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Hepatitis E virus: assessment of the epidemiological situation in humans in Europe, 2014/15

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Highlights

- Surveillance systems not harmonised across EU/EEA countries
- Analysis indicates a common trend of increased case numbers on Western EU/EEA countries
- Knowledge of testing algorithms and clinical diagnosis is variable
- Autochthonous cases harbour genotype 3 viruses which are also found in pigs
- Sharing of human and animal data needed to understand transmission/epidemiology

ABSTRACT

Background: Hepatitis E virus (HEV) is endemic in EU/EEA countries, but the understanding of the burden of the infection in humans is inconsistent as the disease is not under EU surveillance but subject to national policies.

Study: Countries were asked to nominate experts and to complete a standardised questionnaire about the epidemiological situation and surveillance of HEV in their respective EU/EEA country. This study reviewed surveillance systems for human cases of HEV in EU/EEA countries and nominated experts assessed the epidemiology in particular examining the recent increase in the number of autochthonous cases.

Results: Surveillance systems and case definitions across EU/EEA countries were shown to be highly variable and testing algorithms were unreliable. Large increases of autochthonous cases were reported from Western EU/EEA countries with lower case numbers seen in Northern and Southern European countries. Lack of clinical awareness and variability in testing strategies might account for the observed differences in hepatitis E incidence across EU/EEA countries. Infections were predominantly caused by HEV genotype 3, the most prevalent virus type in the animal reservoirs.

Conclusion: Discussions from the expert group supported joint working across countries to better monitor the epidemiology and possible changes in risk of virus acquisition at a European level. There was agreement to share surveillance strategies and algorithms but also importantly the collation of HEV data from human and animal populations. These data collected at a European level would serve the ‘One Health’ approach to better informing on human exposure to HEV.

Abbreviations: EU/EEA: European Union and European Economic Area; **MS:** Member State; **HEV**: Hepatitis E virus; Regions in EU/EEA countries were used according to http://eurovoc.europa.eu/drupal/?q=request&view=mt&mturi=http://eurovoc.europa.eu/100277&language=en

Keywords: hepatitis E virus, Europe, epidemiology, surveillance, zoonotic infections

Article

Objectives

Hepatitis E virus (HEV) is one of the most common causes of hepatitis worldwide.[1] HEV is endemic in regions of Asia and Africa where it causes an acute self-limiting hepatitis in young adults, except in pregnant women who have a case fatality rate of approximately 25%. In these regions, infection is usually linked to HEV genotypes (gt) 1 and 2 which are spread faecal-orally via contaminated water, resulting in both sporadic cases and large outbreaks.[1]

Until a decade ago, cases of hepatitis E in Europe were thought to be restricted to travellers returning from endemic areas. However, it is now well-established that HEV is endemic in the EU/EEA.[2] Here, the virus is transmitted zoonotically with infections linked mainly to gt3 viruses. Cases of acute hepatitis E caused by HEV gt3 occur mainly in older males and chronic infection in immunosuppressed individuals, including transplant recipients, have been recognised.[1] Excess mortality has not been observed in pregnant women in EU/EEA, but infection in patients with underlying chronic liver disease has a reported case fatality rate of 27%.[3] However, the burden of HEV infection in humans in Europe remains poorly documented. HEV infection is not under EU surveillance, and reporting systems, case definitions and populations under surveillance are subject to national policies, which vary across countries. National incidence and prevalence estimates have been previously published for a number of EU/EEA countries.[4, 5] However, a comparative EU-wide situational analysis has not previously been reported. The aim of this study was to elucidate the emergence of HEV infection in humans across the EU/EEA Member States by reviewing the surveillance systems and reported number of hepatitis E cases.

Study

EU/EEA countries were invited to nominate national public health experts, clinicians, and experts in blood safety working on HEV. In addition, a standardised questionnaire collected information about national surveillance systems, and reported number of cases of hepatitis E.

Results

Information on surveillance systems was available from 29 countries and experts from 17 countries contributed to the assessment of the epidemiological situation. A considerable heterogeneity in surveillance arrangements, diagnostic testing algorithms and case definitions between countries was noted (Figure 1, Table).

In 2014/15, increasing and large numbers of cases of HEV were reported in France, Germany, England & Wales, the Netherlands, and increases in Finland, Hungary and Italy (Table, Figure 2).

Data from France, Germany, England & Wales, and the Netherlands indicated more hepatitis E case notifications than hepatitis A cases (data not shown). Considerably lower numbers of cases of hepatitis E were confirmed in Northern and Southern European countries (Table 1).

In EU/EEA, infections were predominantly autochthonous and caused by HEV gt3, the most prevalent virus type in humans and animal reservoirs in Europe.[6, 7] Viruses detected in England & Wales between 2003 and 2009 were mainly gt3efg, while between 2010 and 2013, gt3c viruses predominated in humans. In contrast, HEV from United Kingdom pigs tested in 2013 were gt3efg.[8] A very small number of autochthonous cases caused by gt4 have been documented in France and Italy.

Seroprevalence data were available in a minority of countries and showed considerable heterogeneity possibly due to differences in the performance of the assays used and in the characteristics of the study population studied (data not shown). Data on HEV viraemia in blood donations have been reported from several countries and showed a similar heterogeneity, ranging from 1:762 in the Netherlands to 1:14,520 in Scotland.[9, 10]

Discussion

There has been a common trend amongst the Western European countries of a year on year increase in reported hepatitis E case numbers. In some countries these numbers have exceeded reported hepatitis A cases. This increase may reflect a true rise in the incidence of hepatitis E in some parts of Europe suggesting that there has been a change in the risk of acquiring HEV. This is supported by the observed increase in HEV RNA prevalence in blood donors over time reported from England and the Netherlands.[9, 11-13] The increase may also be due to improved case-ascertainment: clinicians are increasingly aware of HEV as a cause of hepatitis in patients without a travel history, as suggested by the increased numbers of tests performed for HEV in these countries. In Spain and France, the number of tested specimens increased simultaneously to the rise of HEV cases, however, the positivity rate remained constant (12%–17% in Spain).

The reason for the low numbers of cases in Northern and Southern European countries is unknown. It could relate to differences in clinical awareness, diagnostic testing algorithms/criteria or surveillance systems/practices. Less exposure to HEV in such countries seems unlikely, given the estimated number of viaremic blood donors in Spain[14] and the very high seroprevalence of 49% in blood donors in central Italy (unpublished data). In addition to differences *between* countries, there may be differences in viral pressure *within* a geographical region. In England, HEV seroprevalence was 12–16% and 1:2,848 blood donors were viraemic, compared to Scotland where seroprevalence was 5% and 1:14,520 donors were viaremic.[10, 11, 15]

The number of laboratory-confirmed/notified cases is almost invariably an underestimate of true incidence and this 'tip-of-the-iceberg' effect is likely to be particularly pronounced with respect to HEV.[16, 17] Poor clinical awareness of the differential diagnosis in patients with hepatitis might contribute to the underestimation of symptomatic infection. Hepatitis E may be frequently misdiagnosed as drug-induced liver injury.[18] Finally, recent data have shown that HEV infection may present with a range of neurological symptoms, including Guillain–Barré syndrome, neuralgic amyotrophy and meningo-encephalitis.[19] Such patients are currently not routinely tested for HEV. Thus, the numbers of laboratory-confirmed cases documented here are likely to be underestimates of the true incidence of clinical cases as suggested by data on numbers of viraemic blood donors.

The increased awareness and better testing systems might have contributed to the reported increase of locally acquired cases recently, but does not explain the recent replacement of

predominant virus subtypes gt3efg by gt3c in humans with a continued circulation of gt3efg in the local pig population in the United Kingdom, while in the Netherlands gt3c is detected in both, humans and pigs. HEV is highly prevalent in European pig herds[20] and consumption of contaminated pork products is one major risk factor for human infection.[17, 21] Monitoring activities in the food production chain for HEV need to be enhanced to identify sources of infection. To understand the relationship of human and animal virus types across Europe, trade relations and the compilation of food ingredients should be reviewed.

Our understanding of the epidemiology of HEV and its burden of human infections at the EU/EEA level is currently inconsistent. Increasing numbers of laboratory-confirmed autochthonous cases in many Western European countries suggest a common trend and possibly common risks e.g. due to eating habits. Clinical testing algorithms and numbers of diagnostic assays performed need to be known to be able to put the data into perspective. A common EU-wide strategy to better understand case numbers and determine circulating strains of the virus across human and animal populations employing a 'One Health' approach are needed to address these issues. The development of a joint sequence database covering also clinical data would be one suggestion.

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Contributions

All authors provided contribution to the research article and approved the final version.

Cornelia Adlhoch, coordinated the work, interpreted the data and led the writing of the article

Ana Avellon, provided Spanish data, and contributed to writing of the article

Sally A. Baylis, provided information on serology and detection systems and contributed to the writing of the research article

Anna Rita Ciccaglione, provided virological data from Italy, and contributed to writing of the article

Elisabeth Couturier, provided data from France

Rita de Sousa, provided Portuguese data and contributed to data interpretation

Jevgenia Epštein, provided data from Estonia and contributed to writing of the article

Steen Ethelberg, provided data from Denmark and contributed to writing of the article

Mirko Faber, provided data from Germany and contributed to writing of the article

Ágnes Fehér, provided data from Hungary and contributed to writing of the article

Samreen Ijaz, provided data from UK, interpretation of virological data and contributed to writing of the article

Heidi Lange, provided data from Norway and contributed to writing of the article

Zdenka Manďáková, provided data from Czech Republic

Kasiani Mellou, provided Greek data

Antons Mozalevskis, contributed to data interpretation

Ruska Rimhanen-Finne, provided data from Finland, and contributed to writing of the article

Valentina Rizzi, contributed to data interpretation

Bengü Said, provided UK data and writing of the article

Lena Sundqvist, provided data from Sweden, and data interpretation

Lelia Thornton, provided data from Ireland, and contributed to writing of the article

Maria Elena Tosti, provided epidemiological data from Italy

Wilfrid van Pelt, provided data from the Netherlands, and contributed to the data interpretation

Esther Aspinall, developed questionnaire and collection of surveillance data

Dragoslav Domanovic, responsible for blood safety data

Ettore Severi, contribution to analysis of data

Johanna Takkinen, contribution to interpretation of data and writing of the article

Harry R. Dalton, provided clinical data, contribution to interpretation of data and writing of the article

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REFERENCES

1. Kamar N, Bendall R, Legrand-Abravanel F, Xia NS, Ijaz S, Izopet J, et al. Hepatitis E. Lancet. 2012;379:2477-88.

2. Dalton HR, Bendall R, Ijaz S, Banks M. Hepatitis E: an emerging infection in developed countries. Lancet Infect Dis. 2008;8:698-709.

3. Blasco-Perrin H, Madden RG, Stanley A, Crossan C, Hunter JG, Vine L, et al. Hepatitis E virus in patients with decompensated chronic liver disease: a prospective UK/French study. Aliment Pharmacol Ther. 2015;42:574-81.

4. Faber MS, Wenzel JJ, Jilg W, Thamm M, Höhle M, Stark K. Hepatitis e virus seroprevalence among adults, germany. Emerging infectious diseases. 2012;18:1654-57.

5. Renou C, Moreau X, Pariente A, Cadranel JF, Maringe E, Morin T, et al. A national survey of acute hepatitis E in France. Alimentary Pharmacology and Therapeutics. 2008;27:1086-93.

6. Tedder RS, Tettmar KI, Brailsford SR, Said B, Ushiro-Lumb I, Kitchen A, et al. Virology, serology, and demography of hepatitis E viremic blood donors in South East England. Transfusion. 2016.

7. Reuter G, Fodor D, Forgách P, Kátai A, Szucs G. Characterization and zoonotic potential of endemic hepatitis E virus (HEV) strains in humans and animals in Hungary. Journal of Clinical Virology. 2009;44:277-81.

8. Ijaz S, Said B, Boxall E, Smit E, Morgan D, Tedder RS. Indigenous hepatitis E in England and wales from 2003 to 2012: evidence of an emerging novel phylotype of viruses. J Infect Dis. 2014;209:1212-8.

9. Hogema BM, Molier M, Slot E, Zaaijer HL. Past and present of hepatitis e in the Netherlands. Transfusion. 2014;54:3092-96.

10. Cleland A, Smith L, Crossan C, Blatchford O, Dalton HR, Scobie L, et al. Hepatitis E virus in Scottish blood donors. Vox sanguinis. 2013;105:283-9.

11. Hewitt PE, Ijaz S, Brailsford SR, Brett R, Dicks S, Haywood B, et al. Hepatitis E virus in blood components: a prevalence and transmission study in southeast England. Lancet. 2014;384:1766-73.

12. Hogema BM, Molier M, Sjerps M, de Waal M, van Swieten P, van de Laar T, et al. Incidence and duration of hepatitis E virus infection in Dutch blood donors. Transfusion. 2015.

13. Ijaz S, Szypulska R, Tettmar KI, Kitchen A, Tedder RS. Detection of hepatitis E virus RNA in plasma mini-pools from blood donors in England. Vox sanguinis. 2012;102:272.

14. Sauleda S, Ong E, Bes M, Janssen A, Cory R, Babizki M, et al. Seroprevalence of hepatitis E virus (HEV) and detection of HEV RNA with a transcription-mediated amplification assay in blood donors from Catalonia (Spain). Transfusion. 2015;55:972-79.

15. Beale MA, Tettmar K, Szypulska R, Tedder RS, Ijaz S. Is there evidence of recent hepatitis E virus infection in English and North Welsh blood donors? Vox sanguinis. 2011;100:340-2.

16. Said B, Ijaz S, Kafatos G, Booth L, Thomas HL, Walsh A, et al. Hepatitis E outbreak on cruise ship. Emerging infectious diseases. 2009;15:1738-44.

17. Guillois Y, Abravanel F, Miura T, Pavio N, Vaillant V, Lhomme S, et al. High Proportion of Asymptomatic Infections in an Outbreak of Hepatitis E Associated With a Spit-Roasted Piglet, France, 2013. Clin Infect Dis. 2016;62:351-7.

18. Crossan CL, Simpson KJ, Craig DG, Bellamy C, Davidson J, Dalton HR, et al. Hepatitis E virus in patients with acute severe liver injury. World J Hepatol. 2014;6:426-34.

19. Kamar N, Bendall RP, Peron JM, Cintas P, Prudhomme L, Mansuy JM, et al. Hepatitis E virus and neurologic disorders. Emerg Infect Dis. 2011;17:173-9.

20. Baechlein C, Schielke A, Johne R, Ulrich RG, Baumgaertner W, Grummer B. Prevalence of Hepatitis E virus-specific antibodies in sera of German domestic pigs estimated by using different assays. Veterinary microbiology. 2010;144:187-91.

21. Wichmann O, Schimanski S, Koch J, Kohler M, Rothe C, Plentz A, et al. Phylogenetic and case-control study on hepatitis E virus infection in Germany. Journal of Infectious Diseases. 2008;198:1732-41.

Figure 1: EU/EEA countries reporting a national notification system for hepatitis E virus infection, 2016

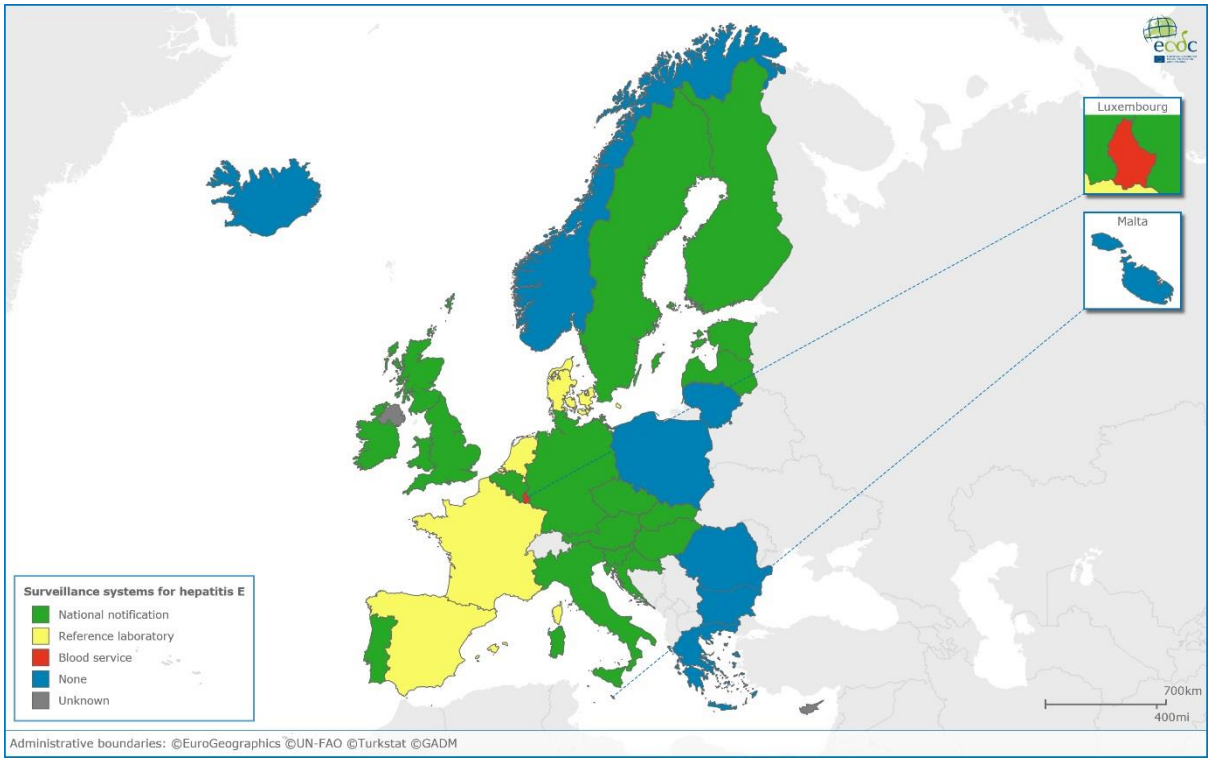
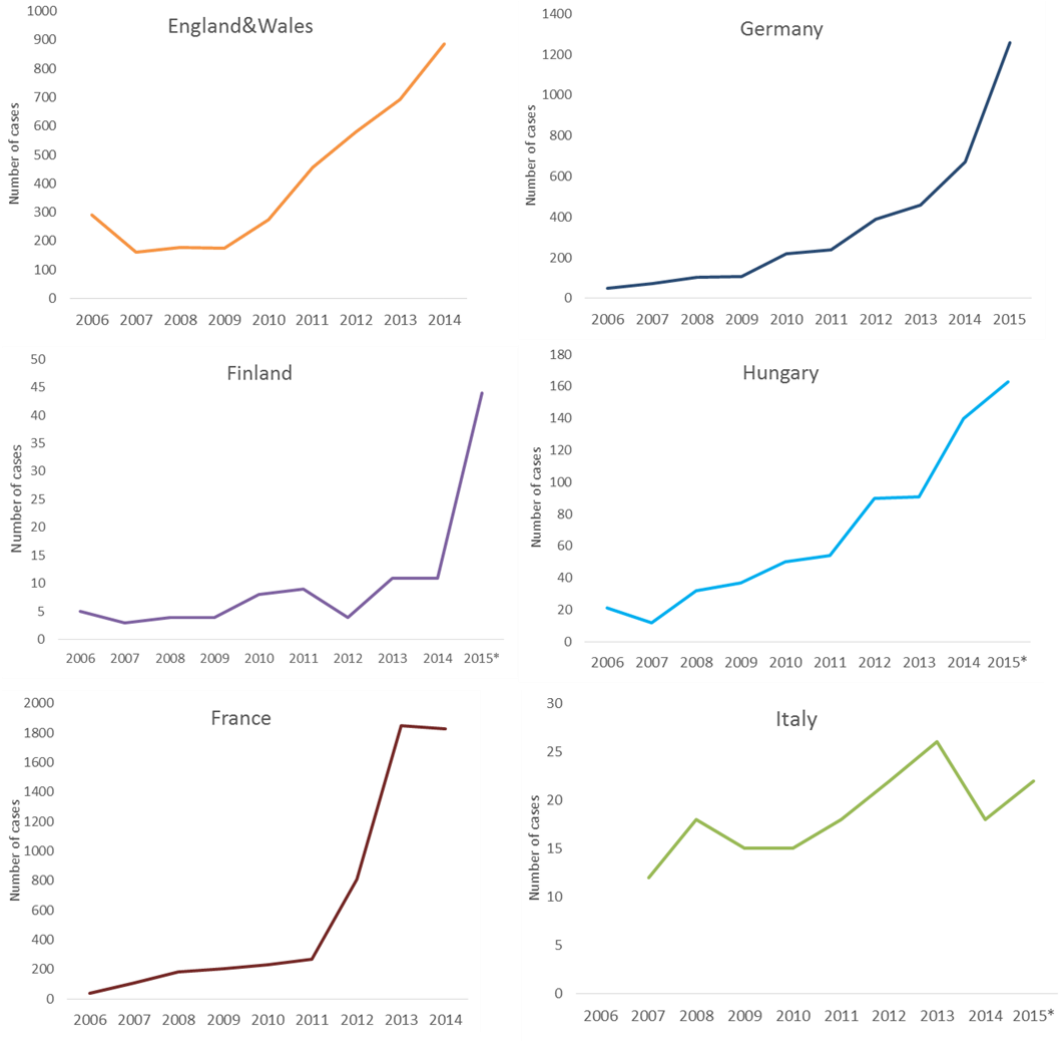


Figure 2: Number of reported laboratory-confirmed cases of hepatitis E virus (HEV) by country, 2006–2015*



*2015 data not complete

Table: Characteristics of hepatitis E surveillance systems in participating EU/EEA countries with number of cases and genotype/subtype

Country	Is HEV notifiable? (Year)	Surveillance through reference laboratory (period)	Case definition/positivity criteria	Comments	Number of reported cases of Hepatitis E (autochthonous)	Predominant autochthonous HEV genotype/subtype
Austria	Yes				2014: 17 (15) 2015: 36 (30)	
Belgium	Yes				2014: 35 2015: 65	
Bulgaria	No				2015: 54	gt3
Croatia	Yes				2014: 0 2015: 2	
Czech Republic	Yes (2008)		Laboratory diagnosis • Anti-HEV IgM, IgG • HEV RNA in serum and stool		2014: 290 (288) 2015: 412 (398)	
Denmark	No	Yes		Diagnostics and typing performed at SSI[d]. HEV scheduled to become notifiable in 2016.	2014: 9	gt3
England & Wales	Yes (2010)		Available at: https://www.gov.uk/government/publications/hepatitis-e-health-protection-response-to-reports-of-infection	Viral hepatitis has been notifiable since the 1980's. Hepatitis E has been notifiable since 2010. National guidelines on case definition and testing algorithms are established.	2014: 886 (729) 2015: 848 (694)	gt3c
Estonia	Yes (1997)			First case notified in 2012.	2014: 1 2015: 1	gt3
Finland	Yes (1995)		Notification criteria: serology, PCR.	From the beginning of 2016, the laboratories are encouraged to notify only anti-HEV IgM-positive cases.	2014: 11 2015: 44	
France	No	Yes (2002-2014)	Diagnostic algorithm Immunocompetent • IgM(+) = recent infection to confirm by PCR • IgM(-) = no recent infection Immunocompromised • IgM(+) and HEV RNA(+) = recent or active infection Clearance or persistence by testing for HEV RNA • IgM(-) and HEV RNA(-) = no recent infection		2014: 1,825 (1,813)	gt3f
Germany	Yes (2001)		Notifiable are laboratory confirmed cases (IgM or IgG increase in paired samples or PCR) with clinical symptoms.		2014: 671 2015: 1,266	gt3c
Greece	No			Based on a recent study of laboratory capacity of Greek		

				hospitals, hospital laboratories do not test for HEV. 2003-2015: No reported clusters of HEV infection.		
Hungary	Yes (1993)		Confirmed case: acute viral hepatitis with positive anti-HEV IgM.	Reports based on syndromic surveillance. Acute viral hepatitis is notifiable (infectious hepatitis), testing is mandatory to determine aetiology since 1993.	2014: 140 (140) 2015: 166 (166)	gt3
Iceland	No					
Ireland	Yes (2015 Dec)		**Clinical criteria:** Not relevant for surveillance purposes **Laboratory criteria:** **Acute case:** At least one of the following two: • HEV IgM **and** IgG antibody positive • Detection of HEV RNA **Chronic case:** HEV RNA persisting for at least 3 months.		2015: 30[e]	
Italy	Yes (2007)		**Clinical criteria:** acute illness compatible with hepatitis, and ALT[a] > 10 times the upper limit of the normal range; **Serological criteria:** IgM anti-HEV positive, IgM anti-HBc[b] negative, IgM anti-HAV[c] negative. Cases IgM anti-HEV positive, in absence of clinical signs, are included among "acute hepatitis E cases".	Italian surveillance for HEV is voluntary and currently covers 77% of the Italian population.	2014: 18 (15) 2015: 22 (16)	gt3e, 3c, 3f
Latvia	Yes				2014: 16 (14) 2015: 10 (8)	
Lithuania	No					
Luxembourg	Yes					
Malta	No					
Netherlands	No	Yes			2014: 142 2015: 200	gt3e (1%), 3c (90%), 3e (1%), 3f (8%)
Norway	No				2014: 1 2015: 6	
Poland	No				2014: 6 (4) 2015: 2 (2)	
Portugal	Yes (2015)			Most cases are confirmed by serology.	0	
Slovakia	Yes				2014: 16 (14) 2015: 27 (24)	
Slovenia	Yes				2014: 1 (1) 2015: 0	gt3
Spain	No	Yes (2006-2015)	PCR-positive or IgM and PCR-positive. IgM positive without PCR: IgG seroconversion is needed for confirmation.	80% of the territory is covered.	2014: 100 2015: 105 (103)	gt3f
Sweden	Yes (1993)		**Suspected case:** Clinical illness compatible with the diagnosis and an epidemiological link to a laboratory-confirmed case.		2014: 22 (11) 2015: 29 (16)	

			Confirmed case: A laboratory-confirmed case Laboratory criteria (at least one of the following two): • Detection HEV specific antibody-response in serum indicating current infection. • Detection of HEV RNA in serum or faeces.			

The data shown are for the most recent year available, 2015 data might not be complete.

[a] ALT: alanine aminotransferase

[b] anti-HBc: antibodies to hepatitis B core antigen

[c] HAV: Hepatitis A virus

[d] Statens Serum Institut

[e] Report from the National Virus Reference Laboratory only