JOINT ECDC–EFSA RAPID
OUTBREAK ASSESSMENT

Outbreak of hepatitis A virus infection in four Nordic countries

15 April 2013

Main conclusions and recommendations

Between 1 October 2012 and 8 April 2013, 16 confirmed cases of hepatitis A virus (HAV) infections with subgenotype IB and identical RNA sequence were reported in four Nordic countries.

As none of the cases have a travel history outside the EU within their period of potential exposure, this represents a multicountry outbreak, with exposure currently taking place in the EU. The descriptive epidemiology indicates foodborne transmission originating from a persistent common source in the EU with possibly multiple vehicles of infection that are contaminated with viruses sharing an identical sequence.

Epidemiological investigations in affected countries strongly point towards frozen berries as the vehicle of infection. This hypothesis is being further investigated. RNA sequencing, interviews of cases in affected countries, food investigations, and purchase history research should provide additional evidence.

According to the available information, it is likely that additional cases will be identified and reported. ECDC encourages Member States to raise awareness about a possible increase in HAV subgenotype IB cases, report all new cases in EPIS-FWD, and use the common epidemic case definition and questionnaire to interview recent cases (available in EPIS-FWD and upon request).

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

Public health issue

Multicountry outbreak of hepatitis A (HAV) subgenotype IB in Denmark, Finland, Norway and Sweden.

Source and date of request

The ECDC Round Table requested a Rapid Outbreak Assessment of the available information on 9 April 2013 in response to an EWRS message posted by Denmark on 14 March 2013.

Consulted experts

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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 7500-nucleotide-long, linear, positive-stranded RNA genome. Genotypes are defined based on analysis of the 900 nucleotides of the complete capsid protein VP1. Based on this sequence, six HAV genotypes have been defined: genotypes I to VI. Genotypes I, II, and III, divided into subtypes A and B, infect humans. Data on genotype distribution show that genotype I is the most prevalent worldwide, with IA being reported more frequently than IB, and that subgenotype IIIA is prevalent in Central Asia. In areas of low endemicity, such as the United States and Western Europe, subgenotype IA dominates, but all genotypes and subtypes have been reported [1].

The disease, often asymptomatic or mild, particularly in children below five years, is a highly transmissible disease with an average incubation period of 28 to 30 days (range 15 to 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 between one and two weeks, up 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 is low (0.1 to 0.3%) but might be elevated (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, 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 treatment exists. Strict control measures like enforcing personal hygiene, contact tracing and administration of vaccine to exposed persons have shown to be effective [13, 14]. Active and passive immunisation is effective if administered within two weeks after 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 HAV notification rate in the EU has been decreasing consistently over the last 15 years, from 14.0 in 1997 to 2.6 per 100 000 population in 2010 [21, 22]. This most likely reflects improved living conditions as seroprevalence rates of HAV are highly 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 clear seasonal pattern with a peak in autumn, which may reflect increases following travel to endemic countries during holidays [22]. The low incidence in the EU populations can result in a high proportion of susceptible individuals if vaccination coverage is low. When the infection is then introduced, there is risk for infection among adolescents and young adults who have not encountered the virus at an early age or have not been vaccinated.

Food-borne transmission of HAV has been implicated in several outbreaks in the last years. EFSA and ECDC reported 11 outbreaks between 2007 and 2011, with strong evidence of hepatitis A as the causative agent. The implicated food vehicles were: fish and fish products, crustaceans, shellfish, molluscs and products containing these, vegetables, juices and semi-dried tomatoes [24-28]. For example, France reported an HAV infection outbreak involving 59 cases; 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 August and November 2012, the Netherlands reported two clusters of HAV IA infection with a large proportion of cases which had previously been 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 [32]; in 1997, an outbreak affecting 153 people, associated with consumption of frozen strawberries, was reported in Michigan, USA [33]. Orange juice was implicated in 2004 in a large outbreak with more than 300 cases of HAV infection in travellers from nine European countries returning from Egypt [34].

According to the Rapid Alert System for Food and Feed (RASFF) database, 18 samples of food were found to be contaminated with hepatitis A virus between 1999 and 2013. Hepatitis A virus was found in six EU countries (Belgium, the Czech Republic, Germany, Italy, the Netherlands, and Spain) in the following food items: shellfish (e.g. oysters, mussels, clams, scallops), semi-dried tomatoes, dates, frozen strawberries, and strawberry yoghurt cake.

Event background information

Results of the epidemiological and microbiological investigations

On 1 March 2013, the Staten Serum Institute in Denmark reported through the Epidemic Intelligence Information System for food- and waterborne diseases platform (EPIS-FWD) an increase in non-travel related human cases of HAV infection. The increase was associated with the subgenotype IB and an identical RNA sequence referred to as the 'outbreak sequence' in this document. The outbreak sequence has a length of 1231 nucleotides and contains the capsid protein VP1 gene including VP3/VP1 and VP1/2A junctions (see Annex 2).

Retrospective and prospective investigations in Denmark, Finland, Norway, and Sweden identified 16 non-travel-related HAV cases with the outbreak sequence (confirmed cases) and 40 additional non-travel-related HAV cases with unknown sequence (probable cases) between 1 October 2012 and 8 April 2013. The first confirmed case was reported in Denmark with onset of symptoms on 1 October 2012, and the last confirmed case was reported by Finland with onset of symptoms on 28 March 2013.

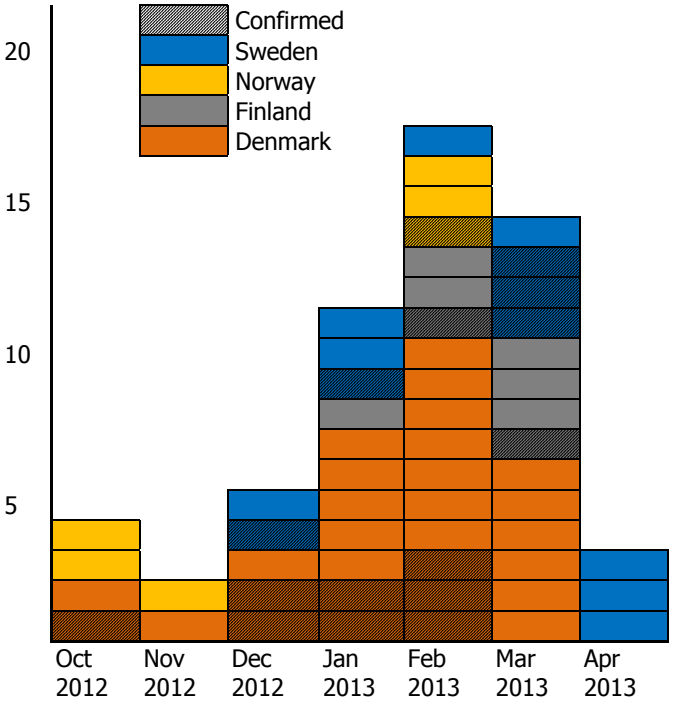
Table 1. Distribution of reported hepatitis A virus infections by confirmation status and affected country, 1 October 2012 – 8 April 2013

	Denmark	Finland	Norway	Sweden [b]	Total
Probable cases [a]	21	6	5	8	40
Confirmed cases [a]	8	2	1	5	16
Total	**29**	**8**	**6**	**13**	**56**

[a] *See Annex 1 for the recommended epidemic case definition for EU/EEA countries (adapted from the Danish case definition).*

[b] *Cases in Sweden are reported from 1 December 2012 to 8 April 2013.*

Figure 1. Distribution of probable and confirmed cases of hepatitis A virus by Member State and reporting month, October 2012–April 2013 (N=56)**



*** As of 8 April 2013*

Among confirmed cases, the median age is 26.5 years, ranging between 5 and 73 years; among probable cases, the median age is 30.5 years, ranging between 4 and 62 years. Twelve of the confirmed cases are female (75%) and 23 of the probable cases are female (58%).

A laboratory investigation in the affected countries is currently ongoing in order to sequence recent HAV cases with subgenotype IB.

Epidemiological investigations in Denmark included trawling questionnaires and a matched case-control study enrolling 25 cases and 50 controls. Most cases had consumed frozen berries; frozen berries in freshly prepared smoothies were found to be associated with illness (matched OR: 12.5, 95% CI; 2.8–54.8). Frozen strawberries were the food item with the strongest association with the disease (matched OR: 15.8, 95% CI; 3.6–68.6). An investigation based on the purchase history of detected cases is currently ongoing in Denmark, but no conclusions on a specific vehicle of infection, brand or food chain have yet been drawn.

Finland has used an adapted version of the Danish trawling questionnaire to interview cases. Of eight cases, six had been exposed to frozen berries, five had been exposed to frozen strawberries, but exposure to several other berries and mixed berry products was also reported.

Sweden has also used a questionnaire adapted from the Danish case-control study; the analysis of responses is still ongoing.

Norway performed a case-control study with an extended version of the questionnaire used in the Danish case-control study. No conclusive results were found.

In all affected countries, samples of frozen berries were taken from the freezers of HAV cases; laboratory investigations are ongoing. So far, no HAV could be isolated from food samples.

After Denmark's initial urgent inquiry on EPIS-FWD on 1 March 2013, four EU countries (Estonia, Germany, Ireland and the Netherlands) reported that they had not observed an unusual increase of HAV infections associated with the outbreak sequence.

Cases reported by the Netherlands in August and November 2012 through EPIS-FWD had been exposed to strawberries, and the isolated hepatitis A viruses shared an identical RNA sequence, yet this sequence was different from the current outbreak sequence.

Closely related HAV sequences (99% and 98.7%) were previously identified in Canada, France and the Netherlands in travellers returning from Egypt. The subgenotype IB shows 99% homology with GenBank accession number HQ401265 from Spain 2010, and 98% homology with EF190998 from Hungary 2006.

Other information

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.

The Belgian food authorities shared samples of the contaminated frozen strawberries from China with the Dutch public health laboratory for sequencing. Unfortunately, the virus could not be isolated for further typing.

INFOSAN issued an alert on 16 March 2013 to identify cases outside of the EU but so far no country has reported associated cases.

Public health action taken

Following the epidemiological investigations the food authorities in Denmark (14 March 2013), Finland (20 March 2013) and Sweden (11 April 2013) recommended that citizens should boil all frozen berries or berries of non-domestic origin before consumption.

On 12 April, the Norwegian Food Safety Authority (http://www.mattilsynet.no/) and the Norwegian Institute of Public Health (http://www.fhi.no) informed consumers on their official websites that the risk of contracting HAV through frozen imported berries can be reduced by boiling the berries prior to consumption.

Threat assessment for the EU

An outbreak of HAV infections has been reported in Denmark, Finland, Norway and Sweden since October 2012. The identification of an identical HAV sequence in cases from four different countries confirms a multinational outbreak. The distribution of cases over time suggests a persistent common-source outbreak. The most recent case had onset of disease on 28 March 2013, which indicates that the outbreak is still ongoing. Considering the delay in case reporting, the number of probable cases reported in March is currently underestimated.

Interviews with cases in all affected countries and a case-control study in Denmark linked cases to the consumption of berries, in particular frozen berries in smoothies. However, it has not yet been possible to identify any specific type of berry, brand, food chain or distribution channel. Due to the non-travel-related nature of these cases and the absence of linked cases outside the Nordic countries, the most likely hypothesis is transmission through a contaminated food item, potentially through frozen berries, distributed in Denmark, Finland, Norway and Sweden. It is possible, however, that the same contaminated food items are still distributed in other Member States.

At this stage, laboratory investigations on suspected food items, bought before the incubation period and collected in the residences of HAV cases, is still ongoing in the affected countries. Authorities are also researching the purchase history of consumers with HAV infection.

Food safety and public health authorities in the affected countries are actively collaborating to detect the vehicle of the infection in order to prevent the occurrence of additional cases.

For recent and new cases, ECDC recommends the use of the epidemic case definition and the Danish questionnaire; both were specifically adapted for these cases. The epidemic case definition (see Annex 1) and questionnaire were shared with all national contact points for food- and waterborne diseases through EPIS-FWD.

ECDC is encouraging all Member States experiencing an increase in non-travel-related HAV cases with subgenotype IB to perform HAV RNA sequencing and compare their results with the outbreak sequence available in EPIS-FWD and Annex 2.

The identification of frozen berries found positive for the outbreak strain through RNA sequencing would allow confirmation of the suspected vehicles of transmission and source of infection.

Considering that the suspected vehicle of infection (frozen berries) has a long shelf life, EU/EEA citizens may still be exposed to the contaminated food item. Therefore, additional cases of HAV infections are likely to be reported in the affected countries, with the possibility of additional Member States reporting cases linked to the outbreak. Any new cases linked to this outbreak should be reported on EPIS-FWD in order to enable effective monitoring and information sharing.

Conclusions

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

Contact

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Annex 1. Case definition

Recommended EU/EEA epidemic case definition for hepatitis A multicountry outbreak

Probable case

A person positive for HAV IgM antibodies and with clinical illness associated with hepatitis A

– and –

no travel history

– and –

no other known hepatitis A exposure (e.g. person who inject drugs)*

– and –

disease onset on *or* after 1 October 2012.

Confirmed case

A probable case with HAV subgenotype IB infection

– and –

sequence identical to the outbreak sequence.

Exclusion criteria

Being typed as having a subgenotype or sequence other than the outbreak subgenotype or sequence

– or –

epi-link to case with other subgenotype or sequence than the outbreak subgenotype or sequence.

(Note: Finland has so far not used this exclusion criterion.)

Annex 2: Outbreak sequence

Protein VP1 gene including VP3/VP1 and VP1/2A junctions:

GGTAAATGTTTACCTTTCAGCAATTAATTTGGAGTGTTTTGCTCCTCTTTATCATGCAATGGATGTCACCACACAGGTTGGAGAT
GATTCTGGAGGTTTTTCAACGACAGTTTCTACAGAGCAGAATGTTCCAGATCCACAAGTTGGCATAACAACCATGAAGGATTTAA
AGGGAAAAGCCAATAGAGGGAAAATGGATGTTTCAGGAGTGCAAGCACCTGTGGGAGCTATTACAACAATTGAGGATCCAGTTTT
AGCAAAGAAAGTACCTGAGACATTTCCTGAATTGAAACCTGGAGAATCCAGGCACACATCAGATCATATGTCTATTTACAAGTTT
ATGGGAAGGTCTCACTTTTTGTGCACTTTTACTTTCAATTCAAACAATAAAGAATACACATTTCCTATAACCTTGTCTTCAACCT
CCAATCCTCCTCATGGTTTGCCATCTACATTGAGGTGGTTTTTCAATTTGTTTCAGTTGTATAGAGGACCTTTAGATCTAACAAT
TATAATTACAGGAGCAACTGATGTGGATGGCATGGCCTGGTTCACTCCAGTAGGTCTTGCTGTTGATACGCCTTGGGTAGAAAAG
GAGTCAGCTTTGTCCATTGACTACAAAACTGCTCTTGGAGCTGTCAGATTTAATACAAGGAGAACAGGGAATATTCAGATCAGAT
TACCATGGTATTCTTATTTATATGCTGTGTCTGGAGCACTGGATGGTTTGGGAGATAAAACGGATTCCACATTTGGATTGGTCTC
TATTCAGATTGCAAATTACAATCACTCTGATGAATATTTGTCTTTTAGTTGCTATTTGTCTGTCACAGAACAATCAGAGTTTTAT
TTTCCCAGAGCTCCATTGAATTCAAATGCCATGTTATCCACTGAATCAATGATGAGCAGGATTGCAGCTGGAGACTTGGAGTCAT
CAGTGGATGATCCTAGATCAGAGGAGGACAGAAGATTTGAGAGTCACATAGAATGCAGGAAGCCATATAAAGAATTGAGATTAGA
AGTTGGGAAACAAAGACTCAAGTATGCTCAGGAAGAATTGTCAAATGAAGTACTTCCACCCCCTAGGAAAATTAAGGGACTGTTT
TCACAAGCCAAAATTTCTCTTTTTTATACTGAGGAGCATGAAATAATGAAATTTTCTTGGAGAGGAGTGACTGCTGATACTAGAG
CTTTAAGGAGGTTTGGATTCTCTTTGGCTGCTGGGAGAAGT