸,⁎, Zdenka Manďáková⁹, Steen Ethelberg⁷, Jevgenia Epštein⁸, Ruska Rimhanen-Finne⁸, Julie Figoni⁷, Sally A. Baylis⁸, Mirko Faber⁹, Kassiani Mellou⁸,⁹, Niamh Murphy⁸,⁹, Joanne O’Gorman⁸,⁹, Maria Elena Tosti⁸,⁹, Anna Rita Ciccaglione⁸,⁹, Agnetha Hofhuis⁹, Hans Zaaljer⁹, Heidi Lange⁹, Rita de Sousa⁹,⁹, Ana Avellón⁹,⁹, Lena Sundqvist⁹,⁹, Bengü Said⁹,⁹, Samreen Ijaz⁹,⁹

⁸European Centre for Disease Prevention and Control (ECDC), Gustav III:s boulevard 40, 169 73, Solna, Sweden
⁹National Institute of Public Health, Prague, Czech Republic

ARTICLE INFO

Keywords:
Hepatitis E virus
EU/EEA Surveillance
Testing

ABSTRACT

Background: Hepatitis E virus (HEV) infection is not notifiable at EU/EEA level, therefore surveillance relies on national policies only. Between 2005 and 2015, more than 20,000 cases were reported in EU/EEA countries. HEV testing is established in 26 countries and 19 countries sequence HEV viruses.

Objective and study design: WHO’s European Action plan for viral hepatitis recommends harmonised surveillance objectives and case definitions. ECDC’s HEV expert group developed minimal and optimal criteria for national hepatitis E surveillance to support EU/EEA countries in enhancing their capacity and to harmonise methods.

Results: The experts agreed that the primary objectives of national surveillance for HEV infections should focus on the basic epidemiology of the disease: to monitor the incidence of acute cases and chronic infections. The secondary objectives should be to describe viral phylotypes or subtypes and to identify potential clusters/outbreaks and possible routes of transmission. Seventeen of 20 countries with existing surveillance systems collect the minimal data set required to describe the epidemiology of acute cases. Eleven countries test for chronic infections. Twelve countries collect data to identify potential clusters/outbreaks and information on possible routes of transmission.

https://doi.org/10.1016/j.jcv.2019.09.005

Received 3 July 2019; Received in revised form 5 September 2019; Accepted 11 September 2019

© 2019 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/BY-NC-ND/4.0/).
**Discussion:** Overall, the majority of EU/EEA countries collect the suggested data and meet the outlined requirements to confirm an acute case.

### 1. Background

Hepatitis E virus (HEV) is a multifaceted pathogen: its epidemic genotypes 1 and 2 are transmitted faecal-ORally through contaminated water and circulate mainly in Asia and Africa, while its genotypes 3 and 4 are zoonotic infections with an animal reservoir. In EU/EEA countries, genotype 3 predominates and has been mainly linked to the consumption of undercooked pork, processed pork products (including ready-to-eat sausages) and shellfish products but also to occupational exposure via direct contact with pigs and their manure [1–5]. Rarely, transfusion- or transplantation-transmitted infections related to contaminated blood products or infected organs have been reported [6]. In healthy adults, infection with HEV may result in acute self-limiting hepatitis, which will often be mild or asymptomatic. In immunosuppressed patients or in those with pre-existing liver disease, HEV infection may lead to severe courses of disease and chronic or...
persistent infection [7]. Chronic hepatitis E virus infection among immunocompromised individuals is characterised by a prolonged viraemia, sometimes without clinical signs of viral hepatitis as well as absence of IgM or IgG antibodies, and may rapidly lead to cirrhosis and death [8]. Risk factors for symptomatic or complicated infection include male sex, older age, and pre-existing liver disease [9]. Extra-hepatic manifestations of HEV infection with different clinical presentations, in particular neurological, renal and haematological disorders, are not uncommon [10].

HEV infection is not notifiable at EU/EAA level. ECDC conducted a survey among the EU/EAA Member States to evaluate HEV testing, diagnosis, surveillance, and the availability of epidemiological data covering the period 2005–2015 [11,12]. This study highlighted that progress on HEV testing and surveillance in EU/EAA countries has been heterogeneous: 20 of the 30 Member States responding to the ECDC survey have well-established HEV-specific surveillance systems and testing protocols and 10 have no such surveillance at all (Table 1). Twenty-six Member States indicated that they have testing capacity for HEV and five also have national guidelines. During the study period, the number of reported confirmed cases of hepatitis E increased year on year with more than 20,000 cases notified in total. Of 13,833 cases with travel information, 13,511 (97.7%) were locally acquired, 82 (0.6%) were related to travel within the EU/EAA and 240 (1.7%) had travelled outside the EU/EAA [11,12].

2. Objective and study design

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’ [13]. It describes priority actions, including the assessment and strengthening of surveillance systems and case definitions as well as the development and roll-out of national viral hepatitis testing and diagnostic guidelines. One milestone to be achieved by 2018 was ‘harmonized surveillance objectives...and case definitions’ and a target for 2020 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...’. ECDC identified a need to support Member States in the implementation of the WHO European Action plan, especially in enhancing or adapting their HEV surveillance capacity. A operational guidance has been developed with nominated experts from the Member States to suggest minimal and optimal criteria for national hepatitis E surveillance according to specific primary and secondary objectives [14]. The document outlines reporting schemes in the countries, criteria for clinical testing following the guidelines of the European Association for the Study of the Liver (EASL) as well as case definitions for acute and chronic hepatitis E virus infection. This perspective analyses the proposed criteria in the context of the existing Member States surveillance systems as described in a previous ECDC surveillance report on hepatitis E in the EU/EAA for the period 2005–2015 [12].

3. Results

3.1. Objectives of national surveillance for HEV infections

In general, a surveillance system should enable the ongoing collection, analysis, and dissemination of data to prevent and control a particular infection and/or disease. The primary objective of national surveillance for HEV infections should focus on the core epidemiology of the disease in terms of time, place and person. Both acute (distinguishing between asymptomatic and symptomatic) and chronic cases should be covered (although one expert felt that the monitoring of chronic hepatitis E epidemiology should be a secondary objective). A minimum data set to describe the epidemiology of laboratory-confirmed cases was suggested to include date of diagnosis, age, sex and place of residence. As of 2019, 20 EU/EAA Member States performed HEV-specific surveillance and four additional countries had syndromic surveillance (collecting data only on patients with signs of acute or chronic hepatitis without reference to a specific pathogen) systems for viral hepatitis in place. Of the 20 countries with pathogen-specific surveillance, 17 collected a data set to describe the epidemiology of acute hepatitis E virus infection (unique patient identifier, date of notification, source of notification, date of birth/age, sex, date of onset of disease), which overlaps largely with the minimal data set. Laboratories in 11 countries have testing for chronic cases in place (see Table 2 in Aspinall et al. 2017 [11]) and two countries have a national case definition for chronic cases.

Secondary surveillance objectives agreed upon were to collect data on phylogenotypes or subtypes of HEV e.g. according to Smith et al, 2016 [15], identify potential clusters/outbreaks and collect information on possible routes of transmission. The surveillance systems should enable the identification of outbreaks and trends for the initiation of public health responses. The long incubation period of HEV and delay of reporting might hamper cluster detection. The secondary objectives would require collection of case-based data including information on laboratory confirmation (method used), viral geno- or sub-type, source of notification, travel history, hospitalisation, case status (acute, chronic) and clinical presentation (asymptomatic, hepatic or extra-hepatic). A subset of countries reported the collection of such data: travel history within the EU/EAA (17 countries), travel history outside the EU/EAA (16 countries), hospitalisation (15 countries), source of notification (19 countries), and symptoms (13 countries). Nineteen of the 26 countries testing for HEV reported to also sequence and determine the viral geno- and subtype.

Specific research questions, e.g. on risk factors, route of transmission or disease burden and severity could be more efficiently addressed by dedicated epidemiological studies. Data routinely collected in some Member States include such variables, see Table 1. In addition, some countries also collect information on HEV-related death (14 countries), ethnicity (6 countries), medication (5 countries), and migration background/refugee status (2 countries).

3.2. Data collection

A national comprehensive or at least representative and stable surveillance system collecting a minimum of clinical and epidemiological data on laboratory-confirmed cases was found to be the best way to meet the surveillance objectives. However, pre-existing surveillance systems have to be considered when setting up or integrating surveillance for HEV. Seventeen countries have an established national surveillance and 12 of them reported a full population coverage. The minimum frequency of reporting should be annual while monthly reporting was considered optimal. Eleven of 15 countries providing this information collect daily surveillance data on HEV cases, one country does so weekly, two countries quarterly and the remaining one annually (Table 1).

A sentinel surveillance system (that collects data from selected, representative specific sampling sites such as primary care, hospitals, hepatological clinics, transfusion/transplantation centres, microbiology laboratories, etc. following a case definition) could also be used to collect relevant information in a representative population and fulfil specific surveillance objectives. The Netherlands is the only country to rely on sentinel laboratory surveillance for HEV.

Routine surveillance could be complemented by prevalence and incidence data from a representative blood donor screening programme and would be able to collect data according to the primary objective to monitor HEV infections in a population. Universal screening programmes have been implemented in Ireland, the Netherlands and the United Kingdom (2017) and will be introduced in Germany (2020) and possibly France [6]. Such blood donor screening should be based on a national risk assessment and may not be cost-effective in each country. Luxembourg indicated that they use their blood service as the sole data
source for HEV surveillance.

3.3. Testing and case confirmation

Testing guidelines for HEV have been published by EASL [16], the Spanish Society of Infectious Diseases and Clinical Microbiology [17] and British Transplantation Society [18]. ECDC’s expert group agreed with the recommendations that all patients with symptoms consistent with viral hepatitis and specific groups at risk for chronic HEV should be tested for HEV. Such specific groups include immunosuppressed patients with unexplained abnormal LFTs, patients with suspected drug-induced liver injury, neuralgic amyotrophy, Guillain-Barré syndrome and encephalitis/myelitis as well as patients with unexplained acute neurological symptoms and a raised ALT. Testing should generally follow national recommendations, which will take national risk assessments into account.

A broad and unspecific range of symptoms has been described for HEV infection, not only including signs of viral hepatitis, but also neurological and other extra-hepatic manifestations. Therefore, only laboratory criteria were considered relevant for case confirmation. The source of information, e.g. whether a case was reported by a physician or laboratory or derives from blood donor screening, should be reported as this may help to distinguish between symptomatic and asymptomatic cases. Fifteen EU/EEA Member States have either case definitions or clinical criteria for the confirmation of an acute case. A national case definition for acute cases is available for 12 countries with laboratory confirmation required in all of them. Ireland and the UK (England and Wales) also have a case definition for chronic cases.

For surveillance purposes, the ECDC expert group suggested anti-HEV IgM and IgG positivity as minimum criteria to confirm an acute case. However, for reasons of cost, not all laboratories perform subsequent IgG testing in IgM-positive patients with symptoms indicative of viral hepatitis. Detection of HEV RNA by PCR, even in the absence of serological testing, can be considered sufficient to confirm an acute case, but the expert group assumed that PCR testing might not be available in all laboratories and countries. 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. In 2017, anti-HEV IgM testing was undertaken in 22 countries and anti-HEV IgG testing in 21 countries. Of these, 19 countries also performed PCR testing.

Molecular testing to demonstrate the presence of HEV RNA for at least three months is essential for confirmation of a chronic hepatitis E case. Eleven countries use PCR testing of serum/plasma for this purpose. Interestingly, 26 Member States have HEV testing in place and 19 already perform sequencing of virus isolates. The expert group suggests to sequence a representative subset of virus isolates. For the molecular epidemiological analysis of HEV sequences, an online sequence database and voluntary network is available: HEVnet [19,20].

4. Discussion

The operational guidance document “Options for national testing and surveillance for hepatitis E virus in the EU/EEA” [14] developed by the ECDC’s HEV expert group offers suggestions on the implementation or adjustment of national HEV surveillance and proposes criteria for clinical testing (following EASL guidelines), case definitions for acute and chronic HEV infection and reporting schemes. Systematic and continuous monitoring of acute and chronic cases will allow a better assessment of the epidemiology of HEV in the Member States. Information on acute and chronic cases will also support decisions on whether to implement/discontinue blood donor screening programmes. The suggestions for national surveillance of HEV overlap with recommendations for the surveillance of other forms of infectious hepatitis, including hepatitis B and C virus infections, where case definitions also rely on laboratory confirmation only [21,22]. The majority of EU/EEA countries already perform testing for HEV and the ECDC guidance could support countries without structured monitoring to fulfill WHO’s action plan [13]. The majority of EU/EEA countries already have longstanding stable surveillance systems for HEV, and this experience has contributed to shaping the suggestions of the ECDC expert group. Continuous epidemiological data on numbers of acute cases and chronic infections from a representative population over time will provide evidence on the public health impact of HEV. Solid and representative surveillance data, together with molecular information on circulating viruses in humans, will also provide evidence for risk assessment useful for public and animal health. This will enable food safety authorities to implement preventive and control measures in the animal population and in food production, thereby reducing the risk of transmission to humans.

The majority of Member States with established HEV surveillance systems in the EU/EEA already address most of the suggested criteria or have performed specific studies to better understand the epidemiological situation in the country.

Credit author statement

This work was coordinated by Cornelia Adlhoch and all co-authors, ECDC’s HEV expert group members, contributed equally to the data analysis, discussions, and development of the guidance document and manuscript. All co-authors have approved the final version of the manuscript.

Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

We declare no conflicts of interest.

Acknowledgements

The authors would like to thank previous expert group members for their great commitment and support: Wilfried van Pelt (Netherlands, until 2018), Lelia Thornton (Ireland, until 2018), Elisabeth Couturier (France, until 2018), Ágnes Fehér (Hungary, until 2017), Rita Korotinska (Latvia), and Harry Dalton (United Kingdom).

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.

The work was supported by two service contracts No. ECD.7600 (HEV epidemiological support - NP/2017/OCS/253) and No. ID 5132: Hepatitis B, C, and E in the EU/EEA: monitoring and testing activities. Staff that were involved in the contracts: Esther Aspinall (Glasgow Caledonian University and Health Protection Scotland), Andrew Rideout (NHS Dumfries and Galloway), Chris Biggam (Glasgow Caledonian University), Gill Hawkins (Health Protection Scotland), and Alison Smith-Palmer (Health Protection Scotland).

We would also like to acknowledge ECDC staff members who supported the project and critically reviewed all documents: Piotr Kramarz, Johanna Takkinen, and Phillip Zucs.

References

[1] Hazards EP, A. Ricci, A. Allende, D. Bolton, M. Chemaly, R. Davies, et al., Public health risks associated with hepatitis E virus (HEV) as a food-borne pathogen, EFSJ P. 15 (3) (2018), https://doi.org/10.2903/j.esfa.2017.4886 e4886-n/a.
[2] M. Faber, M. Askar, K. Stark, Case-control study on risk factors for acute hepatitis E in Germany, 2012 to 2014, Eurosurveillance 23 (19) (2018) 17-00469, https://doi.
[3] B. Said, S. Ijaz, M.A. Chand, G. Kafatos, R. Tedder, D. Morgan, Hepatitis E virus in England and Wales: indigenous infection is associated with the consumption of processed pork products, Epidemiol. Infect. 142 (7) (2013) 1467–1475, https://doi.org/10.1017/S0950268813002518.

[4] A.D. Tulen, H. Vennema, W. van Pelt, E. Franz, A. Hofhuis, A case-control study into risk factors for acute hepatitis E in the Netherlands, 2015-2017, J. Infect. (February 77) (2019), https://doi.org/10.1016/j.jinf.2019.02.001.

[5] F. Abravanel, J. Pique, E. Couturier, F. Nicot, C. Dimeglio, S. Lhomme, et al., Acute hepatitis E in French patients and neurological manifestations, J. Infect. 77 (3) (2018) 220–226, https://doi.org/10.1016/j.jinf.2018.06.007 2018/09/01/.

[6] D. Domanovic, R. Tedder, J. Blumel, H. Zaaijer, P. Gallian, C. Niederhauser, et al., Hepatitis E and blood donation safety in selected European countries: a shift to screening? Euro Surveill. 22 (April (16)) (2017),https://doi.org/10.2807/1560-7917.ES.2017.22.16.30514.

[7] S. Lhomme, O. Marion, F. Abravanel, S. Chapuy-Regaud, N. Kamar, J. Izopet, Hepatitis e pathogenesis, Viruses 8 (August (8)) (2016), https://doi.org/10.3390/v8080212.

[8] S. Fujisawa, Y. Yokokawa, K. Morino, K. Hayasaka, M. Kawabata, T. Shimizu, Chronic hepatitis E: a review of the literature, J. Viral Hepat. 21 (2) (2014) 78–89.

[9] S. Ijaz, B. Said, E. Boxall, E. Smit, D. Morgan, R.S. Tedder, Indigenous Hepatitis E in England and Wales from 2003 to 2012: evidence of an emerging novel phylotype of viruses, J. Infect. Dis. 209 (8) (2014) 1212–1218.

[10] N. Kamar, F. Abravanel, S. Lhomme, L. Rostaing, J. Izopet, Hepatitis E virus: chronic infection, extra-hepatic manifestations, and treatment, Clin. Res. Hepatol. Gastroenterol. 39 (1) (2015) 20–27, https://doi.org/10.1016/j.clinre.2014.07.005.

[11] E.J. Aspinall, E. Couturier, M. Faber, B. Said, S. Ijaz, I. Tavoschi, et al., Hepatitis E virus infection in Europe: surveillance and descriptive epidemiology of confirmed cases, 2005 to 2015, Euro Surveill. 22 (June (26)) (2017), https://doi.org/10.2807/1560-7917.ES.2017.22.26.30561.

[12] European Centre for Disease Prevention and Control (ECDC), Hepatitis E in the EU/EEA 2005-2015: Baseline Assessment of Testing, Diagnosis, Surveillance and Epidemiology, ECDC, Stockholm, 2017 Available from: https://ecdc.europa.eu/en/publications-data/hepatitis-e-eueea-2005-2015.

[13] World Health Organization Regional Office for Europe, Action Plan for the Health Sector Response to Viral Hepatitis in the WHO European Region World Health Organization, (2017).

[14] European Centre for Disease Prevention and Control, Operational Guidance: Options for National Testing and Surveillance for Hepatitis E Virus in the EU/EEA, ECDC, Stockholm, 2019 Available from: https://ecdc.europa.eu/en/publications-data/options-national-testing-and-surveillance-hepatitis-e-virus-eueea-operational.

[15] D.B. Smith, P. Simmonds, J. Irope, E.F. Oliveira-Filho, R.G. Ulrich, R. John, et al., Proposed reference sequences for hepatitis E virus subtypes, J. Gen. Virol. 97 (March(3)) (2016) S37–542, https://doi.org/10.1099/jgv.0.000393.

[16] European Association for the Study of the Liver, Electronic address eee, European association for the study of the L EASL clinical practice guidelines on hepatitis e virus infection, J. Hepatol. 68 (June (6)) (2018) 1256–1271, https://doi.org/10.1016/j.jhep.2018.03.005.

[17] A. Rivero-Juarez, A. Aguilar, A. Avellan, M. Garcia-Deltoro, F. Garcia, C. Gortazar, et al., Executive summary: consensus document of the diagnosis, management and prevention of infection with the hepatitis E virus: study Group for Viral Hepatitis (GEHEP) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), Enferm. Infec. Microbiol. Clin. 30 (July) (2018), https://doi.org/10.1016/j.eimc.2018.06.014.

[18] S. McPherson, A.M. Elsharkawy, M. Ankeorn, S. Ijaz, J. Powell, I. Rowe, et al., Summary of the british transplantation society UK guidelines for hepatitis e and solid organ transplantation, Transplantation 102 (January (1)) (2018) 15–20, https://doi.org/10.1097/TP.0000000000001908.

[19] National Institute for Public Health and the Environment (RIVM), HEVNet [02/10/2018]. Available from: https://www.rivm.nl/en/Topics/H/HEVNet.

[20] A.C. Mulder, A. Krolewski, E. Franz, H. Vennema, A.D. Tulen, J. Takkinen, et al., HEVnet: a one-heath collaborative inter-disciplinary network and sequence data repository for enhanced hepatitis E virus molecular typing, virus characterisation and epidemiological investigations, Eurosurveillance (2019) Accepted Feb.

[21] Eurohep.net, Recommendations for Hepatitis a and B Surveillance and Prevention Strategies: Proposal from the EUROHEP.NET Project to the European Commission, [22/08/2018]. Available from (2005) http://www.eurohep.net/RecommendationsDec2005.pdf.

[22] European Centre for Disease Prevention and Control (ECDC), EU/EEA Capacity for the Surveillance of Hepatitis B and C Using Molecular Methods, [10/12/2018]. Available from: (2018) https://ecdc.europa.eu/en/publications-data/eueea-capacity-surveillance-hepatitis-b-and-c-using-molecular-methods.