



RAPID OUTBREAK ASSESSMENT

Outbreak of hepatitis A virus infection in residents and travellers to Italy

28 May 2013

Summary

- Since 1 January 2013, 15 laboratory-confirmed cases of HAV infection have been reported in Germany, the Netherlands and Poland. All cases had travelled 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 the province of Trento and at national level. As the cases do not have a travel history outside the EU within their period of potential exposure, this strongly suggests an outbreak involving several EU Member States, with exposure currently occurring in one EU Member State.
- The descriptive epidemiology points at a continuous common source of infection. Preliminary epidemiological and environmental investigations indicate mixed frozen berries as the most likely vehicle of infection for this outbreak.
- A large number of cases reported consumption of berries prior to disease onset. In addition, HAV was isolated from a pack of mixed frozen berries at the residence of one case. RNA sequencing and interviews of patients should provide further evidence to confirm the hypothesis of mixed frozen berries as the vehicle of infection. Viral sequences information on human and food viral specimens are expected from Italy, and on human viral specimens from Poland. Italy is currently developing a multi-state case-control study.
- According to the available information, it is likely that additional cases will be identified and reported. ECDC invites Member States to raise awareness of a possible increase in HAV cases with a travel history to northern Italy, 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 confirm the link with the current outbreak in northern Italy.
- Travellers to areas reporting HAV outbreaks should be reminded of the availability of vaccination to prevent the risk of HAV transmission while travelling. Member States, in accordance with their national guidelines, may consider active or passive immunisation of close contacts to cases in order to avoid secondary transmission.
- ECDC, EFSA and the European Commission, in cooperation with the affected countries, will continue to closely monitor this event and will update the risk assessment as soon as new, relevant information becomes available.
- Another two HAV-related outbreaks are simultaneously under investigation in four Nordic countries and in travellers returning from Egypt. At present, there is no evidence of links between these outbreaks.

Public health issue

Outbreak of hepatitis A virus infection (HAV) in residents of Italy and travellers to Italy from Germany, Poland and the Netherlands.

Source and date of request

ECDC Round Table, 22 May 2013.

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, 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 was the most prevalent worldwide, with IA being reported more frequently than IB, and that sub-genotype IIIA was 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 below 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 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 faecal-oral route among close contacts (e.g. household contacts, sexual contacts, in 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 foodborne 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 populations 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 foodborne outbreaks. For example, France reported an HAV infection outbreak involving 59 cases where frozen semi-dried tomatoes were identified as the vehicle of infection in all primary cases [29]. Semi-dried tomatoes were also implicated in an outbreak involving 144 HAV cases in Australia in 2009 [30] and were suspected in a cluster of cases in the UK 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.

Event background information

Results of the epidemiological and microbiological investigations

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 autonomous 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 26 HAV cases in 2013 in the province of Trento, 11 of which were reported in May. No HAV cases had been reported in the same province in the previous two years. Italy also reports a 70% increase in HAV notifications at national level between March and May 2013 compared to the same months in 2012. 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, prepared a 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. The hotels are currently closed due to the mid-season break. Information on food items distributed is under analysis.

Preliminary information from some of the cases reported in Italy shows either a history of travel to the provinces of Trento and Bolzano, or consumption of frozen mixed berries as potential risk factors. Four Italian cases, who attended a private dinner in north-eastern Italy, reported consumption of berries. HAV was identified in mixed berries found in the freezer at the residence of the case that prepared the dinner.

Both human and food laboratory investigations are underway to define the genotype and sequence of the hepatitis A virus involved in human and in food samples.

Information on genotype and sequence is currently available only for the Dutch case. The case was associated with the sub-genotype IA and the sequence is available on EPIS-FWD or from ECDC upon request. This case did not report having eaten berries during the visit to Italy.

As of 24 May 2013, 41 cases of hepatitis A have been reported associated with the provinces of Trento and Bolzano: nine in Germany, five in Poland, one in the Netherlands and 26 in Italy, in the province of Trento.

Other information

There are currently two additional outbreaks of HAV affecting EU/EEA countries. The first is on-going in four Nordic countries [37] and imported frozen strawberries are the suspected vehicle of infection. The second outbreak involves travellers returning from Egypt to several European countries [38]; foodborne transmission is suspected, but no specific food item has been implicated to date. These two, so far unrelated outbreaks have been found to be associated with unique outbreak strains. At present, no similar strains have been identified in the outbreak affecting the north of Italy.

In November 2012, two RASFF notifications involved strawberries:

- Notification 2012.1603 from Germany: hepatitis A virus in strawberry yoghurt cake from Germany.
- Notification 2012.1534 from Belgium: hepatitis A virus in frozen strawberry cubes from China.

A sample of the contaminated frozen strawberries from China was shared by the Belgian food authorities with the Dutch public health laboratory for sequencing, but the virus could not be isolated for further typing.

On 17 May 2013, a RASFF notification (notification 2013.0694) was sent out by Italian food authorities regarding the mixed frozen berries found to be contaminated with HAV in north-eastern Italy. The frozen berry mix originated from Italy, with raw berry material from Poland, Bulgaria, Canada and Serbia. Following the notification, the distributor of the mixed frozen berries voluntarily withdrew these from the national market. Investigation into the traceability of the product is currently underway.

Threat assessment for the EU

An outbreak of HAV infections has been reported among travellers to different villages in the provinces of Trento and Bolzano, northern Italy, from Germany, Poland and the Netherlands. Italy is reporting an increase in HAV notifications, both in the province of Trento and at national level since the beginning of 2013.

The distribution of symptom onset over time suggests a common, continuous source outbreak with the majority of the non-Italian cases infected around mid-March. The most recent cases have been reported by Germany, Italy and Poland with onset of symptoms in early May, indicating that the outbreak is still on-going. Considering the delay in case reporting and the on average one-month-long incubation period, more cases are expected to be reported.

The consumption of berries reported by many of the cases, the previous positive HAV findings in frozen berries and the identification of mixed, frozen berries contaminated with HAV from the fridge of HAV cases strengthen the hypothesis that the origin of this outbreak is food-borne.

Genotype and RNA sequence analysis of strains from human and food samples may provide additional evidence to support the link between cases and berries. In addition, on-going epidemiological studies may provide additional evidence to confirm the hypothesis that mixed frozen berries are the vehicle of infection in this outbreak.

The voluntary withdrawal of the mixed frozen berries by the distributor has decreased the risk of infection for residents and visitors to northern 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 a part of the initial 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.

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-nonspecific questions to identify risk groups and agent-specific screening questions concerning a history of possible exposure to HAV. In non-affected areas temporary questions on recent (30 days before donation) travel history to affected areas (Trento and Bolzano) 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 [39].

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

For recent cases, and should new cases arise, ECDC recommends the use of the epidemic case definition prepared specifically for this outbreak.

ECDC is encouraging all Member States experiencing an increase in HAV cases with a travel history to the autonomous provinces of Trento and Bolzano in northern Italy to perform HAV RNA sequencing and to compare their results with the Dutch sequence available in EPIS-FWD.

It should be noted that the genotype and the RNA sequence of the virus isolated from the Dutch case returning from Italy are different to the sequence type revealed for the strains isolated in the non-travel related HAV outbreak currently affecting the Nordic countries. The same applies to the strains isolated in the outbreak associated with travel to Egypt which is affecting several EU/EEA countries. Consequently, at this point, no link can be established between the three simultaneous outbreaks. It is also possible, however, that the Dutch case is a sporadic case and not linked to the current outbreak in northern Italy.

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 travel history 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. As the cases do not have a travel history outside the EU within their period of potential exposure, this strongly suggests an outbreak involving several EU Member States, with exposure currently occurring in one EU Member State.

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Travellers to areas reporting HAV outbreaks should be reminded of the availability of vaccination to prevent the risk of HAV transmission while travelling. Member States, in accordance with their national guidelines, may consider active or passive immunisation of close contacts to cases in order to avoid secondary transmission.

ECDC, EFSA and the European Commission, in cooperation with the affected countries, 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 in travellers returning from Egypt. At present, there is no evidence of links between these outbreaks.

Contact

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Annex

The European epidemic case definition defines a case as:

a symptomatic person positive for HAV IgM
and

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

with travel history to Northern Italy
and

no other known hepatitis A exposure.