RAPID RISK ASSESSMENT

Outbreak of hepatitis A virus infection in travellers returning from Egypt

30 April 2013

Main conclusions and recommendations

From 1 November 2012 to 30 April 2013, 15 confirmed cases of hepatitis A virus (HAV) infections with subgenotype IB and identical RNA sequence, and 89 probable cases, have been reported in 14 EU/EFTA countries. All cases have a travel history to Egypt.

Due to the fact that 15 of these cases, identified in three different countries, have identical sequences, a multistate outbreak has been confirmed with exposure occurring in Egypt. The descriptive epidemiology points at a possible persistent common source of infection contaminated with viruses sharing an identical sequence.

Preliminary epidemiological investigations in affected countries do not definitively point at any particular source of infection. RNA sequencing of probable cases and interviews of probable and confirmed cases should enable the development of a more conclusive hypothesis on the source of infection.

According to the available information it is likely that additional cases will be identified and reported. ECDC invites Member States to raise awareness about a possible increase in HAV subgenotype IB cases with a travel history to Egypt, to report all new cases in the epidemic intelligence information system for food- and waterborne diseases platform (EPIS-FWD), using the common epidemic case definition and questionnaire to interview recent cases.

Travellers should be sensitised to HAV vaccination recommendations when travelling to HAV endemic areas[i]. Member States should consider vaccination of all contacts of HAV cases following their national guidance.

ECDC and the European Commission, in cooperation with the affected countries and WHO, will continue to closely monitor this event and will update the risk assessment as soon as new relevant information becomes available. In addition, all the European stakeholders will collaborate with the Egyptian authorities to investigate the source or vehicle of infection.

[i] See map of endemic areas: http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/hepatitis-a.htm

Public health issue

Multi-country outbreak of hepatitis A virus infection in travellers to Egypt from Denmark, Estonia, Finland, France, Germany, Ireland, Latvia, Lithuania, the Netherlands, Norway, Slovakia, Sweden, Switzerland and the United Kingdom (UK).

Source and date of request

ECDC decision on 24 April 2013 in response to an EWRS message posted by Norway on 19 April 2013.

Consulted experts

External experts

Line Vold (Norway), Emily MacDonald (Norway), Sofie Gillesberg Lassen (Denmark), Sofie Elisabeth Midgley (Denmark), Koye Balogun (England), Jonathan Crofts (England), Joanne Lawrence (England).

ECDC experts

Ettore Severi, Céline Gossner, Jaime Martinez Urtaza, Robert Whittaker, Dragoslav Domanovic, Johanna Takkinen.

Disease background information

Hepatitis A virus (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 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 showed that genotype I was the most prevalent worldwide, with IA being reported more frequently than IB, and that subgenotype IIIA was 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 is often asymptomatic or mild, particularly in children below five years, however the severity increases with age. HAV is a highly transmissible disease 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 between 1 to 2 weeks, or 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 to 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 faecal-oral route among close contacts such as 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: people who inject drugs [7–9] or use other illicit drugs [10], men having sex with men (MSM) [4], homeless people [10, 11] and those using contaminated blood products [12]. Regarding the latter, HAV transmission through blood is a rare but well documented event [13].

No specific treatment exists for HAV. Strict control measures like enforcing personal hygiene, contact tracing and administration of vaccine to exposed persons have shown to be effective [14, 15]. 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, surviving well in water, and resists several preservation methods used in the food industry, e.g. acidification or freezing [16–21], thus possible foodborne transmission should be investigated when cases are reported.

The notification rate in the EU for HAV shows a steady decreasing trend in the last 15 years, from 14.0 in 1997 to 2.6 per 100 000 population in 2010 [22, 23]. This most likely reflects improved living conditions as sero-prevalence rates of HAV are highly correlated with socioeconomic status and access to clean water and sanitation [24].

The highest notification rates in the EU are reported among the young (under 15 years old) [23]. There is a clear seasonal pattern with a peak in the autumn, which may reflect increases following travel to endemic countries during holidays [23]. 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.

Although the incidence of HAV infection in travellers to Egypt has decreased considerably since the 1980s [25], HAV incidence remains very high in the resident Egyptian population; a sero-prevalence study from 1996 found 100% of the 155 1-3-year-old children participating to be positive for HAV [26]; a sero-prevalence study in 2008 found that 61.4% of the 296 children tested between 2.5 and 18 years of age were positive for HAV [27]. The subgenotype IB is the predominant circulating strain in the country [28].

EU/EEA countries reported in the European Surveillance System (TESSy) an average per year of 52 HAV cases returning from Egypt between 2008 and 2011 (ranging between 75 in 2008 and 39 in 2009; there are no available data for 2012 yet). Clusters and outbreaks of cases among European travellers returning from Egypt have been previously reported [29–32]. The largest of these outbreaks involved more than 350 cases of HAV infection in travellers from nine European countries returning from Egypt in 2004; on this occasion the implicated vehicle of infection was orange juice.

Food-borne transmission of HAV has been implicated in several outbreaks within the EU in previous years. The European Food Safety Authority (EFSA) and ECDC have reported 11 outbreaks between 2007 and 2011 with strong evidence of hepatitis A as causative agent. The incriminated food vehicles were: fish and fish products (crustaceans, shellfish, molluscs and products containing these), sandwiches, vegetables, juices and semi-dried tomatoes [33–37].

Event background information

Results of the epidemiological and microbiological investigations

On 15 April 2013, the Norwegian Institute of Public Health reported through the Epidemic Intelligence Information System for food- and waterborne diseases platform (EPIS-FWD), that they had noticed an increase in travel related human cases of HAV infection. The increase was associated with travellers returning from Egypt and several cases had an identical RNA sequence referred to as the 'outbreak sequence' in this document. The outbreak sequence included two different genomic regions: a fragment of 441-nucleotide sequence of the VP1/2PA junction; and a second 466-nucleotide long fragment from the VP1 region.

The European epidemic case definition defines a probable 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 November 2012 and
- with travel history to Egypt two to six weeks before onset of symptoms (or date of testing if onset date not available) and
- no other known hepatitis A exposure.

And a confirmed case as: a probable case with RNA sequence matching the Norwegian outbreak sequence.

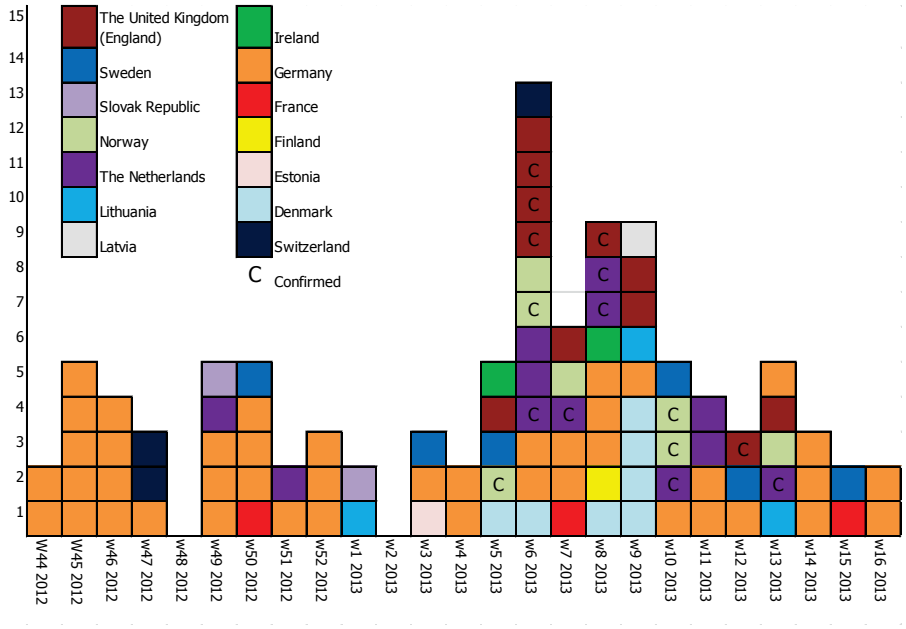
Exclusion criteria were: Different genotype (IB) or different sequence to the outbreak strain.

Following the post on EPIS-FWD, Denmark, Estonia, Finland, France, Germany, Ireland, Latvia, Lithuania, the Netherlands, Norway, Slovakia, Sweden, Switzerland and the United Kingdom reported that they had identified 89 probable cases and 15 confirmed cases. Onset of symptoms (or laboratory testing date for those with no available onset dates) ranged from 2 November 2012 to 17 April 2013.

Table 1. Distribution of reported hepatitis A virus infections with travel history to Egypt by confirmation status and reporting country, 1 November 2012–30 April 2013

Reporting country	Probable cases	Confirmed cases	Total
Denmark	7	0	7
Estonia	1	0	1
Finland	2	0	2
France	5	0	5
Germany	43	0	43
Ireland	2	0	2
Latvia	1	0	1
Lithuania	3	0	3
Norway	3	4	7
Slovak Republic	2	0	2
Sweden	6	0	6
Switzerland	3	0	3
The Netherlands	5	6	11
The United Kingdom (England)	6	5	11
Total	**89**	**15**	**104**

Figure 1. Distribution of probable and confirmed cases of hepatitis A virus by country and week of onset*, 1 November 2012–30 April 2013 (n=101)**



* *date of testing or date of notification was used when date of onset was missing.*

** *for three cases no precise date was available*

Cases appear to be distributed over time in three waves, with most cases occurring in the third wave, beginning week three of 2013. Only cases from the third wave were confirmed. The highest number of cases per week was reported during week six. In this week an identical RNA sequence was identified in all three countries reporting confirmed cases.

Among the 83 cases for whom information on sex was available, 47 (57%) were female; of the 15 confirmed cases, 10 (67%) were female. For the 83 cases with age information available, mean age was 40 ranging from four to 76 years; for confirmed cases, the mean age was 36, ranging from four to 63. Overall, eleven cases were reported to be hospitalised and two cases were reported to be deceased due to HAV disease.

Confirmed cases reported having travelled to at least two different locations in the Red Sea region (Sharm-El-Sheikh and Hurghada). Preliminary analysis of the places of stay pointed at several different hotels and resorts. Three clusters of confirmed cases were identified: two in Sharm-el-Sheikh (with five and two cases) and one in Hurghada (with three cases). Different airlines and different airports have been used, with most cases travelling on direct flights to their destination.

Information about vaccination status is available for 68 cases and all were unvaccinated.

Other information

After the initial Norwegian urgent inquiry on EPIS-FWD on 17 April 2013, Greece, Hungary, Iceland, Malta, Romania and Slovenia reported that they had not observed an unusual increase of HAV infections associated with travellers to Egypt or cases infected with the virus presenting with the outbreak sequence.

Under provision of the International Health Regulations (IHR) Norway informed WHO on 19 April 2013.

At least four cases (two in Denmark and two in France) presenting with HAV showing a different sequence from the outbreak strain were excluded as not fitting the case definition.

Large numbers of European tourists visit Egypt every year: Germany reports more than 1 200 000 travels by air in 2012, England reported an average of 540 000 annual visits in the last five years, Sweden reported about 170 000 travels in 2012, the Netherlands indicates about 241 000 visits per year in the last five years and Norway estimates that approximately 40 000 tourist go to Egypt per year. The number of English travellers to Egypt have been decreasing in the last five years, on the other hand, Swedish travellers to Egypt increased in 2012 compared to 2011; the number of travellers in the other three countries appeared to be stable in recent years [38].

Public health actions taken

ECDC coordinated the development of a common EU questionnaire to interview cases in the affected countries. This EU questionnaire is based on questionnaires recently used by the Netherlands and Norway to interview their respective cases and also on the questionnaire that was used during the HAV outbreak in German travellers returning from Egypt in 2004 [31]. The questionnaire, in English, is available in EPIS-FWD.

In addition, ECDC is liaising with the food-borne virus network in the Netherlands for the coordination and support of the microbiological investigations in the EU. The National Institute for Public Health and the Environment in the Netherlands developed a protocol for sequencing HAV cases. The protocol was shared on the EPIS-FWD platform on 27 April.

In coordination with WHO office for the European region and the WHO office for the Easter-Mediterranean region, ECDC is sharing the relevant information (e.g. list of hotels visited by the cases, case details) with the Egyptian authorities to support them in their local investigations.

The Danish, German and Norwegian Public Health Institutes and National Travel Health Network and Centre in England published information on their websites about the increased number of tourists returning from Egypt with HAV and they reinforced already existing vaccine-advice [39–41]. Previously, the Danish Public Health Institute informed the Association of Danish Travel Agents and Tour Operators about the increase of cases with travel to Egypt as well as the companies and hotels involved. Following this information, the Association of Danish Travel Agents and Tour Operators wrote a special announcement to all its members encouraging them to pay extra attention to inform customers to contact their own doctor for vaccination advice before travelling to Egypt. The affected tour operators also made contact with their quality assurance managers in Egypt.

In order to rapidly inform other countries about the increase in number of travellers infected with HAV returning from Egypt, Denmark, England, Germany, the Netherlands, Norway and Sweden published a rapid communication in Eurosurveillance on 25 April 2013 [38].

Threat assessment for the EU

In the context of this outbreak, 104 travellers returning from Egypt have been infected with HAV in Denmark, Estonia, Finland, France, Germany, Ireland, Latvia, Lithuania, the Netherland, Norway, Slovakia, Sweden, Switzerland and the United Kingdom (England) since November 2012. This information, related to a time period of less than seven months, compares with an average of 52 cases reported each year between 2008 and 2011. The significant increase of cases compared to the historical baseline ($p<10^{-8}$) as well as the identification of the same HAV sequence in cases from the Netherlands, Norway and England confirms a multinational outbreak.

The distribution of cases over time suggests a persistent source outbreak with three waves of cases, the last being the larger. The peak observed in week six suggests an increased exposure at the beginning of 2013, during the winter holidays in Europe when many tourists travel to Egypt. The most recent case had onset of disease on 17 April 2013. Therefore, the outbreak is still on-going. Considering the long incubation period and the delay in case reporting, the number of probable cases reported in March is currently underestimated. On the other hand, with more sequencing information becoming available, a number of probable cases will be excluded, being part of the baseline cases routinely reported in travellers returning from Egypt and not associated with this outbreak.

A strong hypothesis on the source of the infection has not yet been formulated but the planned multi-country survey of cases could shed more light on this. At this point of the investigation, the identification of cases with identical sequence who travelled to different locations in Egypt, from different airports and airlines, and stayed in different hotels may suggest a food product distributed to these holiday resorts as the vehicle of infection.

At this stage, laboratory investigations on probable cases and the use of a common questionnaire to interview probable and confirmed cases in the affected countries will enable the development of hypotheses about the source of the outbreak.

The current outbreak in several EU/EFTA countries poses a slightly elevated risk of secondary transmission through infected travellers after their return in Europe. Transmission through infected food handlers and through household contacts should be taken into consideration. There is also a very low risk of HAV transmission through blood donors. The use of specific questions concerning a history of clinical HAV and history of travel to the endemic countries, in addition to screening for HAV in blood donated, should prevent transmission through transfusion [42].

Despite the explicit vaccination recommendations in all involved countries for travellers to HAV endemic areas, almost no cases were vaccinated prior to travel. This outbreak suggests that vaccination recommendations for travellers to hepatitis A endemic countries should be reinforced.

ECDC, WHO and public health authorities in the affected countries are actively collaborating to identify the vehicle of the infection in order to prevent the occurrences of additional cases.

For recent cases, and should new cases arise, ECDC recommends the use of the epidemic case definition and the questionnaire adapted specifically for this outbreak. The epidemic case definition and the EU questionnaire were shared with affected countries and were posted on EPIS-FWD.

ECDC is encouraging all Member States experiencing an increase in HAV cases with a travel history to Egypt and subgenotype IB to perform HAV RNA sequencing and to compare their results with the outbreak sequence available in EPIS-FWD and in Annex 1.

Considering that the possible source of infection has not been yet identified, unimmunised EU/EFTA citizens travelling to Egypt, and particularly to the Red Sea region, may still be exposed to the source of infection. Therefore, additional cases of HAV infection are likely to be reported in the affected countries, with the possibility of new Member States reporting cases linked to the outbreak. Any new cases linked to this outbreak should be reported on EPIS-FWD to enable effective monitoring and information sharing.

It should be noted that the identical RNA sequence isolated from all confirmed cases returning from Egypt is different from the strains isolated in the non-travel related HAV outbreak currently affecting the Nordic countries. Consequently, at this point, no link can be established between the two simultaneously on-going outbreaks.

Conclusions and recommendations

From 1 November 2012 to 30 April 2013, 15 confirmed cases of HAV infections with subgenotype IB and identical RNA sequence and 89 probable cases have been reported in 14 EU/EEA/EFTA countries. All cases have a travel history to Egypt.

Due to the fact that 15 of these cases, identified in three different countries, have identical sequences, a multistate outbreak has been confirmed with exposure occurring in Egypt. The descriptive epidemiology points at a possible persistent common source of infection contaminated with viruses sharing an identical sequence.

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Travellers should be sensitised to HAV vaccination recommendations when travelling to HAV endemic areas[i]. Member States should consider vaccination of all contacts of HAV cases following their national guidance.

ECDC and the European Commission, in cooperation with the affected countries and WHO, will continue to closely monitor this event and will update the risk assessment as soon as new relevant information becomes available. In addition, all the European stakeholders will collaborate with the Egyptian authorities to investigate the source or vehicle of infection.

[i] See map of endemic areas: http://wwwnc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-diseases-related-to-travel/hepatitis-a.htm.

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Annex 1 Outbreak sequence reported by Norway to EPIS, 17/04/2013

NOR-2013-V9-Egypt_VP1/2PA:
CAATCACTCTGATGAATATTTGTCTTTTAGTTGCTATTTGTCTGTCACAGAACAATCAGAGTTTTATTTTCCCAGAGCTCCATT
GAATTCAAATGCCATGTTATCCACTGAATCAATGATGAGCAGAATTGCAGCTGGAGACTTGGAGTCATCAGTGGATGATCCTA
GATCAGAGGAGGACAAAAGATTTGAGAGTCACATAGAATGCAGGAAGCCATATAAAGAATTGAGATTAGAAGTTGGGAAACA
AAGACTTAAGTATGCTCAGGAAGAATTGTCAAATGAAGTACTTCCACCCCCTAGGAAAATTAAAGGACTGTTTTCACAAGCCA
AAATTTCTCTTTTTTATACTGAGGAGCATGAAATAATGAAATTTTCTTGGAGAGGAGTGACTGCTGATACTAGAGCTTTAAGG
AGGTTTGGATTCTCTTTGGCTGCTGGG

NOR-2013-V9-Egypt_VP1:
GATGTCACCACACAGGTTGGAGATGATTCTGGAGGTTTTTCAACGACAGTTTCTACAGAGCAGAATGTTCCAGATCCACAAGT
TGGCATAACAACCATGAAGGATTTAAAGGGAAAAGCCAACAGAGGGAAAATGGATGTTTCAGGAGTGCAAGCACCTGTGGGA
GCTATTACAACAATTGAGGATCCAGTTTTAGCAAAGAAAGTACCTGAGACATTTCCTGAATTGAAACCTGGAGAATCCAGGCA
CACATCAGATCATATGTCCATTTACAAGTTTATGGGAAGGTCTCACTTTTTGTGCACTTTTACTTTCAATTCAAACAATAAAGA
ATACACATTTCCTATAACCTTGTCTTCAACCTCCAATCCTCCTCATGGTTTGCCATCTACATTGAGGTGGTTTTTCAACTTGTT
TCAGTTGTATAGAGGACCTTTGGATCTAACAATTATAATTACAGGAGCAA