

TECHNICAL REPORT

Outbreak of hepatitis A in EU/EEA countries - Second update¹

European Centre for Disease Prevention and Control

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ABSTRACT

Since 1 January 2013, 1 315 cases of hepatitis A virus (HAV) infection have been reported by 11 Member States as potentially linked to the ongoing HAV outbreak. Of these, 240 were confirmed outbreak cases, sharing the same sequence KF182323 at the junction VP1-2a of the viral genome. When first declared, the outbreak was associated with travel to Italy. In addition to Italy, seven other Member States have now reported cases with no travel history: France, Germany, Ireland, Norway, the Netherlands, Sweden and the UK. Epidemiological, microbiological and environmental investigations indicate frozen berries as the vehicle of infection for this outbreak and suggest that it could be a single outbreak, linked to a common, continuous source in the EU/EEA. However other hypotheses cannot be excluded, such as cross contamination in a food production environment or an outbreak strain that is already widespread but has, to date, gone undetected. Due to the characteristics of the pathogen (i.e. low infectivity dose and long incubation period) and of the food vehicle (i.e. long shelf-life and complex processing and distribution chain), it is expected that more cases will be reported and other Member States may become involved. In accordance with their national guidelines, Member States may consider active or passive immunisation of those in close contact with cases in order to prevent secondary transmission. Despite coordinated efforts from EFSA, ECDC, affected Member States and the European Commission (HAV-Trace Working Group), the ongoing trace-back investigation has not yet identified a likely source of contamination. The Working Group will continue the trace-back exercise and extend participation, on voluntary basis, to countries that have recently become involved, namely France, Norway and Sweden. All relevant information on national trace-back investigations shall be gathered and integrated into the HAV-Trace exercise via the RASFF (Rapid Alert System for Food and Feed) platform. Given the epidemiological and laboratory evidence of contaminated frozen berries, the risk to human health, and ongoing transmission with increasing geographical spread, affected Member States could consider implementing mitigating measures at national level. In particular, Member States could consider promoting risk communication, recommending heat treatment of frozen berries before consumption and encouraging HAV vaccination of those in contact with cases and throughout the larger community. Implementation of an enhanced sampling scheme for frozen berries at the processing and distribution level could also be considered. Enhanced epidemiological and microbiological surveillance for HAV in the EU/EEA should also be encouraged. A whole genome sequencing approach needs to be considered to

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* Changes were made as follows: Reference 37 for the outbreak in Prague in 2008 has been replaced with reference 40. In 'Results of the food investigations' information about the vehicle of the infection in Norway has been added, and the number of RASFF notifications and news alerts has been corrected from eight and four to ten and seven respectively. In the 'Conclusions and options for action' the paragraph on a harmonised analytical protocol has been amended.

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examine viral isolates from different points in time during the outbreak in order to confirm the hypothesis of a single outbreak. ECDC, EFSA and the European Commission, in cooperation with the affected Member States, will continue to their efforts to identify the vehicle and source of infection and closely monitor this event. The risk assessment will be updated as soon as any new relevant information becomes available.

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KEY WORDS

hepatitis A virus, HAV, food-borne outbreaks, food-borne diseases



RAPID OUTBREAK ASSESSMENT

Outbreak of hepatitis A in EU/EEA countries

Second update
11 April 2014

Summary

Since 1 January 2013, 1 315 cases of hepatitis A virus (HAV) infection have been reported by 11 Member States as potentially linked to the ongoing HAV outbreak. Of these, 240 were confirmed outbreak cases, sharing the same sequence KF182323 at the junction VP1-2a of the viral genome. When first declared, the outbreak was associated with travel to Italy. In addition to Italy, seven other Member States have now reported cases with no travel history: France, Germany, Ireland, Norway, the Netherlands, Sweden and the UK.

Epidemiological, microbiological and environmental investigations indicate frozen berries as the vehicle of infection for this outbreak and suggest that it could be a single outbreak, linked to a common, continuous source in the EU/EEA. However other hypotheses cannot be excluded, such as cross contamination in a food production environment or an outbreak strain that is already widespread but has, to date, gone undetected.

Due to the characteristics of the pathogen (i.e. low infectivity dose and long incubation period) and of the food vehicle (i.e. long shelf-life and complex processing and distribution chain), it is expected that more cases will be reported and other Member States may become involved. In accordance with their national guidelines, Member States may consider active or passive immunisation of those in close contact with cases in order to prevent secondary transmission.

Despite coordinated efforts from EFSA, ECDC, affected Member States and the European Commission (HAV-Trace Working Group), the ongoing trace-back investigation has not yet identified a likely source of contamination. The Working Group will continue the trace-back exercise and extend participation, on voluntary basis, to countries that have recently become involved, namely France, Norway and Sweden. All relevant information on national trace-back investigations shall be gathered and integrated into the HAV-Trace exercise via the RASFF (Rapid Alert System for Food and Feed) platform.

Given the epidemiological and laboratory evidence of contaminated frozen berries, the risk to human health, and ongoing transmission with increasing geographical spread, affected Member States could consider implementing mitigating measures at national level. In particular, Member States could consider promoting risk communication, recommending heat treatment of frozen berries before consumption and encouraging HAV vaccination of those in contact with cases and throughout the larger community. Implementation of an enhanced sampling scheme for frozen berries at the processing and distribution level could also be considered.

Enhanced epidemiological and microbiological surveillance for HAV in the EU/EEA should also be encouraged. A whole genome sequencing approach needs to be considered to examine viral isolates from different points in time

Errata. The following changes were made on 24 April 2014:

Reference 37 for the outbreak in Prague in 2008 has been replaced with reference 40.

In 'Results of the food investigations' information about the vehicle of the infection in Norway has been added, and the number of RASFF notifications and news alerts has been corrected from eight and four to ten and seven respectively.

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during the outbreak in order to confirm the hypothesis of a single outbreak.

ECDC, EFSA and the European Commission, in cooperation with the affected Member States, will continue to their efforts to identify the vehicle and source of infection and closely monitor this event. The risk assessment will be updated as soon as any new relevant information becomes available.

Public health issue

Ongoing outbreak of hepatitis A virus (HAV) infection in EU/EEA citizens.

Source and date of request

Following the report of a hepatitis A virus infection outbreak in Norway, ECDC and EFSA decided on 28 March 2014 to update their rapid outbreak assessments '[Joint ECDC-EFSA rapid outbreak assessment: Outbreak of hepatitis A virus infection in residents and travellers to Italy](#)' and its update '[Update: Outbreak of hepatitis A virus infection in Italy and Ireland](#)'.

Consulted experts

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ECDC and EFSA acknowledge the valuable contributions from the above-mentioned experts and institutions. All experts have signed a Declaration of Interest. Opinions expressed by individual experts do not necessarily represent the opinion of their institutions.

Disease background information

HAV is a small, non-enveloped hepatotropic virus classified in the genus *Hepatovirus* within the family Picornaviridae. Its genome consists of a 7 500-nucleotide linear, positive-stranded RNA. Genotypes have been traditionally defined based on analysis of a 168-nucleotide segment of the VP1-2A region. Based on this sequence, six HAV genotypes, from I to VI, have been defined. Genotypes I, II and III, divided into subtypes A and B, infect humans. Data on genotype distribution showed that genotype I is the most prevalent worldwide, with IA being reported more frequently than IB, and that sub-genotype IIIA is prevalent in central Asia. In areas of low endemicity, such as the United States and western Europe, sub-genotype IA dominates, but all genotypes and subtypes have been reported [1].

The disease, often asymptomatic or mild, particularly in children under five years, is highly transmissible with an average incubation period of 28 to 30 days (range 15–50 days). In adults, the onset of illness is usually abrupt with fever, malaise and abdominal discomfort. Jaundice is the predominant symptom. Symptoms may last from one or two weeks to months. Prolonged, relapsing hepatitis for up to one year occurs in 15% of cases. No chronic infection is known to occur and infection confers lifelong immunity [2].

The case-fatality ratio is low (0.1–0.3%) but might be higher (1.8%) in adults over 50 years of age or persons with underlying chronic liver disease [2,3]. The maximum infectivity is during the second half of the incubation period (i.e. while asymptomatic) and most cases are considered non-infectious after the first week of jaundice.

HAV can be transmitted through contaminated water, food and via the faecal–oral route among close contacts (e.g. household contacts, sexual contacts, day-care centres or schools [4-6]). The following risk factors or risk groups have also been associated with illness in outbreaks: use of contaminated blood products [7], people who inject drugs [8-10] or use other illicit drugs [11], men having sex with men (MSM) [4], and homeless people [11,12]. No pharmacological treatment exists. Strict control measures, such as reinforcing personal hygiene, contact tracing and administration of vaccine to exposed persons, have proved to be effective [13,14]. Active (antigen) and passive (antisera) immunisation is effective if administered within two weeks of exposure. Several inactivated vaccines are available for prevention.

The virus is very resistant in the environment as well as to several preservation methods used in the food industry, e.g. acidification or freezing [15-20], thus possible food-borne transmission should be investigated when cases are reported.

The notification rate in the European Union for HAV has been steadily decreasing over the last 15 years, from 14.0 in 1997 to 2.6 per 100 000 population in 2010 [21,22], despite the fact that some countries are still experiencing high notification rates. This overall decline in the notification rate most likely reflects improved living conditions, as HAV seroprevalence rates are strongly correlated with socioeconomic status and access to clean water and sanitation [23].

The highest notification rates in the EU are reported among the young under 15 years old [22]. There is a marked seasonal pattern, with a peak in the autumn, which may reflect increases following travel to endemic countries during summer holidays [22]. The low incidence in the EU population can result in a high proportion of susceptible individuals if vaccination coverage is low. If the infection is then introduced, there is a risk that adolescents and young adults will be infected if they have not been vaccinated or were not infected at an early age.

Food-borne transmission of HAV has been implicated in several outbreaks during recent years. Between 2007 and 2012, EFSA and ECDC reported 14 outbreaks with strong evidence of hepatitis A as the causative agent. The food vehicles responsible were fish and seafood products (crustaceans, shellfish, molluscs and products containing these), sandwiches, vegetables, juices, semi-dried tomatoes, bakery products and other foods [24-29]. In addition, minimally processed food products may be at the origin of food-borne outbreaks. For example, Australia reported an outbreak of HAV infection involving 144 cases where frozen semi-dried tomatoes were identified as the vehicle of infection [30]. Semi-dried tomatoes were also implicated in simultaneous outbreaks involving 59 HAV cases in France in 2010 [30] and 14 cases in the Netherlands [31], and were suspected in a cluster of cases in the UK and in the Netherlands in 2011 [32]. In August and November 2012, the Netherlands reported two clusters of HAV sub-genotype IA infection associated with consumption of mussels (EPIS-FWD). In several outbreaks associated with fresh products, food handlers involved in harvesting or preparing foods have been identified as the source [33]. For example, in 2004, an outbreak of 269 cases detected in Belgium was associated with the consumption of raw beef, traced back to an infected food handler in a distribution plant [34].

Berries were implicated in HAV infection outbreaks in 1987 when 24 HAV cases, associated with consumption of frozen raspberries, were reported in Scotland, UK [35] and in 1997, when an outbreak affecting 153 people associated with consumption of frozen strawberries was reported in Michigan, USA [36]. In 2004, orange juice was implicated in a large outbreak with more than 300 cases of HAV infection in travellers from nine European countries returning from Egypt [37]. More recently, in 2013, two multinational outbreaks of HAV infection affected EU/EEA countries. The first was reported in Finland, Denmark, Sweden and Norway. The second was reported in travellers returning from Egypt to several European countries. Each outbreak affected over 100 patients and food-borne transmission was suspected, through frozen and fresh strawberries respectively [38]. In addition, in 2013, an HAV infection outbreak was investigated in eight different States across the USA. Pomegranate seeds from Turkey were implicated as the vehicle of infection [39]. These three, so far unrelated, outbreaks have been found to be associated with unique outbreak strains, different to the one associated with the outbreak described in this document.

According to the Rapid Alert System for Food and Feed (RASFF) database, there were 35 notifications of HAV in food reported between 1999 and 2013. HAV was found in eight EU countries (Belgium, Czech Republic, Denmark, France, Germany, Italy, the Netherlands and Spain) in the following food items: shellfish (e.g. oysters, mussels, clams and scallops), semi-dried tomatoes, dates, frozen strawberries, strawberry yoghurt cake and frozen berry mix.

Updated event background information

Results of the epidemiological and microbiological investigations

Descriptive epidemiology

On 8 May 2013, Germany reported in EPIS-FWD and the Early Warning and Response System (EWRS) seven cases of HAV infection genotype IA in persons with a travel history to ski resorts in northern Italy. Following the alert from Germany, Italy reported an increase in the number of HAV cases at national level in 2013 and declared an outbreak. Some of the cases identified were infected with HAV genotype IA with an identical sequence (KF182323).

In collaboration with the affected Member States, ECDC prepared the European case definition for this outbreak. Confirmed cases were defined as HAV cases with onset on or after 1 January 2013, laboratory confirmation and an identical RNA sequence (KF182323). Probable cases were HAV cases with onset on or after 1 January 2013, laboratory confirmation, no sequence available and epidemiological links detailed in Annex 1.

Since May 2013, Italy has been reporting confirmed and probable cases on a monthly basis. Confirmed or probable cases with a travel history to Italy were also reported by Bulgaria, Denmark, Germany, Ireland, the Netherlands, Poland, Sweden and the United Kingdom. In addition, Ireland and the Netherlands reported clusters or outbreaks of confirmed cases with no travel history. France, Germany, Sweden and the United Kingdom also reported sporadic confirmed cases of hepatitis A in patients with no travel history.

On 10 March 2014, Norway posted an urgent enquiry in EPIS-FWD and on 1 April 2014 a message in EWRS, reporting a cluster of HAV infection cases during the period November 2013 to March 2014. All confirmed cases in Norway and the other countries mentioned above were infected with an identical strain.

Since 1 January 2013, 1 315 cases have been reported that are associated with this HAV infection outbreak (Table 1). Of these, 240 cases (18.3%) were confirmed and 1 075 were probable (81.7%). Italy reported over 90% of the cases. Of the 113 cases reported by other EU/EEA countries, 40 had a history of travel to Italy during the relevant exposure period. The remaining 73 cases most probably acquired their infection domestically. Seven-hundred-and-forty-one cases were reported as primary cases and 27 as secondary (for 550 cases this information is not available).

The median age of patients is 35 years (ranging from 1 to 92 years, 1 283 cases with available information) and 54% are male (1 288 cases with available information).

Table 1. Distribution of confirmed and probable hepatitis A cases by reporting country, confirmation status and travel history to Italy (data as of 31 March 2014)

Reporting country	Cases reported		Confirmed cases		Travel-related cases to Italy*	
	n	% overall	n	% reported	n	% reported**
Bulgaria	1	0.1	0	0.0	1	100.0
Denmark	1	0.1	1	100.0	1	100.0
France	5	0.4	5	100.0	0	0.0
Germany	30	2.3	5	16.7	24	80.0
Ireland	25	1.9	21	84.0	4	16.0
Italy	1202	91.4	161	13.4	not available	not available
The Netherlands	15	1.1	15	100.0	1	6.7
Norway	23	1.7	19	82.6	0	0.0
Poland	5	0.4	5	100.0	5	100.0
Sweden	4	0.3	4	100.0	2	50.0
United Kingdom	4	0.3	4	100.0	2	50.0
Total	1315	100.0	240	18.3	40	35.4

* For one French and one British case this information is not available.

** Not including Italian cases.

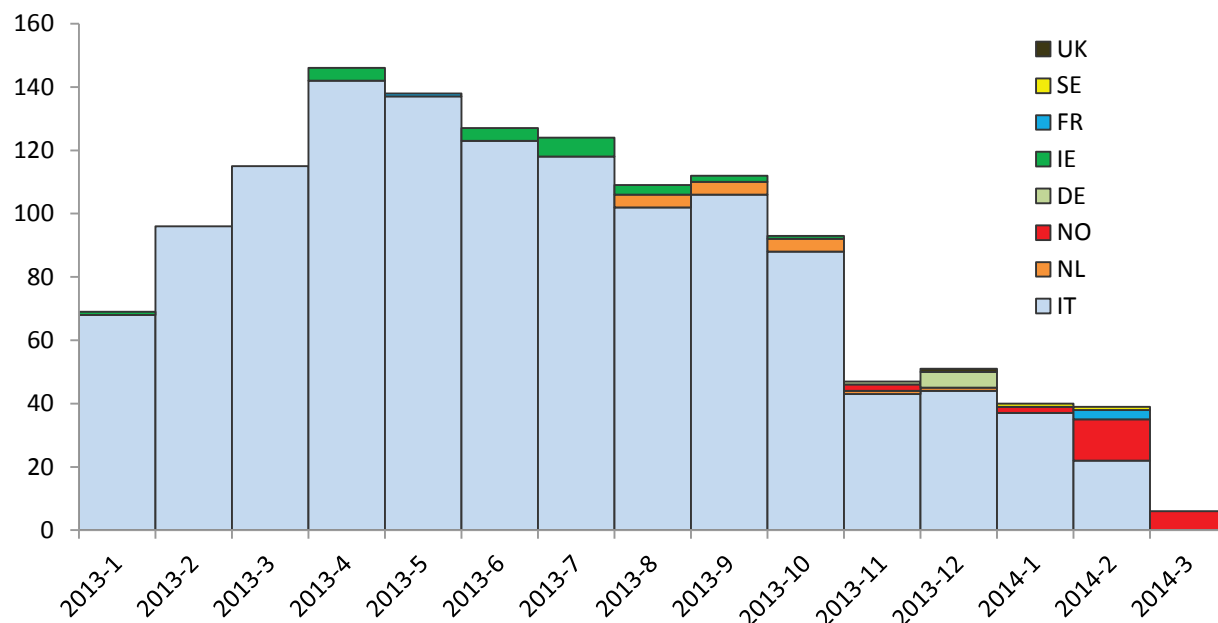
The highest number of cases associated with this outbreak was reported in April 2013 (Figure 1). From March to September 2013, more than 100 cases were reported on a monthly basis. Since November 2013, the number of cases reported per month has decreased to below 70. For the whole period, Italy reported most of the confirmed and probable cases. Due to the large extent of the outbreak, Italy performed molecular sequencing only on a proportion of isolates, mostly between May and July 2013, after the outbreak was declared.

Ireland reported sporadic or clusters of confirmed cases with no travel history between April and October 2013. The Netherlands reported sporadic or clusters of confirmed cases with no travel history between August and December 2013. Most cases reported in Germany had a travel history to Italy. However, in November and December 2013, Germany also reported six confirmed cases with no travel history, four of these were part of a family cluster, living near the Dutch border and they occasionally bought food in the Netherlands. The UK reported four confirmed cases, two of which had a travel history to Italy, one could not be interviewed and one, with onset in December 2013, had no travel history outside the UK. Sweden reported four confirmed cases; two had a history

of travel to Italy. The other two cases did not have a travel history and had onset in January and February 2014. France reported five confirmed cases, three of which had symptoms onset in February 2014 and were found to have an epidemiological link.

Norway is currently experiencing an outbreak of hepatitis A. The first confirmed case had onset in November 2013 and 16 of the 19 confirmed cases had onset in February (n=12) and March 2014 (n=4). The other Member States involved, namely Poland, Bulgaria and Denmark, only reported cases with travel history to Italy.

Figure 1. Distribution of confirmed and probable cases of hepatitis A by month of onset and probable country of infection, EU/EEA countries, January 2013 to March 2014 (n=1 313*)



*Information on the month of onset is not available for two cases.

Microbiological investigation

Information on the molecular characterisation of isolates is available for the 240 confirmed cases. All isolates are sub-genotype IA and share an identical or closely related sequence (i.e. one nucleotide difference in an RNA fragment 460 nucleotides long). The outbreak sequence GenBank number is KF182323 and is available on EPIS-FWD or from ECDC upon request. The German reference laboratory sequenced a genomic region 349 nucleotides long at the VP1-2a junction. All other laboratories, except the Norwegian reference laboratory in the initial phase, used a common protocol from the Dutch National Institute for Public Health and the Environment (available on request from HAVNET@rivm.nl) and sequenced a genomic region 460 nucleotides long in the VP1-2a region. The Norwegian reference laboratory initially sequenced a partially overlapping genomic region 466 nucleotides long at the VP3-VP1 junction for the first 16 isolates. For three of these and an additional three made available later, the Norwegian reference laboratory repeated the sequencing operations using both the in-house protocol for the VP3-VP1 region and the VP1-2a region. All isolates proved to be identical in both regions sequenced. The Netherlands reported that the outbreak strain is identical to that of an outbreak in Prague, Czech Republic, in 2008 [40].

Questionnaire interviews

The majority of the cases have been interviewed with questionnaires harmonised among the different countries. Consumption of mixed frozen berries has been implicated as a source for HAV infections since May 2013. Information on consumption of berries (i.e. fresh or frozen) during the relevant exposure period was available for 613 cases: of these, 419 (68.3%) recalled having consumed berries. Restricting the analysis to confirmed cases, information is available for 158 cases (65.8% of all confirmed cases): of these, 134 (84.8%) reported consumption of berries during the relevant exposure period. Data from the EFSA Comprehensive European Food Consumption Database, including information for 52 852 subjects, shows that 24.3% of European consumers consumed berries at least once during the reporting period [41].

It is noteworthy that the exposure to berries may be subject to recall bias, due to the long interval between exposure and onset of symptoms/diagnosis and the fact that berries may be a minor ingredient or may only have been used as decoration in the food. On the other hand, lack of exposure to berries may be suggestive of a different or a secondary route of infection (e.g. cross-contamination, person-to-person transmission).

Analytical epidemiology

Retrospective case-control studies were carried out separately in Italy and Ireland in order to identify risk factors for HAV infection and test the hypothesis of an association between hepatitis A and consumption of frozen berries. The Italian Public Health Institute (National Centre for Epidemiology Surveillance and Health Promotion, Istituto Superiore di Sanità – CNESPS-ISS) carried out a study in five different Italian regions, including probable and confirmed cases notified from January to May 2013. For each of the 119 cases, about three controls, matched by age and place of residence, were enrolled in the study, resulting in 538 study participants (of which 419 controls). The study found HAV infection cases independently associated with consumption of frozen berries (matched adjusted odds ratio, OR 4.2, 95% confidence interval CI 2.5-7.0), but also with consumption of raw seafood (matched adjusted OR 3.8; 95% CI 2.2-6.8) and travel to an HAV highly-endemic area (matched adjusted OR 2.0; 95% CI 1.2-3.4). Both raw seafood consumption and travel to HAV endemic areas are risk factors previously described in Italy.

In Ireland, the Health Protection Surveillance Centre (HPSC) carried out a study in July 2013, including 11 cases and 42 controls matched by age, sex and area of residence. The case-control study found cases independently associated with consumption of frozen berries or products containing frozen berries (matched OR 12.0; 95% CI 1.5–94.0). The questionnaire developed by the HPSC and used for the national case-control study was subsequently shared with all the affected Member States through EPIS-FWD and used to interview new cases in most countries affected after August 2013.

A case-control study is currently ongoing in Norway. The questionnaire used is an adapted version of the HPSC questionnaire.

Results of the food investigations

After the outbreak was declared, the national task-force for HAV outbreak investigation appointed by the Italian Ministry of Health conducted extensive tracing exercises (back and forward) on the suspected food batches. Similar activities were carried out by the Irish and the Dutch authorities. On 23 October 2013, the European Commission requested EFSA, through a mandate, to coordinate the trace back and trace forward exercises in the affected Member States. EFSA established a working group (HAV Trace) with the participation of the affected Member States, the European Commission, ECDC, the Polish Food Safety Authorities and the German Institute for Risk Assessment (BfR). The project is coordinating the collation of tracing information via the RASFF platform and performing network analysis in order to identify possible 'hot spots' in the supply chain for further investigation. Using this methodology, different hypotheses can be investigated (common source in primary production or cross contamination) and the traced food items can be weighted based on the robustness of evidence and on epidemiological links and laboratory analysis (including analyses of food samples by nested RT-PCR). The network analysis performed by BfR uses a GPL-licensed open-source software tool called 'FoodChain-Lab' which was developed in-house.

A risk-based approach has been adopted to identify the brand and the lots of frozen berries possibly contaminated with HAV. Berries have been prioritised, based on the level of evidence of HAV contamination, as confirmed lots (analytical evidence), suspected lots (epidemiologically related to either confirmed or possible cases), and possible products (any brand of frozen mix berries consumed by at least one confirmed case, before the onset of symptoms, with no available lot number).

In Italy, the food investigation has been coordinated by the HAV task force and the laboratory analyses have been carried out by the Istituto Zooprofilattico Sperimentale of Brescia (IZSLER) and the Italian Ministry of Health. As of 28 February 2014, 15 samples of frozen berries had tested positive for HAV by nested RT-PCR. The HAV sequence (region VP1/2A) obtained from one of the berries sampled was identical with the 'outbreak sequence' obtained from human cases. In addition, 44 suspected lots and two possible products have been found.

Collection of the traceability information for all the confirmed lots detected in Italy is still ongoing. To increase the possibility of finding a common contamination source of the frozen berries, even by way of a cross-contamination mechanism, Italy extended the data collection beyond the confirmed lots and the berry ingredients that were used for the contaminated lots.

The food investigation in Ireland was supported by the Italian IZS, using the same methodology as for the national food investigation. Out of the 16 food items tested, none were positive for HAV.

In the Netherlands, the National Institute for Public Health and the Environment (RIVM) carried out detailed interviews of the ten primary confirmed cases with no travel history using structured questionnaires. All these cases indicated that they had consumed fresh berry fruits, mainly fresh strawberries. Only one case recalled having also eaten frozen berries. Therefore, the traceback activities of the Netherlands Food and Consumer Product Safety Authority (NVWA) have focused on the identification of a common supplier of fresh strawberries (and other fresh berry fruits) to two main supermarket chains named by those affected as the purchase address. Moreover, data from traceback activities in Ireland and Italy were also taken into account. No fresh or frozen berry fruit samples have been tested for the presence of HAV RNA as these were no longer available.

Food trace back activities are currently ongoing in Sweden, France and Norway and their results will be incorporated into the HAV Trace exercise. The investigation of three French cases with onset in February 2014 showed that these were linked by the consumption of mixed berry cakes. HAV was identified in a sample of the implicated berries and a RASFF notification was issued on 7 April 2014. Sequencing results are pending. The national outbreak investigation and food trace back in Norway has led to the identification of an imported frozen berry mix cake as suspected vehicle of the infection. Norway issued a RASFF (and EWRS) notification on 11 April 2014. The product was immediately recalled by the Norwegian importer company. Samples of the cake have been sent for analysis, but the analytical results are not yet available. So far, ten RASFF notifications concerning HAV contaminated lots and seven RASFF news alerts have been posted by Member States food authorities. Currently tracing activities have focused on frozen blackberries, raspberries, blueberries, red currants and black currants supplied to Italy and Ireland and fresh berries supplied to or produced within the Netherlands.

Based on the available traceback data, there is no conclusive evidence for the specific vehicle of infection or for the source of contamination.

Updated threat assessment for the EU

Since 1 January 2013, outbreaks or clusters of confirmed HAV infections with no travel history have been reported in Italy, Ireland, the Netherlands and Norway. During the same time period, France, Germany, Sweden and the United Kingdom reported sporadic confirmed cases of hepatitis A infection with no travel history. Finally, most of these countries and Denmark reported confirmed cases of HAV infection with a travel history to Italy during the relevant exposure period. All viral isolates from the confirmed cases shared an identical RNA sequence.

The identification of the exact same HAV RNA sequence in isolates from patients without a travel history reported in eight different EU/EEA countries and in one isolate from a sample of frozen berries in Italy is suggestive of a common, continuous source outbreak. However other hypotheses cannot be excluded, such as cross contamination in a food production environment, secondary transmission or an outbreak strain that is already widespread but has, to date, gone undetected. The epidemiological evidence from analytical studies of an association between hepatitis A infection and consumption of frozen berries, along with the commonly identified exposure to frozen berries by patients in countries reporting sporadic cases, reinforces the hypothesis of a food-borne outbreak and of contaminated frozen berries distributed in eight EU/EEA countries as the vehicles of infection.

The distribution of onset dates, the long incubation period and the delay in regional case-reporting in Italy suggest that additional HAV cases might be expected during the coming weeks in Italy and Norway. In addition, given the long shelf-life of frozen berries, the lack of identification of the specific berry type and the point of contamination associated with this outbreak, it is not possible to exclude the occurrence of associated cases in other EU Member States.

Molecular characterisation of isolates from hepatitis A patients has facilitated the linking of sporadic and outbreak cases in different countries. However, sequencing practices for HAV isolates are not standardised and only a proportion of EU/EEA countries perform HAV RNA sequencing on a routine basis. Despite an increase in HAV typing since the outbreak declaration, it is likely that some cases infected with the outbreak strain have not been identified.

Italy is the only country reporting a high proportion of probable cases (>85%), compared to all other affected countries reporting mostly confirmed cases or probable cases with a travel history to Italy. Considering that Italy traditionally experiences a baseline number of HAV infections associated with raw seafood consumption and with travel to countries of intermediate and high endemicity, it is likely that the overall number of Italian cases reported as associated with this outbreak is over-estimated. It should be noted, however, that all probable Italian cases reporting a history of travel to HAV-endemic countries were excluded from the total number of Italian cases described in this assessment.

A European traceback investigation is currently gathering information from France, Norway and Sweden, in addition to that previously collected from Ireland, Italy and the Netherlands. The exercise is being led by EFSA, with the support of affected Member States, ECDC, the European Commission and BfR. The investigation aims to identify possible 'hot spots' within the supply chain as well as taking into account the strength of evidence linking traced food items to the outbreak. Investigation of hot spots would include identifying the location of contaminated berries that have been distributed to other European countries. Additional epidemiological and microbiological investigations, including the case-control study in Norway and the analysis of implicated food samples in France, may also provide additional evidence to confirm the hypothesis that events in the different countries are part of the same outbreak.

The current outbreak in several EU/EEA countries has been posing a risk of secondary transmission through infected individuals. Transmission through infected food handlers and household contacts should be taken into consideration. There is also a risk of HAV transmission through asymptomatic or incubating viraemic blood donors. Potential blood donors in Europe should be asked questions to identify hepatitis A risk factors (including contacts with HAV infection cases, history of travel and exposure to berries) and questions concerning a history or presence of hepatitis A symptoms. Blood donors reporting hepatitis A risk factors prior to blood donation should be sensitised to immediately report any hepatitis A symptoms to the blood donation services.

Public health and food authorities in the affected countries, ECDC and EFSA are working together to identify the source of the infection in order to prevent additional cases. Together with the affected countries ECDC has developed a European outbreak case definition; distributed a standard questionnaire developed by the Irish Health Protection Surveillance Centre for interviewing cases; collected epidemiological information from all countries reporting cases and, with the support of HAVNET at the National Institute for Public Health and Environment in the Netherlands, disseminated a standard protocol to guide the sequencing of human samples. In addition, ECDC, through the FWD network in EU/EEA countries, is promoting awareness and recommending the enhancement of epidemiological and molecular surveillance for HAV infection.

Conclusions and options for action

Since 1 January 2013, 1 318 cases of HAV infection have been reported by 11 Member States as potentially linked to the ongoing HAV infection outbreak. Of these, 240 were confirmed outbreak cases, sharing an identical or closely related sequence (KF182323) at the junction VP1-2a of the viral genome. When first declared, the outbreak was associated with travel to Italy. In addition to Italy, seven other Member States have now reported acquired cases with no travel history: France, Germany, Ireland, Norway, the Netherlands, Sweden and the UK.

Epidemiological, microbiological and environmental investigations indicate frozen berries as the vehicle of infection for this outbreak and suggest that it could be a single outbreak linked to a common, continuous source in the EU/EEA. However other hypotheses cannot be excluded, such as cross contamination in a food production environment or an outbreak strain that is already widespread but has, to date, gone undetected.

Due to the characteristics of the pathogen (i.e. low infectivity dose and long incubation period) and of the food vehicle (i.e. long shelf-life and complex processing and distribution chain), it is expected that more cases will be reported and other Member States may be involved. In accordance with their national guidelines, Member States may consider active or passive immunisation of close contacts of cases in order to prevent secondary transmission.

In view of the large number of travel-associated infections, Member States may consider promoting vaccination for susceptible travellers. Taking into account the large number of EU/EEA countries reporting confirmed cases, routine vaccination may also be considered for any EU/EEA citizen and not only for those travelling or in contact with HAV infection cases.

Despite coordinated efforts from EFSA, ECDC, affected Member States and the European Commission, the ongoing traceback investigation has not yet identified a likely source of contamination. This may be due to difficulties in linking cases with food items; the long duration of the outbreak which might be caused by more complex transmission routes; challenges inherent in the complexity of production and distribution chains and problems with detecting HAV in contaminated lots due to non-homogeneous contamination within a lot or a very low level of contamination below the detection limit for the applied method in a specific matrix.

There is a need for sustained coordination at EU level for investigation of outbreaks, clusters and sporadic cases as well as investigation of the food chain. To achieve this aim, the HAV-Trace Working Group will continue the traceback exercise and will extend the participation, on voluntary basis, to newly involved countries (France, Norway and Sweden). All relevant additional information on national traceback investigations will be gathered and integrated into the HAV-Trace exercise via the RASFF platform. ECDC will continue to collect epidemiological and microbiological information to monitor the situation, and to recommend interviewing cases using the questionnaire developed by the HPSC.

Given the epidemiological and laboratory evidence of contamination of frozen berries, the risk to human health, and the ongoing transmission with increasing geographical spread, affected Member States could consider implementing mitigating measures at national level. In particular, affected Member States could consider promoting risk communication, as has been done by the Irish and Italian authorities, and recommending heat treatment of frozen berries before consumption.

Implementation of enhanced sampling schemes for frozen berries at the processing and distribution level may also be considered. In particular, Member States may consider reinforcing sampling at processing level as part of the Hazard Analysis and Critical Control Points (HACCP) for HAV hazard in frozen berries. They could also increase the risk-based sampling of suspected lots in affected countries, in order to increase the likelihood of detecting and recalling contaminated products, adopt prompter control measures, and increase the sampling of frozen berries to support studies aimed at identifying and quantifying specific patterns of HAV contamination in frozen berries. Ultimately the information collected through this enhanced sampling scheme may be used for a future risk assessment of HAV in frozen berries.

Enhanced epidemiological and microbiological surveillance for HAV in the EU/EEA may be needed. A whole genome sequencing approach should be considered to examine viral isolates from different points in time during the outbreak. This would help to confirm the hypothesis of a single outbreak.

The existence of more than one diagnostic protocol for HAV sequencing in human and food samples has resulted in partially overlapping nucleotide sequences and suboptimal comparable microbiological evidence. As a lesson learnt from this outbreak investigation, there is a need for the development of a harmonised analytical protocol for HAV sequencing in human and food isolates to facilitate comparability.

In addition, with the aim of increasing the timeliness of HAV data availability and analysis, ECDC will propose a data call for hepatitis A cases on a quarterly basis, as is currently done for salmonellosis and Shiga toxin/verocytotoxin -producing *Escherichia coli* infection.

ECDC, EFSA and the European Commission, in cooperation with the affected Member States, will continue to strengthen efforts to identify the vehicle and source of infection; closely monitor this event and update the risk assessment as soon as new relevant information becomes available.

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Annex 1

Definitions

The ECDC, in consultation with the affected Member States, has developed an European epidemic HAV case definition for the purpose of identifying cases associated with the hepatitis A outbreak occurred in Europe in 2013 to establish the extent of this outbreak.

According to the **European epidemic HAV case definition**, a **confirmed case** is defined as:

a person with laboratory confirmed HAV genotype IA

AND

identical sequence to the 2013 HAV genotype IA outbreak strain (GenBank accession number KF182323) based on the fragment of 460 base pairs at the region of VP1/2A*

OR

99.8% similarity to this sequence (i.e. 1 base pair difference in 460 base pairs)

OR

identical sequence on a shorter fragment of 174 base pairs at the region of VP1/2A

AND

date of symptom onset (or date of testing if onset date not available) on or after 01/01/2013;

According to the European epidemic HAV case definition, a **probable (suspect/possible) case** is defined as:

a person with laboratory-confirmed HAV infection

AND

date of symptoms onset (or date of testing if onset date not available) on or after 1 January 2013

AND

having at least, within 15-50 days before onset, one of the following epidemiological criteria:

1. Travel history to Ireland, Italy or the Netherlands;
2. Exposure to berries, including frozen berries;
3. Consumption of confirmed contaminated food items;
4. Person-to-person contact with a confirmed case (secondary case).

The following exclusion criteria are applied:

1. HAV confirmed case which has a different sequence type to the 2013 HAV genotype IA outbreak strain
2. Existence of an epidemiological link to exclusion criterion number 1
3. History of travel abroad (except to Italy).

In addition, the definitions of secondary case and travel-related case are as following.

Secondary case: a person with no reported exposure to berries, who was judged to have acquired infection by secondary transmission via person to person or unknown route.

Travel-related case: a person with a history of travel abroad 15 to 50 days prior onset of symptoms.

** For Norwegian isolates, identical sequence to GenBank number KF773842 based on the fragment of 466 at the region VP3-VP1.*