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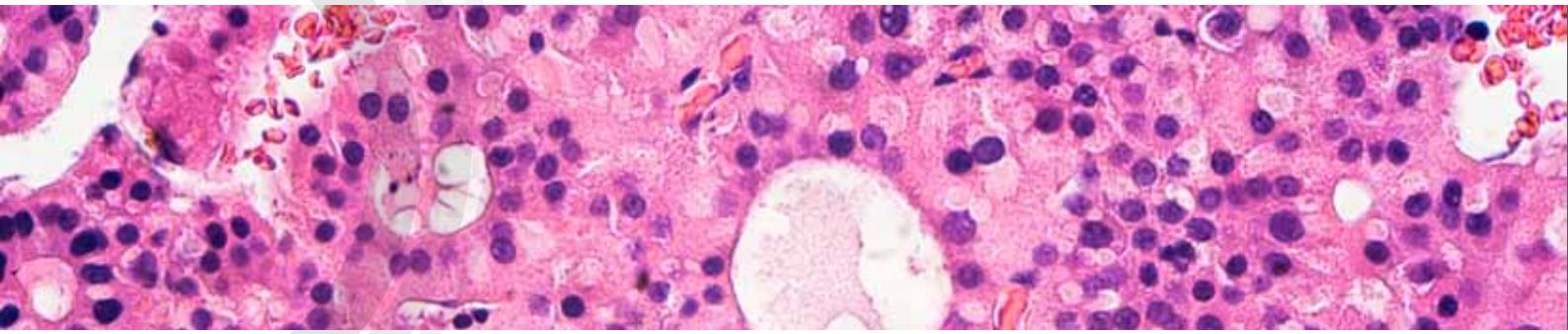

Hepatitis E in the EU/EEA, 2005–2015

Baseline assessment of testing, diagnosis, surveillance and epidemiology

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ECDC SURVEILLANCE REPORT

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This report of the European Centre for Disease Prevention and Control (ECDC) was coordinated by Cornelia Adlhoch, Lara Tavoschi, and Erika Duffell (ECDC) and authored by Esther Aspinall, Sharon Hutchinson, David Goldberg (Glasgow Caledonian University/Health Protection Scotland), and Alison Smith-Palmer (Health Protection Scotland).

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Abbreviations

EEA	European Economic Area
EFSA	European Food Safety Authority
EU	European Union
HEV	Hepatitis E Virus
WHO	World Health Organization

Summary

Hepatitis E virus (HEV) is one of the leading causes of acute viral hepatitis worldwide. HEV genotype 3 (GT3) predominates in high-income countries: transmission is usually zoonotic and has been linked to the consumption of contaminated pork or shellfish products [1-3]. Infection may be asymptomatic or cause an acute self-limiting hepatitis, but may become chronic in a small number of cases, particularly among those who are immunosuppressed or who have pre-existing liver disease. Risk factors for symptomatic or complicated infection include being male, being of an older age, and having pre-existing liver disease. The number of human infections due to HEV in Europe is currently unclear, given widespread variations in awareness, testing, and surveillance activities, and a lack of published information across the majority of European Union/European Economic Area (EU/EEA) Member States. However, there is emerging evidence that HEV is an under-recognised pathogen in high-income countries, and that the incidence of HEV infection has been steadily increasing over the last decade [4,5]. The purpose of this study was to assess current testing, diagnosis, and surveillance for HEV in EU/EEA Member States, and to conduct a baseline assessment of available epidemiological data. This assessment will inform a wider ECDC investigation on the incidence, prevalence, and risk factors for HEV in the EU/EEA.

A semi-structured survey was circulated to the ECDC national focal points for food and waterborne diseases and zoonoses and the European Food- and Waterborne Diseases and Zoonoses Network (FWD-Net) in January 2016. The survey was divided into four sections covering i) surveillance, ii) testing and diagnosis, iii) data on diagnosed cases, and iv) transfusion- and transplant-associated infection.

The study included 30 of the 31 EU/EEA Member States, thus providing a comprehensive picture of HEV activities across Europe. The survey findings demonstrate a relatively mixed picture, with 20 countries having well-established HEV-specific surveillance systems and testing protocols in place. A small proportion of those countries implemented the surveillance system recently or had evolving systems, and ten Member States reported no conduction of HEV surveillance.

Similarly, there is a wide variation in the case definitions used by existing surveillance systems, with a variety of laboratory, clinical, and epidemiological criteria being applied. Although a standardised definition would be beneficial for any European-level reporting and monitoring, this may prove difficult due to the limited use of HEV diagnostic tests in Member States, with only just over half of Member States able to conduct any confirmatory testing in-country.

Twenty-two countries provided data on laboratory-confirmed cases of HEV. The number of confirmed HEV cases has been increasing each year since 2005, with a more than three-fold increase between 2011 and 2015. Infections were mainly locally-acquired, and males and persons above 50 years of age were mostly affected. The largest numbers of confirmed cases were reported from Germany, France, and the UK, accounting for more than 75% of all HEV cases reported. These three countries (representing 41% of the total EU/EEA population) have all conducted national-level surveillance since at least 2005. HEV surveillance is compulsory in Germany and voluntary in the UK and France. Although the reasons for this increase in reported cases are currently unclear, it appears to be unrelated to the number of Member States conducting surveillance or the type of surveillance being conducted. However, it may be that an increased awareness of and testing for HEV has contributed to the rise in diagnosed cases. A small number of Member States also reported that they had introduced HEV tests into laboratory protocols for risk groups, which is likely to further increase the number of diagnosed cases. This increasing awareness amongst general practice clinicians might be also visible in the reduction of the proportion of cases hospitalised, from 73 to 57% between 2005 and 2007, and from 54 to 47% between 2013 and 2015. A small number of deaths associated with HEV were reported, (zero to one case per year between 2005 and 2008, and four to eight cases between 2012 and 2015).

Overall, at least 22 of 30 EU/EEA Member States are able to monitor and report on HEV cases, either through formal surveillance or existing systems of laboratory notifications, and 26 reported that they were able to conduct HEV testing. However, there is a lack of standardised case definitions across Europe, and a broad range in the availability and use of HEV confirmatory tests.

1. Introduction

Hepatitis E virus (HEV) is one of the leading causes of acute viral hepatitis worldwide [1]. There are two main HEV genotypes infecting humans: genotype 1 which predominates in low-income countries, and genotype 3 in high-income countries [6]. Genotype 1 is transmitted by the faecal-oral route (large water-borne outbreaks are common), and may be associated with fulminant hepatitis among pregnant women [7]. Genotype 3 is zoonotic and has been linked to the consumption of contaminated pork or shellfish products [1,2]. Infection with genotype 3 may be asymptomatic or cause an acute self-limiting hepatitis, and outbreaks are much less common [8,9]. A small number of infections may lead to chronic disease progression, particularly among those who are immunosuppressed or who have a pre-existing liver disease [10]. Risk factors for symptomatic or complicated infection include being male, being of an older age, and having pre-existing liver disease [8,11].

In Europe, autochthonous infections are mostly related to genotype 3; however, infections with other genotypes that are either locally acquired (genotype 4) or travel-associated (genotypes 1, 2 and 4) can also be sporadically detected [12]. The number of human infections due to HEV in Europe is currently unclear, given widespread variations in awareness, testing, and surveillance activities, and a lack of published information across the majority of EU/EEA Member States. However, there is emerging evidence that HEV is an under-recognised pathogen in high-income countries and that the incidence of HEV infection has been steadily increasing over the last decade e.g. in Czech Republic, France, Germany and the United Kingdom [11-17]. In addition, some countries like Germany, the Netherlands, and the United Kingdom reported a recent increase in the number of HEV-RNA-positive blood donors in younger age groups [5,18-21].

The purpose of this study was to assess current testing, diagnosis, and surveillance for HEV in EU/EEA Member States, and to conduct a baseline assessment of available epidemiological data. This assessment will inform a wider ECDC investigation on the incidence, prevalence, and risk factors for HEV in the EU/EEA.

2. Methods

This project formed part of a wider assessment of testing, diagnosis, and surveillance of viral hepatitis (B, C, and E) undertaken by ECDC. Aims and objectives of the study are outlined in Table 2.1.

Table 2.1. Aims and objectives of the hepatitis E project

Aims	Objectives
Assess existing surveillance systems, collect data on incidence, and populations at increased risk of HEV	Describe surveillance systems in place, applied case definitions, testing practice, diagnosis, and screening policies for hepatitis E infection
	Request data on the number of cases of HEV over the last 10 years in EU/EEA Member States, and conduct basic data analysis to describe epidemiology by affected age groups, gender, year of diagnosis, potential risk factors, and country

2.1. Survey design and distribution

A semi-structured survey of EU/EEA Member States was conducted. The survey was designed by the project team of Glasgow Caledonian University (GCU) and Health Protection Scotland (HPS) in consultation with ECDC. The survey was divided into four sections to allow EU/EEA Member States to invite separate respondents for the different topic areas. The four sections are outlined in Table 2.2 below. The survey was formatted as an electronic PDF (Adobe InDesign CS6 for Windows) to allow respondents to complete their answers on-screen and submit responses by email (Appendix 1).

Table 2.2. Hepatitis E survey sections and main topic areas covered

Section 1: hepatitis E surveillance	Type, coverage, and organisation of surveillance, data fields collected, case definitions used, recent or planned changes
Section 2: hepatitis E testing and diagnosis	Testing policy, diagnostic tests used, use of HEV sequencing, number of laboratories conducting and reporting on tests
Section 3: data on diagnosed cases of hepatitis E	Data on diagnosed cases including age, sex, travel history, outbreaks, hospitalisation, and mortality
Section 4: transfusion and transplant-associated hepatitis E	Blood screening policy, data on transplant and transfusion-associated infection

The survey was piloted at an ECDC meeting of HEV experts in December 2015. This expert group comprised of Member States' national HEV experts, external scientific experts, and representatives from the European Food Safety Authority (EFSA) and the World Health Organisation (WHO).

A revised survey was subsequently circulated by email to the 30 Member States national focal points for food- and waterborne diseases and zoonoses in the European Food- and Waterborne Diseases and Zoonoses Network (FWD-Net) in January 2016. In the UK, the survey was sent to three separate contacts representing i) England and Wales, ii) Scotland, and iii) Northern Ireland. Respondents were allowed three weeks to complete the survey, and further email and phone reminders were used to follow up those who had not responded.

2.2. Analysis of survey data

Returned survey data were extracted manually into Excel, and all data were double-checked. Descriptive analyses were conducted in Excel and STATA version 13. The denominator used for analyses was the 30 Member States that had provided a response. Results for the three separate UK survey responses (from England and Wales, Scotland, and Northern Ireland) were presented separately in the qualitative results, but the UK was considered to be a single Member State in all quantitative analyses.

3. Results and discussion

All EU/EEA Member States except for Liechtenstein (30 of 31) responded to the survey or provided some information.

3.1. Surveillance of hepatitis E

Of the 30 Member States responding to the survey, 20 (67%) have HEV-specific surveillance systems. The remaining 10 countries have no HEV-specific surveillance, but may have generic viral hepatitis surveillance (Figure 3.1). Of the 20 EU/EEA Member States with HEV-specific surveillance systems, 15 (75%) had national surveillance systems, three had national reference laboratory surveillance (but did not state the level of coverage), one had blood service surveillance (coverage not stated), and one had a sentinel surveillance system (approximately 50% coverage; Table 3.1).

Surveillance systems

Of 20 Member States with HEV-specific surveillance, 12 (60%) had compulsory systems, four (20%) had voluntary systems, and for four (20%), the status was unknown. The majority (13; 65%) of HEV surveillance systems commenced prior to 2010, with some systems in place since the 1980s (Austria). More recently, a HEV surveillance system was implemented in Ireland (2016).

Transfer of HEV data to the national public health authority

Of the 20 Member States with HEV-specific surveillance, six (30%) receive data exclusively from laboratories, three (15%) countries receive data exclusively from clinicians, and nine (45%) countries use both laboratory and clinician reporting. Two countries did not provide this information (Table 3.1). The majority of systems (16; 80%) use case-based reporting, two (10%) use aggregate reporting, one country uses both case-based and aggregate reporting, and one did not provide this information. Eleven Member States (55%) use either real-time or daily reporting of data.

Table 3.1. Summary of HEV-specific surveillance systems by EU/EEA Member State

Member State	Type of HEV surveillance	Coverage	Year commenced	Public health reporting	Case definition
Austria	National	100%	1980s	Both	✓
Belgium	Reference laboratory	Not known	2010	Laboratory	✓
Bulgaria	None				
Croatia	National	100%	2009	Clinician	
Cyprus	None				
Czech Republic	National	100%	1996	Both	✓
Denmark	None				
Estonia	National	100%	1997	Both	
Finland	National	100%	1995	Laboratory	
France	Reference laboratory	Not known	2002	None	✓
Germany	National	100%	2001	Laboratory	✓
Greece	None				
Hungary	National	100%	1993	Both	✓
Iceland	None				
Ireland	National	100%	2016	Both	✓
Italy	National	77%	2007	Clinician	✓
Latvia	National	Not known	Not known	Both	
Lithuania	None				
Luxembourg	Blood service	Not known	Not known	Laboratory	
Malta	None				
Netherlands	Sentinel	50%	2012	Laboratory	✓
Norway	None				
Poland	None				
Portugal	National	Not known	Not known	Clinician	✓
Romania	None				
Slovakia	National	100%	2007	Both	
Slovenia	National	100%	1995	Both	
Spain	Reference laboratory	Not known	Not known	Not known	
Sweden	National	100%	1993	Both	✓
United Kingdom	National	100%	2003 *	Laboratory	✓

** Since 2000 in Scotland, both laboratories and clinicians report to the public health authority*

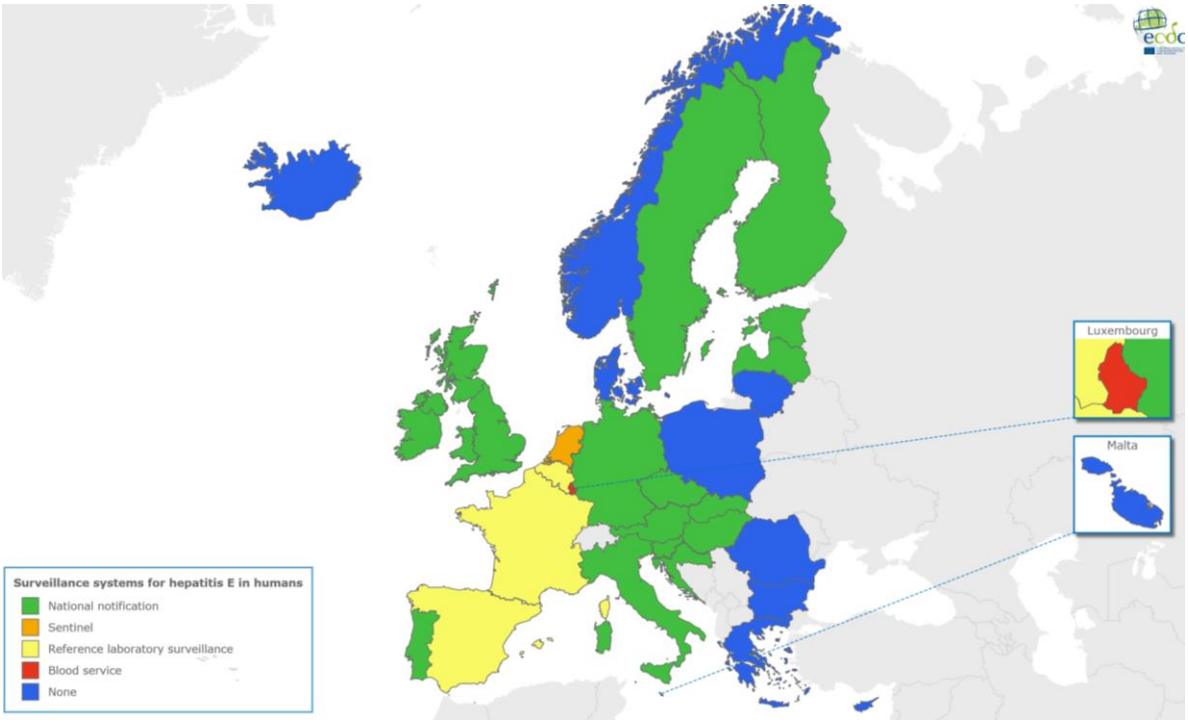
Data collected by HEV surveillance systems

Most surveillance systems collected a unique patient identifier, the date of HEV notification, sex and date of birth. A summary of the data fields collected is shown in Table 3.2.

Table 3.2. Data collected by HEV surveillance systems in 20 EU/EEA Member States

Collected by 70% of HEV surveillance systems	Unique patient identifier, date of notification, source of notification, date of birth, sex, date of onset of disease
Collected by 30 to 70% of HEV surveillance systems	Date of diagnosis, cluster link, occupation, pregnancy, clinical symptoms, travel, food history, contact with animals, hospitalisation, death
Collected by <30% of HEV surveillance systems	Ethnicity, migration status, alcohol consumption, medication, immunosuppression, other medical conditions, recent transfusion/transplant

Figure 3.1. Type of hepatitis E surveillance systems in EU/EEA Member States



Administrative boundaries: © Eurogeographics © UN-FAO © Turkstat © GADM

Hepatitis E case definitions

Of the 20 Member States with HEV-specific surveillance, 12 (60%) had a case definition for confirmed cases (Table 3.1). There was a wide variation in the case definitions used across Member States, with seven using both laboratory and clinical criteria, two using laboratory criteria only, and three using a combination of clinical, laboratory, and epidemiological criteria. The case definitions used are shown in Table 3.3 and in the Appendix 2.

Table 3.3. Definitions of confirmed cases of hepatitis E used by EU/EEA Member States

Member State	Criteria used			Comment
	Clinical	Laboratory	Epidemiology	
Austria	✓	✓	✓	Epidemiological links include person-to-person contact, contact with infected animals or contaminated food.
Belgium	✓	✓		Meeting the clinical AND laboratory criteria fulfils the case definition.
Czech Republic		✓		National reference centre: confirmation of antibodies against hepatitis E virus– Anti HEV/IgG, IgM.
France		✓		
Germany	✓	✓	✓	Meeting the clinical in addition to laboratory or epidemiological criteria fulfils the case definition.
Hungary	✓	✓		Meeting the clinical AND laboratory criteria fulfils the case definition.
Ireland		✓		Meeting the laboratory criteria fulfils the case definition.
Italy	✓	✓		Must be negative for Hepatitis A and Hepatitis B in order to meet the case definition.
Netherlands	✓	✓		Meeting the clinical AND laboratory criteria fulfils the case definition.
Portugal	✓	✓	✓	Probable case meets clinical and epidemiological criteria. Confirmed case meets clinical and laboratory criteria
Sweden		✓		A confirmed case is a laboratory confirmed case. A probable case meets the clinical and epidemiological criteria.
United Kingdom	✓	✓		

Two Member States differentiated between acute and chronic HEV infection in their HEV surveillance systems. The definitions used by these countries are shown in Table 3.4.

Table 3.4. Acute and chronic case definitions used by EU Member States

	Definition of acute HEV	Definition of chronic HEV
Ireland	At least one of HEV IgM and IgG-positive OR detection of HEV RNA	HEV RNA persisting for at least 3 months
United Kingdom	At least one of HEV IgM/IgG-positive OR HEV RNA-positive	HEV RNA persisting for at least 3 months (with or without detectable HEV antibodies)

Communication of surveillance findings

Of the 20 Member States conducting HEV surveillance, 15 reported that they communicated their surveillance findings to the public. Fourteen (70%) Member States reported using proactive communication e.g. press releases or annual reports. The frequency of communication ranged from weekly to annually. One country reported using reactive communication only e.g. responding to queries from clinicians, policy-makers, and government. Five (25%) countries either did not complete the question, or reported that they did not communicate surveillance findings. A number of Member States stated that they published annual reports online. A list of links can be found in Appendix 3.

Recent or planned changes to HEV surveillance

Eight Member States reported that there had been recent changes to their HEV surveillance systems. These changes are outlined in Table 3.5 below.

Table 3.5. Recent changes to HEV surveillance systems in EU/EEA Member States

Austria	Change from paper to electronic reporting (2015)
Belgium	Creation of a national reference centre for HEV (2011) Surveillance of HEV by a network of sentinel laboratories started (2015)
Finland	Laboratories have changed surveillance reporting from cases that are HEV IgG or IgM-positive to IgM-positive only (2016)
Germany	Case notifications are no longer manually checked for completeness and internal validity (2016)
Ireland	HEV became a notifiable disease (December 2015)
Netherlands	Awareness raising and advice to laboratories and clinicians to test for HEV if clinical symptoms of hepatitis (2011) Laboratories advised to use Wantai HEV IgM for serology testing (2014) A number of new laboratories commenced testing for HEV (2015)
Portugal	Commencement of web-based HEV notification system, including integration of surveillance and patient health records to improve under-reporting, under-ascertainment, and timeliness of epidemiological investigation (2014)
United Kingdom (Scotland)	Commencement of enhanced national surveillance, using detailed surveillance questionnaire (2016)

A further nine Member States are planning changes to HEV surveillance in the near future. Proposed plans for surveillance systems are outlined in Table 3.6.

Table 3.6. Planned changes to HEV surveillance systems in EU/EEA Member States

Czech Republic	Screening of blood and organ donations is being discussed. New recommendations for laboratory testing and diagnosis are being developed.
Denmark	A revision of the notifications of infectious diseases is currently underway. It is foreseen that HEV will become notifiable with this revision.
France	HEV surveillance system is currently being evaluated, and changes as a result of this evaluation are likely.
Germany	Changes are planned to the laboratory methods available to diagnose HEV.
Ireland	Enhanced surveillance system to be developed.
Italy	Changes to compulsory viral hepatitis surveillance so that hepatitis A-E can be identified separately.
Luxembourg	HEV will become notifiable in the near future. Surveillance system will involve laboratories reporting to the health directorate.
Netherlands	An updated case definition will be developed. The need for mandatory notification will be discussed.
Portugal	Implementation of electronic laboratory notification.

3.2. Testing and diagnosis of hepatitis E

Ten Member States (33%) provided information on reasons motivating a test for HEV. Eight Member States conducted testing only when requested by a clinician, and two countries conducted testing both according to laboratory protocol and at the request of a clinician. Eight Member States provided further information on who should be tested and when testing should be conducted, summarised in Table 3.7.

Table 3.7. Scenarios in which HEV testing may be conducted in EU/EEA Member States

Belgium	Increased liver enzymes Signs of acute hepatitis and a negative test for HAV In the differential diagnosis of viral hepatitis (HAV, HBV, HCV, HEV screen)
Croatia	In the differential diagnosis of patients with elevated liver transaminases
Czech Republic	In patients with elevated liver transaminases, contacts of patients with HEV or with other positive epidemiological history
Denmark	When other viral hepatitis tests are negative
Ireland	As part of a viral hepatitis screen At the national virus reference laboratory, all specimens submitted for HAV testing are now also routinely tested for HEV In patients with Graft Versus Host Disease On request from a clinician; screening of blood donors
Norway	Acute cases of hepatitis with no other cause, foreign travel, or if immunosuppressed
Poland	Acute cases of hepatitis where HAV, HBV, and HCV tests are negative.
United Kingdom (England and Wales)	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. Immunocompromised individuals with persistently deranged liver transaminases (please 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.
United Kingdom (Scotland)	Some laboratories automatically test for HEV if ALT >/=100 U/L Immunosuppressed patients tested on request with no criteria

ALT: Alanine transaminase

Laboratory diagnosis of hepatitis E

Twenty-six (83%) of 30 Member States reported that they were able to conduct HEV testing in laboratories within their own country (Table 3.8). HEV IgM ELISA was the most commonly used antibody test (used by 21 countries; 81%), followed by IgG ELISA (used by 20 countries; 77%). The most commonly used test for HEV RNA was serum PCR (19; 73%), with some Member States reporting that they used stool PCR (11; 42%) as well as serum PCR. One country did not provide any information on the type of tests used.

Table 3.8. Laboratory tests used by the 26 EU/EEA Member States conducting HEV testing

Lab test	No. (%) using test, N=26	No. (%) using test to diagnose chronic HEV, N=26	Brands of tests most commonly used
IgM ELISA	21 (81%)	5 (19%)	Mikrogen, recomWell
IgM Western Blot	11 (42%)	2 (7%)	Mikrogen, recomLine
IgG ELISA	20 (77%)	5 (19%)	Mikrogen, recomWell, Wantai
IgG Western Blot	9 (35%)	2 (7%)	Mikrogen, recomLine
Serum PCR	19 (73%)	11 (42%)	In-house, Altona, RealStar
Stool PCR	11 (42%)	8 (31%)	In-house, Altona, RealStar
Electron microscopy	1 (4%)	0 (0%)	Not applicable
Not stated	1 (4%)	Not applicable	Not applicable

Hepatitis E sequencing

Of the 26 EU/EEA Member States conducting testing for HEV, 17 reported that they conducted HEV sequencing. The reasons for conducting sequencing are summarised in Table 3.9. Some Member States reported that laboratories within their countries had different approaches to sequencing, i.e. some conducted sequencing routinely, and others only sequenced for research purposes: therefore the total number of responses to this question adds up to >100%.

Table 3.9. Reasons for conducting HEV sequencing

Reason for sequencing	Number conducting sequencing, N=17
Conducted routinely	10
Conducted for research purposes	13
Conducted during epidemiological investigations and outbreaks	15
Not known	8

Screening of blood products

Of 30 EU/EEA Member States, eight (27%) have conducted screening of blood donations: seven routinely, and one as part of a retrospective investigation. Of the seven countries conducting routine screening, one country screened all blood donations, five screened a subset of donations, and one country did not provide any further information. Blood screening policies are shown in Table 3.10.

Table 3.10. HEV blood screening policy in EU/EEA Member States

Member State	HEV blood and blood product screening policy	Date commenced
Austria	Screen blood/blood products for HEV - no further information provided	Not reported
France	Screened blood/blood products are reserved for transplant recipients and people who are immunosuppressed	January 2015
Germany	Screened blood/blood products are reserved for transplant recipients	Not reported
Ireland	All blood and blood products are screened	January 2016
Luxembourg	Screened blood products are reserved for recipients of solvent-detergent inactivated plasma	January 2015
Netherlands	2 000 plasma donations are randomly screened per month	October 2012
Spain	Blood was screened as a one-off event during a look-back investigation of a fatal case of HEV infection	2014
United Kingdom	Screened blood/blood products are reserved for allogeneic stem cell/bone marrow and solid organ transplant recipients, and all patients under one year of age	March 2016

3.3. Hepatitis E epidemiology in EU/EEA Member States

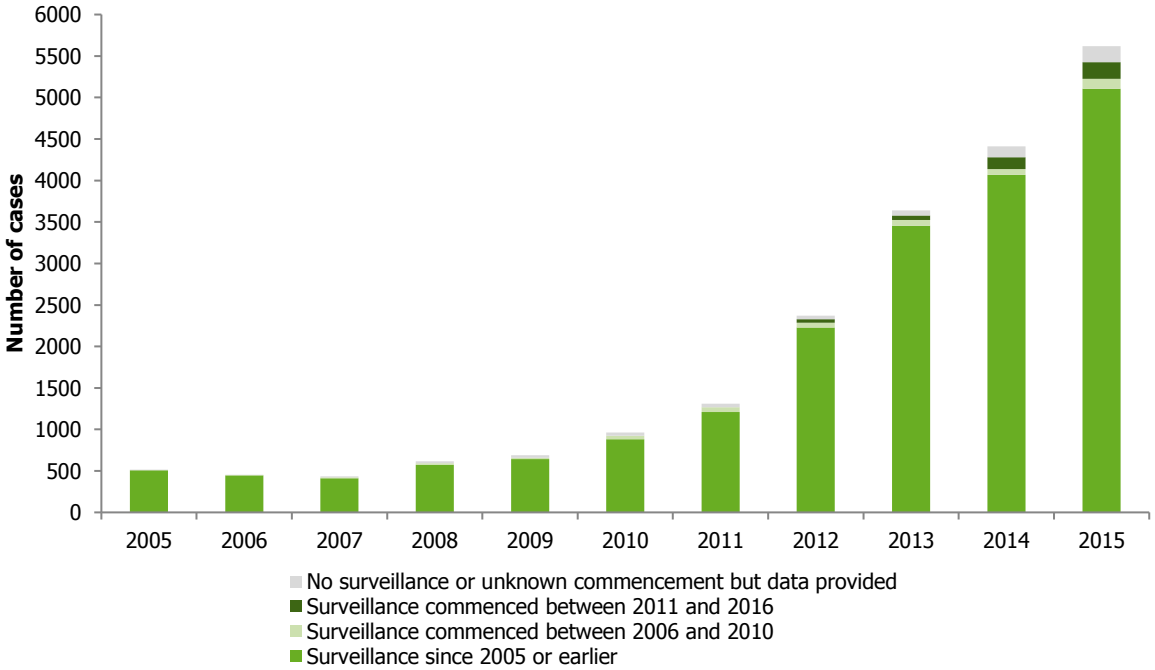
Twenty-two (73%) of 30 EU/EEA Member States provided data on confirmed cases of HEV. The majority of these data were obtained from Member States with HEV-specific surveillance. Two countries with HEV surveillance did not provide any data: Ireland had just commenced HEV surveillance, and Luxembourg did not have access to surveillance data (which are held by the blood service). Four countries (Bulgaria, Cyprus, Norway, and Poland) with no formal HEV-specific surveillance were still able to provide data on confirmed HEV cases.

Number of confirmed cases

Over the period 2005–2015 a total of 21 018 confirmed hepatitis E cases were reported from 22 countries. The largest numbers of confirmed cases, accounting for 80% of all cases reported, were reported from Germany, France, and the United Kingdom. All three Member States have had national-level surveillance since at least 2005. HEV surveillance is compulsory in Germany and voluntary in the United Kingdom and France.

The number of confirmed cases has been increasing every year, with a particularly sharp increase between 2011 and 2015. In Figure 3.2, confirmed cases are shown by the year in which surveillance commenced, demonstrating that the majority of cases are accounted for by Member States that have conducted surveillance since at least 2005.

Figure 3.2. Annual number of confirmed cases of hepatitis E by year of commencement of surveillance, EU/EEA Member States, 2005–2015 *

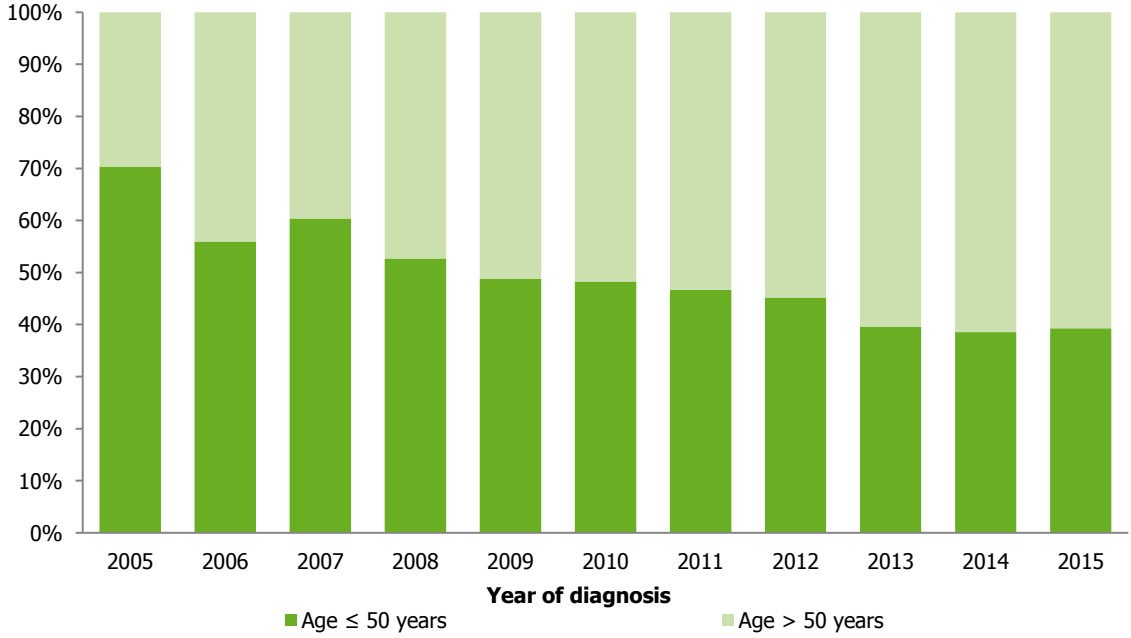


** Data available for: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, the Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom.*

Confirmed cases by age

Sixteen Member States provided data on the age of their confirmed cases. The proportion of cases among those aged >50 years has increased from 30–45% during 2005–2008, to over 60% during 2013–2015 (Figure 3.3).

Figure 3.3. Proportion of reported cases aged ≤ 50 or > 50 years, by year of diagnosis, EU/EEA Member States, 2005–2015*

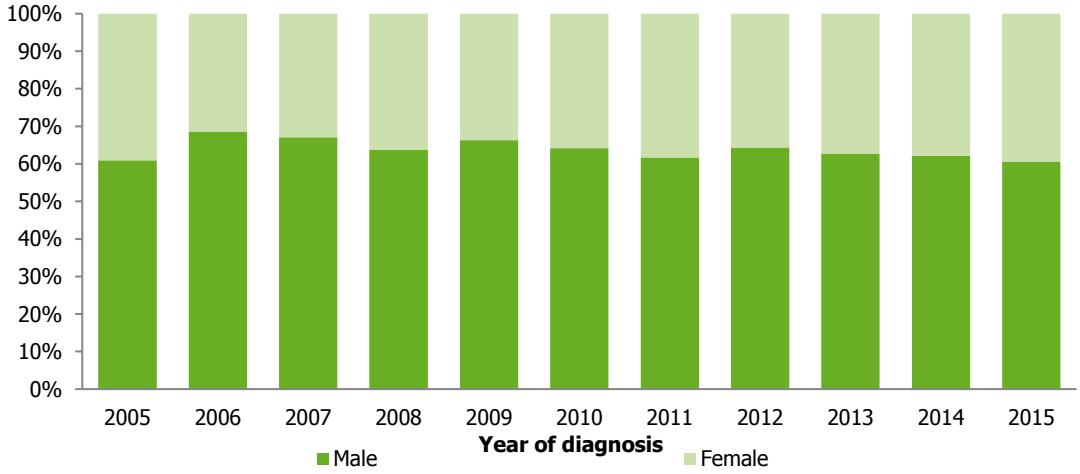


** Data on HEV cases by age group available for: Austria, Belgium, Croatia, Czech Republic, Finland, Germany, Hungary, Italy, Latvia, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, United Kingdom (Northern Ireland, Scotland)*

Confirmed cases by gender

Seventeen Member States provided data on the gender of confirmed cases. The proportion of male confirmed cases has remained relatively stable, ranging from 61 to 69% overall.

Figure 3.4. Proportion of confirmed cases by gender and year of diagnosis, EU/EEA Member States, 2005–2015 *

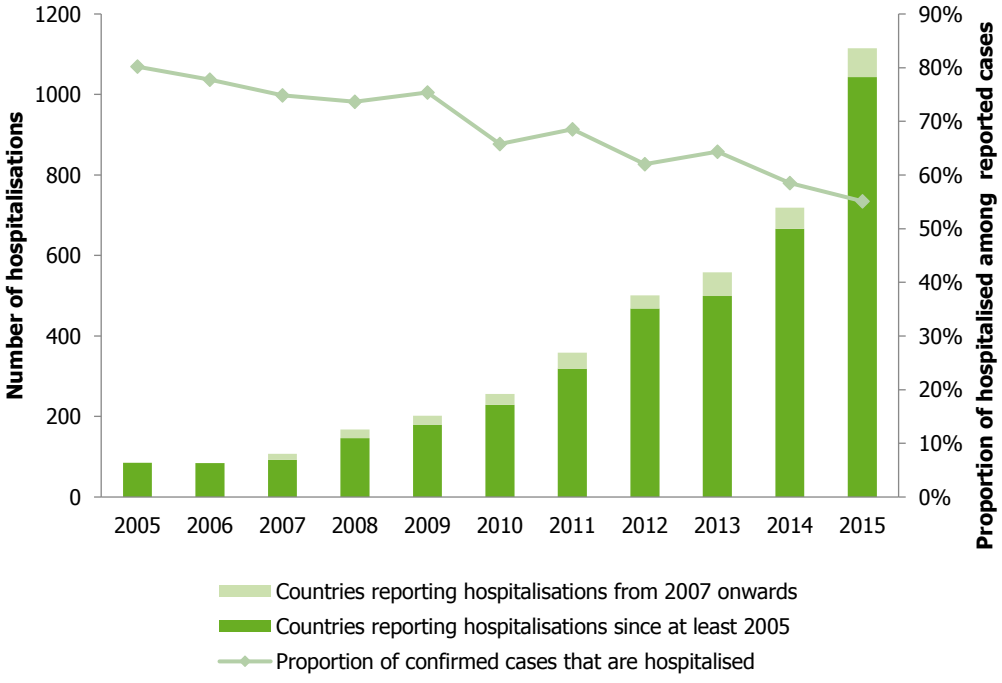


** Data on cases by gender available for: Austria, Belgium, Croatia, Czech Republic, Estonia, Finland, Germany, Hungary, Italy, Latvia, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, United Kingdom (Northern Ireland, Scotland)*

Hospitalisations and deaths related to hepatitis E

Fourteen EU/EEA Member States provided data on hospitalisation and deaths related to HEV. The number of hospitalisations related to HEV increased steadily over the period 2005–2015. The majority of the increase can be accounted for by Member States that have collected data on hospitalisations since at least 2005 (Figure 3.5). Over the same time period, the proportion of cases being hospitalised decreased from 80% in 2005 to 55% in 2015.

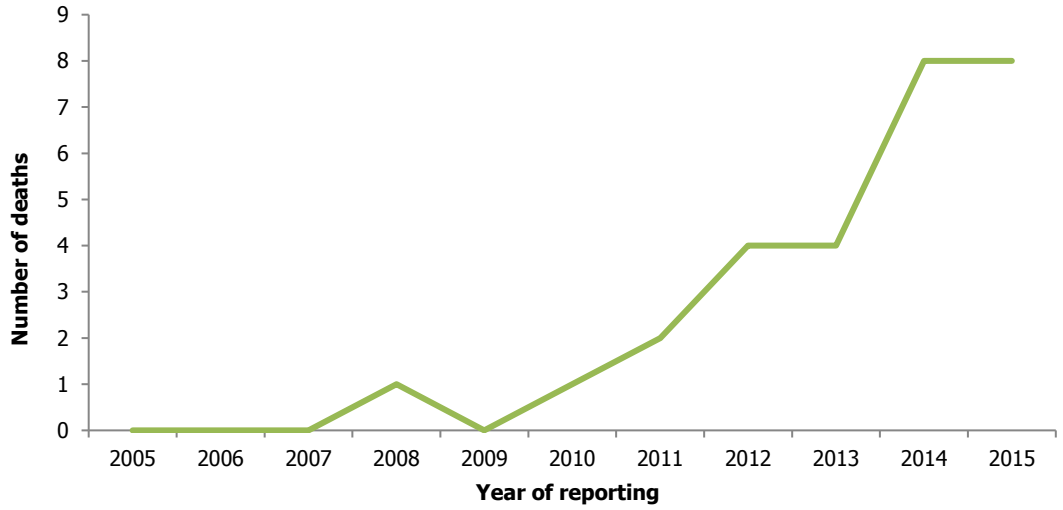
Figure 3.5. Number and proportion of hospitalisations among confirmed cases of hepatitis E, EU/EEA Member States, 2005–2015*



** Data available for: Austria, Belgium, Croatia, Czech Republic, Estonia, Germany, Hungary, Italy, Latvia, Poland, Portugal, Slovakia, Slovenia, United Kingdom (Northern Ireland)*

Twelve countries reported on deaths associated with HEV infection during the studied period with five countries (Austria, Czech Republic, Germany, Hungary, and Italy) reporting a total of 28 fatal cases (Figure 3.6). The number of recorded deaths associated with HEV infection increased from 0–1 cases per year between 2005 and 2008 to 4–8 cases between 2012 and 2015.

Figure 3.6. Number of deaths associated with hepatitis E infection, EU/EEA Member States, 2005-2015*

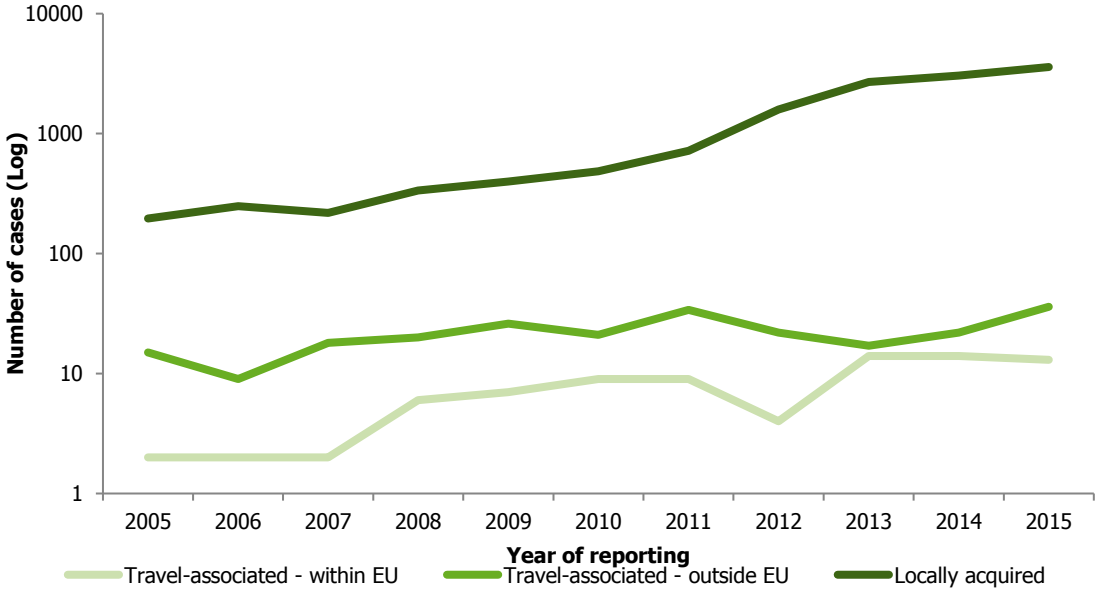


** Data on mortality available for: Austria (from 2012), Croatia (from 2013), Czech Republic (from 2005), Estonia (from 2012), Germany (from 2005), Hungary (from 2008), Italy (from 2007), Latvia (from 2005), Poland (from 2014), Portugal (from 2015), Slovakia (from 2005), Slovenia (from 2005). NB most Member States reported zero cases.*

Travel history of confirmed cases

Fifteen Member States provided data on the travel history of confirmed cases. The majority of cases were autochthonous (locally-acquired) or acquired within the EU/EEA, only 1.5% (240 cases) of the 15 525 human cases, where information on travel was known, were reported to be travel-related to a non-EU country during 2005–2015 (Figure 3.7). A small number of cases (9–36 cases/year) were associated with travel outside of the EU/EEA. Locally-acquired cases accounted for nearly all of the increase in confirmed cases after 2011.

Figure 3.7. Confirmed cases of hepatitis E by travel history and year, EU/EEA Member States, 2005–2015*

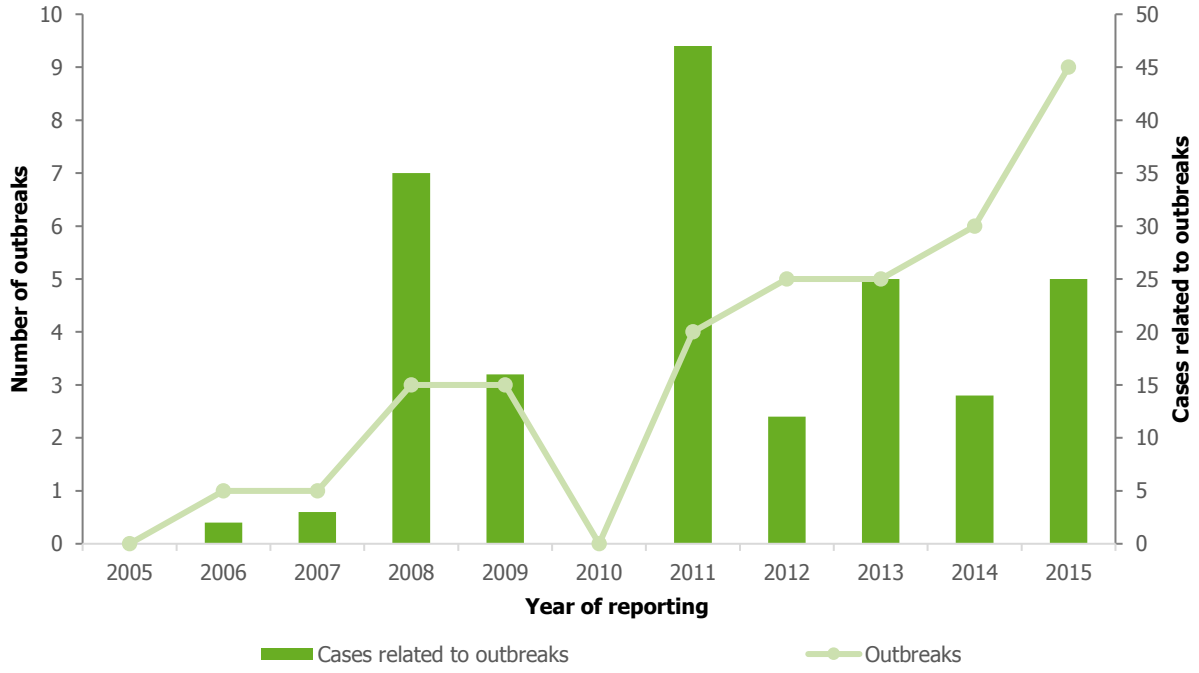


**Data on travel history available for: Austria, Croatia, Czech Republic, Estonia, France, Hungary, Italy, Latvia, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, United Kingdom (England, Wales, Northern Ireland);*

Outbreaks of hepatitis E

Eighteen Member States provided data on HEV outbreaks, including 11 that reported no outbreaks. The total number of outbreaks increased from zero to three per year from 2005 to 2010, to six in 2014 and nine in 2015 (Figure 3.8). The number of cases related to outbreaks varied, ranging from 0 to 47 cases each year.

Figure 3.8. Number of outbreaks and number of cases related to outbreaks, EU/EEA Member States, 2005–2015*



** Data on outbreaks available for: Austria (2015), Croatia (from 2005), Czech Republic (from 2005), Denmark (from 2005), Estonia (from 2005), Finland (from 2005), France (from 2007), Germany (from 2005), Hungary (from 2005), Iceland (from 2005), Latvia (from 2007), Lithuania (from 2005), Poland (from 2014), Romania (from 2005), Slovakia (from 2005), Slovenia (from 2005), Sweden (from 2005), United Kingdom (England, Northern Ireland and Wales from 2005)*

Transfusion- and transplant-associated hepatitis E

There was only one country (the Netherlands) that provided a definition of transfusion-associated hepatitis E:

> 'an acute hepatitis E within 6–8 weeks after transfusion (detected by HEV RNA), where the donor-blood is HEV RNA-positive and at least HEV ORF1/ORF2 hypervariable regions of donor and recipient strains are identical by (Sanger) sequencing'.

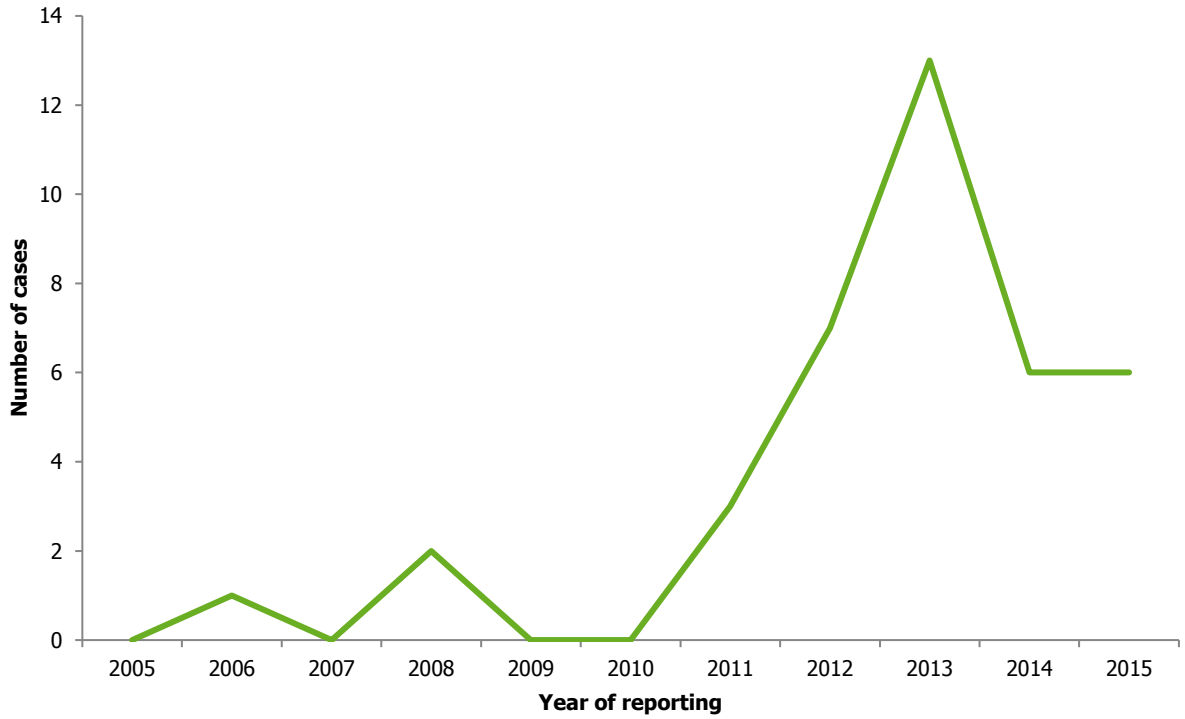
Three EU/EEA Member States reported that they collected data on transfusion-associated cases of HEV and were able to provide data to ECDC (Figure 3.9). Note that the data provided relate to infections associated with transfusion or transplantation, and no further information on confirmatory testing was requested by ECDC. The Netherlands reported that they had received reports of suspected post-transfusion hepatitis E, but had discounted all of these cases through further investigation. The United Kingdom (England and Wales) reported that they had picked up a number of ad hoc reports of transfusion-related infection, but were not able to provide any further information. Work in England and Wales to establish a register for transfusion-related cases is currently underway.

Only one country (the Netherlands) was able to provide a definition of transplant-associated infection:

> 'an acute hepatitis E within 6–8 weeks after transplantation (detected by HEV RNA), where the donor is HEV RNA-positive and at least HEV ORF1/ORF2 hypervariable regions of donor and recipient strains are identical by (Sanger) sequencing'.

Only one country (France) provided data on transplant-associated HEV infection. The number of cases was small and is therefore not reported here due to the risk of deductive disclosure.

Figure 3.9. Hepatitis E associated with blood and/or blood product transfusion, EU/EEA Member States, 2005–2015*



** Data on transfusion-associated HEV infection are available for: France (from 2005), Germany (from 2013), and Italy (from 2007)*

4. Discussion

This study assessed testing, diagnosis and surveillance activities for HEV infection in 30 EU/EEA Member States. The response to the study survey was more than 95%, providing a comprehensive picture of current testing and surveillance activities across Europe.

The survey findings demonstrate a relatively mixed picture, with over half of Member States having well-established surveillance systems and testing protocols, a small proportion with more recent or evolving systems, and a third with no HEV-specific surveillance at all. Similarly, there is a wide range in the case definitions used by existing surveillance systems, with a variety of laboratory, clinical, and epidemiological criteria being applied. Although a standardised definition would be beneficial for any European-level reporting and monitoring, this may prove difficult due to the limited use of HEV diagnostic tests in Member States, with only just over half (57%) of them reporting that they are able to conduct confirmatory (HEV RNA) testing in-country. The remaining countries either conduct HEV antibody testing only or send samples abroad for HEV testing.

Twenty-two Member States (accounting for >90% of the total EU/EEA population) were able to provide data on confirmed cases of HEV for at least some or all of the period 2005–2015. These data demonstrate that the number of confirmed cases has been increasing each year since 2005, with a more than three-fold increase in the number of annual cases between 2011 and 2015. The majority of cases were reported by three EU/EEA Member States (France, Germany, and the United Kingdom), and all have had (relatively unchanged) surveillance systems in place since at least 2005. However, this increase is also prominent in the countries reporting lower numbers of cases. A small number of Member States did report surveillance changes, e.g. Belgium have created a national reference centre for HEV (2011), and Portugal have commenced web-based notification (2014), but none of the changes are likely to have contributed significantly to the observed rise in cases.

The increase in cases of HEV therefore appears to be unrelated to the number of countries conducting surveillance and to the type of surveillance being conducted. Possible explanations for the increase in cases are the impact of raising awareness of and testing for HEV. Although countries (except for the Netherlands) did not report any specific awareness-raising campaigns, it is likely that a generally increased awareness of HEV as a locally-acquired infection will have translated into increased requests for testing. A small number of Member States also reported that they had recently introduced routine HEV testing into laboratory protocols for people with deranged liver function tests (LFTs), which is likely to further increase the number of diagnosed cases. Also the implementation of HEV in blood donations might have an effect on the number of cases identified.

This study also demonstrated that overall morbidity due to HEV, as demonstrated by numbers of reported cases and hospitalisations, is increasing mainly in France, Germany and the United Kingdom accounting for more than 75% of the cases. The increase of cases is also present in the other countries, but on a much lower level pointing to either a regionally different virus prevalence, exposure, or an underestimation of cases due to lower awareness or less sensitive surveillance systems in place. However, this might point to an emergence of the disease in the majority of countries. The proportion of total cases hospitalised is falling (from 80% of all cases in 2005 to 55% in 2015) which may reflect a move from testing exclusively in hospital/specialist settings to testing in community settings and general practice. It could also reflect improved coverage of surveillance in smaller non-reference laboratories, given that many Member States reported a steady increase over time in the number of laboratories able to conduct HEV testing. Although the proportion of cases hospitalised is considerable, data provided by eleven countries suggest that the number of deaths associated with HEV remains low, ranging from two to eight deaths per year from 2011–2015. The estimates are limited by the low and variable number of reporting countries for each year.

Fifteen Member States provided data on the travel history of confirmed cases, which demonstrated a five-fold increase in locally-acquired cases between 2011 and 2015. This increase accounts for the majority of the observed rise in confirmed cases over this time period and could also be related to increased awareness and shift from testing cases known to have travelled. Although genotype data were not requested from Member States, it is known that locally-acquired cases tend to be due to HEV genotype (GT) 3 [8,9,13]. In recent years, there has been a 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 [11,12,22]. These changes suggest a change in the patterns of circulating virus that could be contributing to the emergence of HEV as a significant infection in humans. Another factor to consider is a possible change in patterns of food preparation and consumption. A case-control investigation conducted in England to investigate a rise in HEV cases identified contaminated sausages and ham purchased in supermarkets as a possible source of HEV infection. This raises concerns about whether current practice in preparing these products is sufficient to prevent transmission of HEV [1].

The main limitations of this study are the variations in the denominator data for confirmed cases of HEV (with most countries only able to provide a subset of demographic information, or a limited number of years of data), and the merging of data on confirmed cases of HEV despite the different case definitions used by Member States. These limitations have in part been addressed by showing data by year of introduction of surveillance and by limiting the denominator to cases where the relevant information is known. Also no detailed case-based data was requested including genotype information. Standardisation of HEV surveillance systems will be needed if the true comparison of the number of human infections over time and between countries due to HEV is to be monitored in the future.

In summary, EU/EEA Member States are at different stages in their surveillance to HEV. There are differences in the surveillance systems in operation, and currently there is no standardised European case definition. A majority of EU/EEA Member States were able to report on HEV, either through formal surveillance or existing systems of laboratory notifications; these data demonstrated a Europe-wide increase in HEV cases, and a proportionally smaller increase in hospitalisations. Gaps of knowledge are the applied testing algorithms in the different countries at the various healthcare levels, and the overall number of performed tests to be used as denominator. The major limitation of this study in combining data on confirmed cases despite varied case definitions can be overcome by developing a standardised case definition and harmonising existing surveillance systems and testing policies across EU/EEA Member States. This would allow a better understanding of the epidemiology of HEV as an emerging cause of liver-related morbidity.

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Appendix 1. Questionnaire

Hepatitis E survey to EU/EEA states

Hepatitis E virus (HEV) is considered to be one of the most common causes of acute hepatitis worldwide. Although previously most cases were imported from HEV-endemic areas, increasing numbers of autochthonous cases have been reported across Europe. Population-based studies have shown that HEV infections in Europe are more prevalent than expected and high prevalence areas have been described within some European countries. Transmission of HEV related to transfusion of contaminated blood products or transplantation has been observed, and has been associated with chronic infection and fatal outcomes in some patients.

In Europe, reporting systems, case definitions and population-based surveillance are set by national policy. As the disease is not under EU-wide surveillance, there is no harmonised case definition or reporting system across countries. ECDC has identified a need to further explore and assess the emerging threat of HEV to humans in the EU/EEA region. The key objectives of this inventory of HEV in Europe are to:

- describe surveillance systems in place, applied case definitions and laboratory methods for diagnosis
- collect case numbers, and where possible, describe epidemiology, burden and severity (clinical picture)
- describe populations at risk
- identify rationale and objectives of surveillance at EU/EEA level

The following survey of EU/EEA members relates to the surveillance, testing, diagnosis, and screening of Hepatitis E (HEV). The survey is divided into four sections to allow different individuals/organisations to complete sections of the response where appropriate. It is recognised that the survey covers some topic areas in considerable depth and that some questions may not be answerable by all member states.

Please fill in the survey and return it to: cornelia.adlhoch@ecdc.europa.eu; CC: FWD@ecdc.europa.eu

Which EU/EEA member state are you responding on behalf of? ☐

Section 1: Surveillance of Hepatitis E in your country

Q1. Do any of the following surveillance systems for viral hepatitis exist in your country?

Hepatitis E surveillance ☐
Viral hepatitis surveillance ☐
Non-A, non-B, non-C-hepatitis surveillance ☐
Other ☐ please describe ☐
None ☐

If no HEV-specific surveillance systems exist in your country, please go to Q9.

Q2. Please provide details of any of the following surveillance systems **specifically for Hepatitis E** that exist in your country:

Type of system	**Coverage* (%)**	**Voluntary (V) or compulsory (C)?**	**Years active** (please provide date range)	**How are data transferred from diagnostic laboratories to the PHA?**** (please tick all that apply)	**How often are data reported to the PHA?** (e.g. real-time, weekly)	**Are data case-based (C), aggregate (A), or both (B)?**
National ☐		V ☐ C ☐		Laboratories report direct to PHA ☐ Clinicians report to PHA ☐ Other		C ☐ A ☐ B ☐
Regional ☐		V ☐ C ☐		Laboratories report direct to PHA ☐ Clinicians report to PHA ☐ Other		C ☐ A ☐ B ☐
Sentinel ☐		V ☐ C ☐		Laboratories report direct to PHA ☐ Clinicians report to PHA ☐ Other		C ☐ A ☐ B ☐
Hospital ☐		V ☐ C ☐		Laboratories report direct to PHA ☐ Clinicians report to PHA ☐ Other		C ☐ A ☐ B ☐
Blood service ☐		V ☐ C ☐		Laboratories report direct to PHA ☐ Clinicians report to PHA ☐ Other		C ☐ A ☐ B ☐
Other please state		V ☐ C ☐		Laboratories report direct to PHA ☐ Clinicians report to PHA ☐ Other		C ☐ A ☐ B ☐

* Please provide an estimate of the proportion of the national population covered by this system: e.g. national system = 100% coverage.

** PHA: Public Health Authority.

Q3. Which of the following data on HEV cases are available in your country (please tick all that apply)?

Unique patient identifier ☐	Medication ☐
Date of diagnosis ☐	Immunosuppressive medication or condition ☐
Date of notification to surveillance organisation ☐	Other underlying medical conditions ☐
Source of notification ☐	Recent transfusion of blood components or blood products ☐
Age or date of birth ☐	Recent transplantation ☐
Sex ☐	Travel history within EU/EEA ☐
Cluster link ☐	Travel history outside EU/EEA ☐
Occupation ☐	Food consumption history – detailed food items ☐
Ethnicity ☐	Food consumption history – groups of foods ☐
Migration background/refugee status ☐	Environmental contact with livestock/farm animals ☐
Alcohol consumption ☐	Hospitalisation ☐
Pregnant ☐	HEV related death ☐
Date of clinical onset ☐	Other, please specify ☐
Clinical symptoms ☐	

Q4. Is a case classification (e.g. confirmed/probable/possible) used to distinguish HEV cases in your country?

Yes ☐ No ☐

Q5. If available, please provide your case definition of **confirmed** HEV, translated into English, in the text box. Please also provide a web link to your case definitions, if available:

Case definition	
Weblink	

Q6. Does your surveillance system distinguish between acute and chronic cases?

Yes ☐ No ☐

If yes, please provide the case definitions used in the text box:

Acute	
Chronic	

Q7. How do you communicate surveillance data on HEV (e.g. with the public, services, policy-makers)?

Q8. Have any of the above case definitions, or anything else about the HEV surveillance system(s), changed over the past 5 years (2010-15) that impacts on the collection of the data?

Yes ☐ No ☐ Not known ☐

If yes, please provide brief details:

Q9. Are there future plans in your country either for i) changes to your current HEV surveillance system or ii) the introduction of HEV surveillance (if none currently exists)?

Yes ☐ No ☐ Not known ☐

If yes, please provide brief details:

Section 2: Testing and diagnosis of Hepatitis E

Q10. Are clinical HEV testing guidelines available in your country?

Yes ☐ No ☐ Not known ☐

If yes, please provide brief details:

Q11. Do you have any information on when and why laboratories initiate HEV testing?

Yes ☐ No ☐ Not known ☐

If yes, please provide brief details:

Q12. How many laboratories in your country perform HEV diagnostic tests?

Q13. How many laboratories in your country report HEV cases?

Q14. Please complete the following table on the confirmatory HEV tests used in your country:

Type of test	Used in your country as a confirmatory test? (Y/N)	Accounts for what proportion of all HEV tests performed?	Used to diagnose chronic HEV? (Y/N)	Tests used (brand, version)
Tests to detect HEV IgM antibody				
ELISA (Serum or plasma)	Yes ☐ No ☐		Yes ☐ No ☐	
Western Blot (Serum or plasma)	Yes ☐ No ☐		Yes ☐ No ☐	
Tests to detect HEV IgG antibody				
ELISA (Serum or plasma)	Yes ☐ No ☐		Yes ☐ No ☐	
Western Blot (Serum or plasma)	Yes ☐ No ☐		Yes ☐ No ☐	
Tests to detect HEV RNA				
Reverse transcription PCR (Serum)	Yes ☐ No ☐		Yes ☐ No ☐	
Reverse transcription PCR (Stool)	Yes ☐ No ☐		Yes ☐ No ☐	
Tests to detect HEV viral particles				
Electron microscopy (Stool)	Yes ☐ No ☐		Yes ☐ No ☐	
Other tests, please specify:				
	Yes ☐ No ☐		Yes ☐ No ☐	
	Yes ☐ No ☐		Yes ☐ No ☐	
	Yes ☐ No ☐		Yes ☐ No ☐	

Q15. If known, please provide details on which tests (brand and version) are used at the national HEV reference centre for confirmation of a diagnosis of HEV:

Type of test(s)	
Brand(s)	
Version(s)	

Q16. Is sequencing ever carried out on confirmed HEV RNA positive samples?

Yes ☐ No ☐ Not known ☐

If known, please provide the proportion of HEV RNA positive cases with available sequence details:

Q17. Please indicate the scenarios in which HEV sequencing would be carried out (please tick all that apply)

Routinely conducted on all confirmed positives ☐
Research purposes ☐
Epidemiological investigations/outbreaks ☐
Other ☐ please specify
Not known ☐

Section 3: Data on diagnosed cases of Hepatitis E

Q18. Please complete the table below using the HEV data you have available. Please provide a link or attachment with more detailed HEV-related data, if available*.

Year of diagnosis	**No. of confirmed cases of HEV**	**No. of cases with locally acquired infection**	**No. of travel-associated cases with travel inside EU/EEA**	**No. of travel-associated cases with travel outside EU/EEA**	**No. of hospitalised cases** (please indicate no. of cases where hospitalisation status known)	**No. male** (please indicate no. of cases where sex known)	**No. aged >50 years** (please indicate no. of cases where age is known)	**No. of HEV-related deaths**
Example: 2004	*350*	*250*	*40*	*60*	*10 (60)*	*150 (200)*	*100 (250)*	*5*
2005								
2006								
2007								
2008								
2009								
2010								
2011								
2012								
2013								
2014								
2015								

* Please ensure that any data shared in this survey complies with your country's policy on information governance.

Q19. Please complete the table below using the data you have available on HEV outbreaks in your country:

Year	Number of outbreaks related to HEV	No. of confirmed cases of HEV related to outbreaks	Please comment, if known, on the likely source of the outbreak
2005			
2006			
2007			
2008			
2009			
2010			
2011			
2012			
2013			
2014			
2015			

Q20. If available, please indicate any other potential sources of and links to HEV-related data in your country:

Annual reports (please specify/provide link)

Outbreak reports, case reports, or case series (please specify/provide link)

Peer-reviewed articles or conference abstracts (please specify/provide link)

Animal health service (please specify/provide link)

Other (please specify/provide link)

Section 4: Transfusion- and transplant- associated Hepatitis E infection

Q21. Do you screen blood donations for HEV in your country?

Yes ☐ No ☐ Not known ☐

Q22. If you answered yes to Q21, do you screen all blood donations, or just a subset of donations?

All blood donations ☐ A subset of blood donations ☐ Not known ☐

If you screen a subset of donations, please provide brief details:

Q23. Are data on transfusion and/or transplantation-associated HEV infection available in your country?

Yes ☐ No ☐ Not known ☐

Please specify how transfusion-associated HEV infection is defined:

Please specify how transplant-associated HEV infection is defined:

Q24. If you answered yes to Q23, please complete the table below using the data you have available. Please provide a link or attachment with more detailed HEV-related data, if available.

Year of diagnosis	Blood component and/or blood product recipients		Transplant recipients		
	No. of cases of HEV	No. of deaths due to HEV	No. of cases of HEV	No. of deaths due to HEV	Please comment, if available, on the likely source of infection, e.g. the graft; transfusion at time of transplant; other; unconfirmed
2005					
2006					
2007					
2008					
2009					
2010					
2011					
2012					
2013					
2014					
2015					

Thank you for taking the time to complete this survey.

Appendix 2. Links to case definitions used by EU/EEA Member States

Following countries provided a weblink to their national case definitions:

Austria:
http://www.rki.de/DE/Content/Infekt/IfSG/Falldefinition/Archiv/Falldefinitionen_2007.pdf?__blob=publicationFile

France:

http://www.cnrvha-vhe.org/wp-content/uploads/2012/03/2012-Rapport-VHA-VHE.pdf

Germany:

http://www.rki.de/DE/Content/Infekt/IfSG/Falldefinition/Downloads/Falldefinitionen_des_RKI

Ireland:

http://www.hpsc.ie/NotifiableDiseases/CaseDefinitions/

Italy:

www.iss.it/seieva

Portugal:

https://www.dgs.pt/paginas-de-sistema/saude-de-a-a-z/sinave/legislacao.aspx

Sweden:

https://www.folkhalsomyndigheten.se/publicerat-material/publikationsarkiv/f/Falldefinitioner-vid-anmalan-enligt-smittskyddslagen/

United Kingdom – England and Wales

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/396909/PH_Operational_Guidelines_for_HepE_051214_Standard_template_CT.pdf

Appendix 3. Links to relevant annual reports published by EU/EEA Member States

Following countries provided information about publications of their HEV surveillance data with related web links:

Austria: Annual Statistics of Notifiable Infectious Diseases 1990-1999: https://www.bmgf.gv.at/home/Gesundheit/Krankheiten/Uebertragbare_Krankheiten/Statistiken_und_Fallzahlen/Jahresstatistik_meldepflichtiger_Infektionskrankheiten_1990_1999

https://www.bmgf.gv.at/home/Gesundheit/Krankheiten/Uebertragbare_Krankheiten/Statistiken_und_Fallzahlen/Jahresstatistiken_meldepflichtiger_Infektionskrankheiten_seit_dem_Jahr_2000

Czech Republic: Infections in the Czech Republic: http://www.szu.cz/publikace/data/infekce-v-cr

France: Report of the National Reference Centre: http://www.cnrvha-vhe.org/

Germany: Robert Koch Institute Annual Report: http://www.rki.de/DE/Content/Infekt/Jahrbuch/jahrbuch_node.html

Italy: Reports of the Integrated Epidemiological System for Acute Viral Hepatitis: www.iss.it/seieva

Slovakia: Reports of the Epidemiological Information System http://www.epis.sk/HlavnaStranka.aspx?aspxerrorpath=/InformacnaCast/ Publikacie/VyrocneSpravy.aspx

Slovenia: Epidemiological surveillance of Infectious Diseases – Annual Report: http://www.nijz.si/sl/epidemiolosko-spremljanje-nalezljivih-bolezni-letna-porocila

Sweden: Reports of the Public Health Agency of Sweden: https://www.folkhalsomyndigheten.se/folkhalsorapportering-statistik/statistikdatabaser-och-visualisering/sjukdomsstatistik/hepatit-e/

United Kingdom – England and Wales: Public Health England. Zoonoses Summary Report, 2014; https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/488376/zoonoses-annual-report-2014.pdf

United Kingdom - Scotland: Health Protection Scotland weekly report: http://www.hps.scot.nhs.uk/ewr/index.aspx

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