



RAPID OUTBREAK ASSESSMENT

Update: Outbreak of hepatitis A virus infection in Italy and Ireland

9 July 2013

Summary

Since 1 January 2013, 15 laboratory-confirmed cases of hepatitis A virus (HAV) infection have been reported in Germany, the Netherlands and Poland. All cases have a history of travel to the autonomous provinces of Trento and Bolzano in northern Italy during the exposure period. During the same period, Italy experienced an increase in cases of HAV infection, both in province of Trento and at national level. In the first six months of 2013, Italy reported more than 200 cases in excess of the mean number of cases reported in the same period for the last three years. This increase in cases is likely to be associated with this outbreak. Finally, three Irish cases whose isolates share a sequence identical to that in the Italian outbreak but without any history of travel to Italy, nor contact with other HAV cases, had onset of illness in April 2013 in Ireland. As the exposure of the cases occurred in Italy and Ireland, this suggests that cases have been exposed to the same contaminated vehicle of infection distributed in at least these two countries.

Epidemiological, microbiological and environmental investigations indicate mixed frozen berries as the most likely vehicle of infection for these outbreaks.

A national case-control study is underway in Italy. In addition, sequencing analyses of isolates from human and food samples and environmental and food trace-back investigations are on-going in Italy and Ireland. The results of these investigations are expected to bring more evidence on the implicated vehicle of infection and on the pathway of its contamination.

Despite the withdrawal of the incriminated food product, it is likely that additional cases will be identified and reported in Italy and, possibly, in Ireland, because of the long shelf-life of such frozen products. ECDC invites Member States to raise awareness of a possible increase in HAV cases associated with the Italian outbreak strain, to report all new cases in EPIS-FWD, to use the common epidemic case definition and questionnaire to interview recent cases and to sequence a subset of viral specimens in order to disclose possible links with the current outbreak in Italy. For additional sequence information or comparison, or assistance with sequencing if no facilities are available locally, the HAVNET can be contacted directly (havnet@rivm.nl). Member States, in accordance with their national guidelines, may consider active or passive immunisation of close contacts of cases in order to avoid secondary transmission.

ECDC, EFSA and the European Commission, in cooperation with the affected Member States, will continue to closely monitor this event and will update the risk assessment as soon as new relevant information becomes available.

Two other HAV-related outbreaks are simultaneously under investigation in four Nordic countries and among travellers returning from Egypt. A third food-borne HAV-related outbreak is under investigation in the USA. At present, there is no evidence of common links between these outbreaks.

Public health issue

Outbreak of hepatitis A virus infection (HAV) in residents and/or travellers to Italy and Ireland.

Source and date of request

Based on new information from the epidemiological, microbiological and environmental investigations, ECDC decided on 3 July to update the previous rapid outbreak assessment '[Joint ECDC-EFSA rapid outbreak assessment: Outbreak of hepatitis A virus infection in residents and travellers to Italy](#)'.

Consulted experts

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External experts consulted and acknowledged

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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, 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 old, 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 in 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, in daycare 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 EU 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 some countries still experiencing high notification rates. This 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 who have not been vaccinated or were not infected at an early age.

Food-borne transmission of HAV has been implicated in several outbreaks in recent years. Between 2007 and 2011, EFSA and ECDC reported 11 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 and semi-dried tomatoes [24-28]. 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 [29]. Semi-dried tomatoes were also implicated in simultaneous outbreaks involving 59 HAV cases in France in 2010 [29] and 14 cases in the Netherlands [30], and were suspected in a cluster of cases in the UK and in the Netherlands in 2011 [31]. In several outbreaks associated with fresh products, food handlers involved in harvesting or preparing foods have been identified as the source [32]. 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 [33].

In August and November 2012, the Netherlands reported two clusters of HAV sub-genotype IA infection with a large proportion of cases exposed to strawberries (urgent inquiry in EPIS-FWD). Berries were also implicated in HAV infection outbreaks in 1987 – 24 HAV cases, associated with consumption of frozen raspberries, were reported in Scotland, UK [34]; and in 1997 – an outbreak affecting 153 people associated with consumption of frozen strawberries, was reported in Michigan, USA [35]. 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 [36].

According to the Rapid Alert System for Food and Feed (RASFF) database, 21 samples of food were found to be contaminated with HAV between 1999 and 2013. HAV was found in six EU countries (Belgium, Czech Republic, 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.

Update event background information

Results of the epidemiological and microbiological investigations

Cases exposed in Italy

On 8 May 2013, Germany reported in EPIS-FWD and EWRS seven cases of HAV infection in persons with a travel history to ski resorts in the provinces of Trento and Bolzano in northern Italy.

Following the German report, the Netherlands and Poland reported additional HAV cases, one and five respectively, with a travel history to different villages and hotels in the province of Trento. Following the alert, Italy reported an increase in the number of HAV cases in 2013 in the province of Trento. Italy also reported an increase in HAV notifications at national level in 2013 compared to the three previous years. Germany reported two additional cases on 21 and 24 May; both cases had travelled to the province of Bolzano.

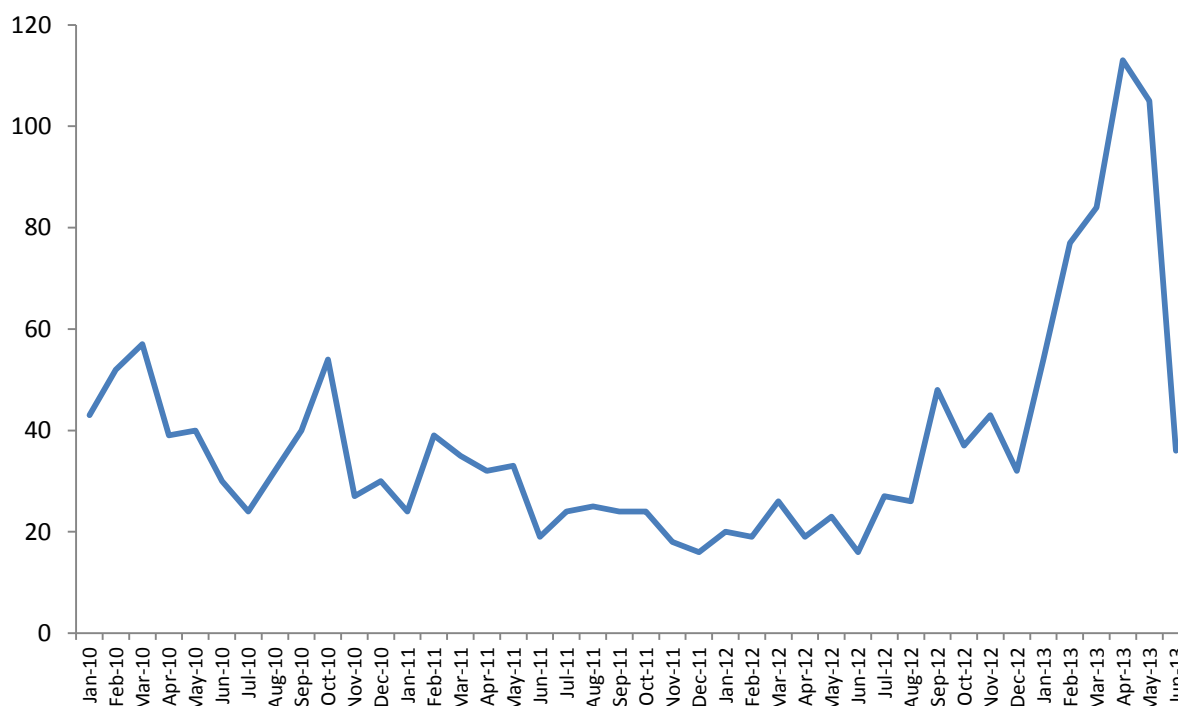
ECDC, in collaboration with the affected Member States, has updated the case definition for this outbreak (see Annex).

The cases from Germany, Poland and the Netherlands had visited Italy between late February and mid-April, with most cases visiting around mid-March. The time of disease onset ranged from late March to early May. The cases had stayed in at least six different villages in the provinces of Trento and Bolzano. Local authorities visited the accommodation reported by these cases and interviewed the staff.

Since the beginning of the year, Italy reported 34 HAV cases in the province of Trento, compared with four cases in 2012, one in 2011 and five in 2010. At national level, as of 30 June, 448 cases were reported in 2013, compared with an average of 190 cases reported in the same period in the previous three years. The increase is particularly evident in April and May 2013 (Figure 1). The number of cases reported in June is lower than in previous months due to delay in case notification. Considering that only a sub-set of the isolates from Italian cases have been

sequenced, it is not possible to quantify precisely the number of cases associated with this outbreak. However, a comparison of the number of notifications in the last four years suggests that there may be more than 200 cases likely to be associated with this outbreak since the beginning of 2013.

Figure 1. Distribution of cases of hepatitis A virus by month of onset, Italy, January 2010 to June 2013, as of 26 June 2013



Preliminary interviews of some cases among the travellers to, and the residents in, Italy showed consumption of frozen mixed berries as a potential risk factor. A matched case-control study is currently on-going in Italy with 37 cases and 96 controls enrolled in two northern regions, Trentino Alto Adige and Friuli Venezia Giulia. As of 10 June 2013, preliminary study results indicated that cases were five times more likely than controls to have eaten berries (matched adjusted odds ratio 5.33; 95% confidence interval 2.14–13.24).

Information on the molecular characterisation of isolates is available from seven travellers to Italy and for 19 residents in Italy. All isolates are sub-genotype IA and share an identical sequence. The outbreak sequence GenBank number is KF182323 and is available on EPIS-FWD or from ECDC upon request. The sequencing was performed in different laboratories. The German reference laboratory sequenced a genomic region 349 nucleotides long at the VP1-2a junction; all other laboratories used a common protocol made available by the Dutch National Institute for Public Health and the Environment (available on request from HAVNET@rivm.nl) and sequenced a genomic region 440 nucleotides long in the same region. The Netherlands reported that the outbreak strain is identical to that of an outbreak in Praha, Czech Republic, in 2008 [37].

Cases exposed in Ireland

On 28 June, Ireland reported in EWRS three cases of HAV infection in Irish residents who had no history of travel to Italy during the exposure period.

The isolates from the Irish cases have an HAV RNA sequence identical to the Italian outbreak strain. The genomic region sequenced was 505 nucleotides long at the VP1-2a junction. The three cases are adults between 30 and 40 years of age, residents in three different geographic regions with no known links to each other. All had onset of illness in April 2013 and reported consumption of frozen berries in the relevant exposure period. Two had no history of travel abroad, one had travelled to Poland in the relevant period. The cases were interviewed with a modified version of the questionnaire used for the Italian outbreak. Additional case finding is under way in Ireland, with sequencing results pending on samples from five cases.

Results of the food investigations

Four Italian cases, who attended a private dinner in north-eastern Italy, reported consumption of berries. HAV was identified in an open package of mixed berries found in the freezer at the residence of the case that prepared the dinner. The HAV strain identified from the food sample showed a VP1-2a region sequence 440 nucleotides long identical to that of the outbreak strain.

Following the identification of the contaminated berries, increased sampling was performed and three additional packages of mixed berries, in closed bags from three different batches and two different brands, tested positive for HAV.

The Italian Food Authority sent out four RASFF notifications regarding the mixed frozen berries found to be contaminated with HAV in Italy on 17 May, 30 May (2) and 24 June 2013 (notifications 2013.0694; 2013.0756; 2013.0757; 2013.0880). The frozen berry mix originated from Italy, with raw berry material from Canada (via Switzerland), Bulgaria, Poland, Serbia and Ukraine (via Austria). Following the notifications, the mixed frozen berries were withdrawn from the national market. An investigation into the traceability of the product is currently underway.

Food trace-back investigations in Ireland are on-going. So far no HAV has been isolated from any sample sent for sequencing as all results are pending. These include berries from the freezer of one of the cases and berries from the supplier to one of the outlets mentioned by another of the cases.

Other information

There have been two additional outbreaks of HAV affecting EU/EEA countries since March 2013. The first is on-going in four Nordic countries [38] and imported frozen strawberries are the suspected vehicle of infection. The second outbreak involved travellers returning from Egypt to several European countries [39]; food-borne transmission is suspected, but no specific food item has been implicated to date. In addition, an HAV-related outbreak is currently being investigated in eight different states of the United States of America; pomegranate seeds from Turkey have been implicated as the vehicle of infection [40]. These three, so far unrelated, outbreaks have been found to be associated with unique outbreak strains different from the one associated with the outbreak affecting Italy and Ireland.

Updated threat assessment for the EU

An outbreak of HAV infections has been reported among European travellers to different villages in the provinces of Trento and Bolzano, northern Italy, from Germany, Poland and the Netherlands. Italy has also reported a large increase in HAV notifications, both in the province of Trento and at national level since the beginning of 2013. In addition, Ireland reported three HAV cases with no travel history to Italy whose isolates share identical sequence to the Italian outbreak with possible link to consumption of frozen berries.

The distribution of symptom onsets over time suggests a common, continuous source outbreak with the majority of the travellers to, and resident in, Italy infected respectively around mid-March and between January and May. Irish cases had onset of symptoms between early and late April, which suggests either a common point source or a common continuous source of infection on-going for few weeks.

The most recent cases have been reported by Italy with onset of symptoms in June, indicating that the outbreak is still on-going at least in Italy. Considering the delay in case reporting and the on average one-month-long incubation period, more cases are expected to be reported.

In Italy, epidemiological evidence links cases to consumption of berries. Identical HAV RNA sequence has also been identified in isolates from travellers to Italy, Italian residents and frozen berries distributed in Italy. These findings strongly support the hypothesis that the origin of this outbreak is food-borne and that the vehicle of infection is frozen berries distributed in Italy during 2012 and 2013.

The same HAV RNA sequence identified in isolates from three Irish cases with no history of travel to Italy suggests that the same contaminated food product may have been distributed also in Ireland around March 2013.

The withdrawal of the mixed frozen berries by the distributor in Italy has decreased the risk of infection for residents and visitors to Italy. However, the specific berry type has not yet been identified and, due to the long shelf-life of frozen berries, it is likely that some of the contaminated batch may still be circulating for some time or will be stored in household freezers. Furthermore, the point of contamination is unknown. Therefore, additional HAV cases may be expected in the coming weeks in Italy and, possibly, in Ireland. At this stage it is not possible to exclude the occurrence of associated cases in other EU Member States, including Ireland.

Trace-back investigations are currently on-going in Italy to identify the origin of the contaminated frozen berries. Further epidemiological and microbiological investigations may provide additional evidence to confirm the hypothesis that the same type of frozen berries distributed in the two countries is the vehicle of infection in this outbreak. An overlap in the information available from the investigations in Italy and in Ireland may provide evidence about the time and the place of contamination of the implicated berries. These pieces of information may also clarify whether the contaminated berries have been distributed to other European countries.

The current outbreak in several EU/EEA countries poses a slightly elevated risk of secondary transmission through infected travellers after their return to their home country. 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. In the affected area potential blood donors should be asked standard agent-non-specific questions to identify risk groups and agent-specific screening questions concerning a history of possible exposure to HAV. In unaffected areas temporary questions on recent (30 days before donation) travel history to affected areas should be introduced in the blood donor questionnaire. In the event of positive exposure and travel history donors should be tested and temporarily deferred for one year if positive [41].

Public health and food authorities in the affected countries, ECDC and EFSA are working together to identify the vehicle of the infection in order to prevent additional cases.

ECDC has contacted all Member States encouraging them to cross-check the sequences available for isolates from their cases with the outbreak sequence from Italy and Ireland. All cases, whether with or without a history of travel during the exposure period, are of interest.

It should be noted that, based on the comparison of the overlapping molecular regions analysed, the genotype and the RNA sequence of the virus associated with the outbreak in Italy and Ireland show approximately 9% nucleotide difference from the sequence type revealed for the strains isolated in the non-travel-related HAV outbreak currently affecting the Nordic countries, in the outbreak associated with travel to Egypt and in the outbreak currently affecting different states of the USA. Consequently, at this point no link can be established between the four simultaneous outbreaks.

Conclusions and recommendations

Since 1 January 2013, 15 laboratory-confirmed cases of HAV infection have been reported in Germany, the Netherlands and Poland. All cases have a history of travel to the autonomous provinces of Trento and Bolzano in northern Italy during the exposure period. During the same period, Italy experienced an increase in cases of HAV infection, both in province of Trento and at national level. In the first six months of 2013, Italy reported more than 200 cases in excess of the mean number of cases reported in the same period for the last three years. This increase in cases is likely to be associated with this outbreak. Finally, three Irish cases whose isolates share a sequence identical to that in the Italian outbreak but without any history of travel to Italy, nor contact with other HAV cases, had onset of illness in April 2013 in Ireland. As the exposure of the cases occurred in Italy and Ireland, this suggests that cases have been exposed to the same contaminated vehicle of infection distributed in at least these two countries.

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Despite the withdrawal of the incriminated food product, it is likely that additional cases will be identified and reported in Italy and, possibly, in Ireland, because of the long shelf-life of such frozen products. ECDC invites Member States to raise awareness of a possible increase in HAV cases associated with the Italian outbreak strain, to report all new cases in EPIS-FWD, to use the common epidemic case definition and questionnaire to interview recent cases and to sequence a subset of viral specimens in order to disclose possible links with the current outbreak in Italy. For additional sequence information or comparison, or assistance with sequencing if no facilities are available locally, the HAVNET can be contacted directly (havnet@rivm.nl). Member States, in accordance with their national guidelines, may consider active or passive immunisation of close contacts of cases in order to avoid secondary transmission.

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Two other HAV-related outbreaks are simultaneously under investigation in four Nordic countries and among travellers returning from Egypt. A third food-borne HAV-related outbreak is under investigation in the USA. At present, there is no evidence of common links between these outbreaks.

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Annex

The European epidemic case definition defines a case as:

a symptomatic person with hepatitis A laboratory confirmation*

and

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

and

with HAV strain sharing sequence identical to the outbreak strain (gen bank number KF182323)

* Through at least one of the following three laboratory criteria:

- Detection of hepatitis A virus nucleic acid in serum or stool
- Hepatitis A virus specific antibody response
- Detection of hepatitis A virus antigen in stool
- Detection of hepatitis A virus antigen in stool