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

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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.

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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

Table 1
Summary of HEV-specific surveillance systems in EU/EEA Member States according to ECDC surveillance report, 2017 [11,12], and updates by expert feedback, 2019.

	Member State	Type of HEV surveillance	Case definition (acute cases)	Testing performed	Sequencing performed	Minimal required information for primary objective (N = 4)[a]	Optimal required information for primary objective (N = 4)[b]	Number of risk factors included (N = 11)[c]	Frequency of reporting
1	Austria	National	Yes	Yes	Unk	All	All	1	Real-time
2	Belgium	Reference laboratory	Yes	Yes	Yes	All	All	3	Annual
3	Bulgaria	None	–	Yes	Yes	None	–	–	–
4	Croatia	National	–	Yes	Yes	All	1	1	Real-time
5	Cyprus	None	–	Yes	No	All	2		Quarterly
6	Czech Republic	National	Yes	Yes	Yes	All	All	11	Real-time
7	Denmark	None	–	Yes	Unk	None	–	–	–
8	Estonia	National	–	Yes	Yes	All	3	2	Real-time
9	Finland	National	–	Yes	Yes	All	1	0	Real-time
10	France	Reference laboratory	Yes	Yes	Yes	None		0	–
11	Germany	National	Yes	Yes	Yes	All	All	1	Within 24 hours
12	Greece	None	–	No	Unk	None	–	–	
13	Hungary	National	Yes	Yes	Yes	All	All	4	Real-time
14	Iceland	None	–	No	No	None	–	–	
15	Ireland	National	Yes[d]	Yes	Yes	All	1	2	Real-time
16	Italy	National	Yes	Yes	Yes	All	3	2	Real-time
17	Latvia	National	–	Yes	No	All	All	8	–
18	Lithuania	None	–	Yes	No	None	–	–	–
19	Luxembourg	Blood service	–	Yes	Yes	None	–	–	–
20	Malta	None	–	Unk	Unk	None	–	–	–
21	Netherlands	Sentinel laboratory	Yes	Yes	Yes	None	–	–	Weekly
22	Norway	None	–	Yes	Yes	None	–	–	–
23	Poland	None	–	Yes	No	None	–	–	–
24	Portugal	National	Yes	Yes	Yes	All	All	5	–
25	Romania	None	–	Unk	No	None	–	–	–
26	Slovakia	National	–	Yes	No	All	All	10	Within 24 hours
27	Slovenia	National	–	Yes	Unk	All	All	8	–
28	Spain	Reference laboratory	–	Yes	Yes	–	–	0	–
29	Sweden	National	Yes	Yes	Yes	All	2	2	Real-time
30	United Kingdom – England&Wales	National	Yes[d]	Yes	Yes	All	All	8	Quarterly
	United Kingdom – Scotland	National	Yes	Yes	Yes	All	All	9	Real-time
	United Kingdom – Northern Ireland	National	Yes	Yes	Unk	All	2	0	–

Unk: Reported to be unknown; -: no information available; Real-time: to be reported whenever data are available; Data from the ECDC surveillance study in EU/EEA countries [11,12].

[a] Variables: date of onset (19 countries) or date of notification (20 countries) or date of diagnosis (15 countries); age or date of birth (19 countries); sex (20 countries); patient identifier (17 countries).

[b] Variables: travel history within (16 countries) or outside EU/EEA (15 countries); hospitalisation (14 countries); source of notification (18 countries); symptoms (12 countries).

[c] Variables: occupation (14 countries); pregnancy (8 countries); alcohol consumption (4 countries); recent transfusion of blood components or blood products (6 countries); recent transplantation (5 countries); immunosuppressive medication or condition (5 countries); other underlying medical conditions (4 countries); cluster (10 countries); food consumption history – detailed food items (6 countries); food consumption history – groups of foods (7 countries); environmental contact with livestock/farm animals (8 countries).

[d] Also case definition for chronic cases [15].

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]. Extrahepatic 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/EEA level. ECDC conducted a survey among the EU/EEA 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/EEA 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/EEA and 240 (1.7%) had travelled outside the EU/EEA [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/EEA 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/EEA 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 phylotypes 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/EEA (17 countries), travel history outside the EU/EEA (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 fulfil WHO's action plan [13]. The majority of EU/EEA countries already have long-standing 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.

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