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# Increase in hepatitis A in tourists from Denmark, England, Germany, the Netherlands, Norway and Sweden returning from Egypt, November 2012 to March 2013

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Since November 2012, there has been an increase in reported cases of hepatitis A in tourists returning from Egypt in several European countries. As of 24 April, 80 HAV cases in travellers with symptom onset after 1 November 2012 visiting different areas in Egypt have been reported. Four cases from Norway, six cases from the Netherlands and five cases from England share an identical hepatitis A viral RNA sequence. This increase in cases suggests that vaccination recommendations for travellers to hepatitis A endemic countries should be reinforced.

## The alert

Since January 2013, six hepatitis A cases with travel history to Egypt during the incubation period (2–6 weeks after infection) were reported to the Norwegian Surveillance System for Communicable Diseases (MSIS). Typically, a single case of hepatitis A with travel history to Egypt is reported in Norway annually. Four of the six cases were genotyped and were found to be infected with the same genotype 1B hepatitis A virus (HAV)-strain. On 15 April 2013, the Norwegian Institute of Public Health posted an urgent inquiry on the Epidemic Intelligence Information System (EPIS) platform asking if any other European countries had observed an increase in HAV with travel history to Egypt in the same period. The genome sequence (N-terminal VP1 and VP1/P2A) shared by the four Norwegian cases was also provided at this time. Initially, four countries (Denmark, Germany, Netherlands and Sweden) responded that they had all observed an increased

number of hepatitis A patients with travel history to Egypt. On 19 April 2013, an alert was also sent through the European Commission Early Warning and Response System (EWRS). Subsequently, an increase in HAV cases in tourists returning to England was also reported. A multi-national investigation has been initiated in order to identify European Union/ European Economic Area (EU/EEA) countries with reported increases in HAV among travellers to Egypt, compare travel history among cases, and potentially identify any common exposures among travellers originating from different countries.

## Background

The incidence of HAV in European countries has decreased from 15.1 in 1996 to 3.9 per 100,000 population in 2006, attributable to improved sanitary and living conditions [1,2]. However, the reduction in circulation of HAV has led to an increase of susceptible individuals, resulting in several outbreaks in recent years, notably among European tourists visiting Egypt [3-6]. In Egypt, the burden of disease due to HAV is one of the highest in the world, with most HAV strains belonging to genotypes 1A and 1B. Recent studies of the presence of HAV in sewage and in the population have shown that the virus circulates widely in Egypt [7]. Egypt is a popular destination for travellers from many European countries (Table 1) [8-12]. HAV vaccination is generally recommended for all travellers to Egypt, although funding the vaccination for tourists or including the vaccine as part of the national vaccination plan is uncommon.

**TABLE 1**

Information on travel to Egypt for Denmark, England, Germany, the Netherlands, Norway and Sweden

Country	Information on travel to Egypt
Denmark	Unavailable
England	The estimated number of annual visits to Egypt by residents of England (on average between 2008 and 2012) is approximately 540,000. However, the number of visits to Egypt has been decreasing over the last four years (367,793 in 2012 compared to 673,227 in 2009).
Germany	According to the National Statistics Office in Germany, 1,275,872 persons travelled by air between Germany and Egypt from March 2012 through February 2013 (most recent data available).
Netherlands	Data from the Central Bureau of Statistics in the Netherlands indicates that the number of visits to Egypt has remained relatively stable over the last five years, with approximately 1%, or approximately 241,000, of all documented travels going to Egypt annually.
Norway	The Norwegian Embassy in Egypt estimates that approximately 40,000 Norwegians visit Egypt annually.
Sweden	According to the Swedish Travel and Tourist database an average number of 170,236 persons travelled annually to Egypt from Sweden during the last four years. The number for 2012 was 178,362 persons.

Hepatitis A cases are mandatorily notifiable in all EU/EEA countries. In Denmark, Germany, the Netherlands, Norway and Sweden, age, sex, vaccination status and location of travel is submitted as part of the notification. In England the same information is recorded at notification with the exception of vaccination status and location of travel which is collected as part of local public health surveillance. In Denmark, Statens Serum Institut performs sequencing for surveillance purposes of all IgM positive samples received from

local diagnostic laboratories. At the Norwegian and Dutch Institutes of Public Health samples are analysed for sequence comparison, on request, such as in suspected outbreaks. In Sweden and Germany, genotyping is not done routinely. In England, HAV IgM positive serum samples are genotyped and sequenced as part of the enhanced surveillance programme.

### Case definition for the outbreak investigation

A probable case is defined as a symptomatic person positive for HAV IgM with onset of symptoms or testing date (if date of symptom onset is unavailable) after 1 November 2012 and with travel history to Egypt two to six weeks before onset of symptoms/date of testing (if date of symptom onset is unavailable) and with no other known hepatitis A exposure.

A confirmed case is defined as a probable case with RNA sequence matching the Norwegian outbreak sequence. HAV cases are excluded if they are a different genotype or have a different sequence to the outbreak strain. Probable cases that are found to have a different genotype or a different sequence are being excluded at this time.

### Description of cases

As of 24 April, 80 HAV cases in travellers with symptom onset after 1 November 2012 visiting different areas in Egypt have been reported (Table 2). Overall, 46%\* of cases are male, and the ages of cases range from three to 76 years (Table 3). Onset of symptoms of HAV cases ranged from week 44 of 2012 (29 October to 4 November) to Week 15 of 2013 (8 April to 14 April) (Figure). Cases occurred in several waves, with a peak in Week 6 (4 February to 10 February). Cases from England, the Netherlands and Norway sharing the outbreak strain are clustered between Week 5 and Week 13. Cases travelled primarily to Sharm-El-Sheik and Hurghada (Table 4), with cases linked by genotyping reporting travel history to both Sharm-El-Sheik and Hurghada.

**TABLE 2**

Hepatitis A cases in travellers to Egypt from Denmark, England, Germany, the Netherlands, Norway and Sweden with symptom onset date<sup>a</sup> after 01 November 2012 as of 24 April 2013 (n=80)

Country of origin	Total number of outbreak cases	Number of probable cases	Number of confirmed cases	Mean number of cases in the same period 2007–2012
Denmark	7	7	0	1.2
England	11	6	5	2.2
Germany	39	39	0	10
Netherlands	11	5	6	2.2
Norway	6	2	4	1.4
Sweden	6	6	0	1.8
Total	80	65	15	–

<sup>a</sup> Date of testing was used when date of symptom onset was unavailable.

**TABLE 3**

Sex and age of hepatitis A cases related to Egypt travel from Denmark, England, Germany, the Netherlands, Norway and Sweden with symptom onset date<sup>a</sup> after 01 November 2012 as of 24 April 2013 (n=80)\*

Country of origin	Median age (range)	Proportion of males (%)
Denmark	28 (10–57)	6/7 (86)
England	30 (4–56)	4/11 (36)
Germany	48 (4–76)	19/39 (49)
Netherlands	38 (21–59)	3/11 (27)
Norway	56 (22–63)	2/6 (33)
Sweden	17 (3–75)	3/6 (50)

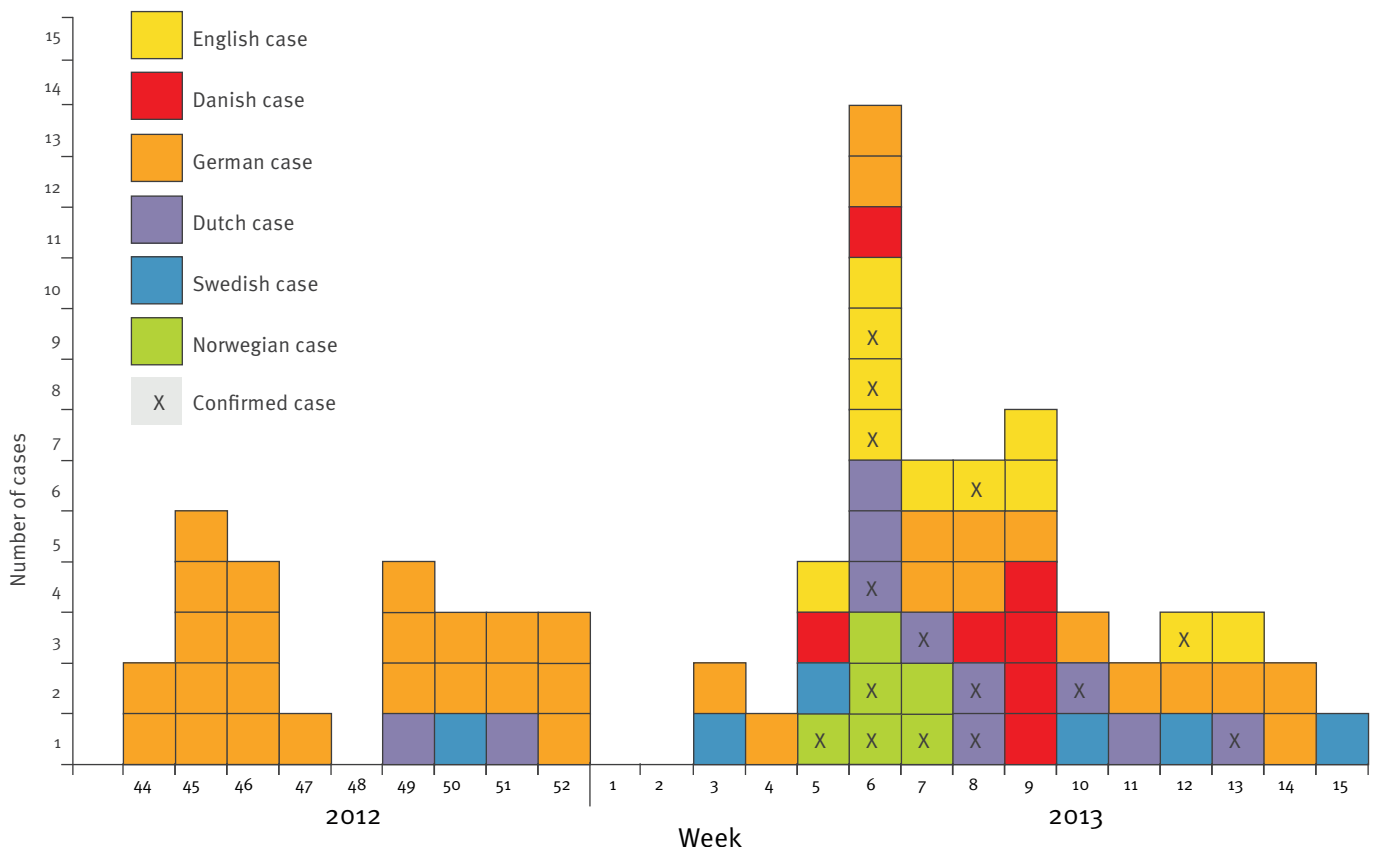
<sup>a</sup> Date of testing was used when date of symptom onset was unavailable.

### Interviews of Norwegian and Danish cases

In Norway, all six cases have been interviewed using a short questionnaire designed to collect information on clinical information, travel history and places of food consumption. Five cases travelled to Sharm-El-Sheik with the same travel company, but stayed in two different hotels; the sixth case travelled to Hurghada with a different company. Four of the cases have been hospitalised. In Denmark, five of seven cases have been interviewed using a similar questionnaire to that used in Norway. Three travelled to Sharm-El-Sheik with the same travel company and stayed at the same hotel. One case also travelled to Sharm-El-Sheik and stayed at a different hotel. One case travelled to Hurghada with a third company. All cases from Norway and Denmark stayed at hotels that were all-inclusive or had on-site restaurants, and all cases reported eating exclusively or almost exclusively from the hotel facilities. A multinational investigation on common exposures among the reported cases from all countries, including hotels, airlines, organised tours and food items, is currently being considered.

**FIGURE**

Distribution of probable and confirmed hepatitis A cases with travel history to Egypt, by country of origin and week of symptom onset after 01 November 2012 as of 24 April 2013



Only 78 of the total 80 cases are represented on the figure as symptom onset date was only available for 37 of 39 German cases.

**TABLE 4**

Location of travel in Egypt of total hepatitis A cases from Denmark, England, Germany, the Netherlands, Norway and Sweden with symptom onset date<sup>a</sup> 01 November 2012 as of 24 April 2013 (n=80)

Country of origin	Location of travel in Egypt					
	Number of cases (number of confirmed outbreak cases)					
	Sharm-El-Sheik	Hurghada	Marsa Alam	Cairo	Multiple locations	Unknown
Denmark	3 (0)	1 (0)	0 (0)	0 (0)	1 (0) <sup>b</sup>	2 (0)
England	6 (4)	2 (1)	0 (0)	1 (0)	1 (0) <sup>c</sup>	1 (0)
Germany	2 (0)	12 (0)	1 (0)	2 (0)	2 (0) <sup>d</sup>	20 (0)
Netherlands	2 (0)	3 (3)	0 (0)	0 (0)	0 (0)	6 (3)
Norway	5 (4)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Sweden	2 (0)	1 (0)	0 (0)	0 (0)	0 (0)	3 (0)
<b>Total</b>	<b>20 (8)</b>	<b>20 (4)</b>	<b>1 (0)</b>	<b>3 (0)</b>	<b>4 (0)</b>	<b>32 (3)</b>
<b>Percentage of all cases</b>	<b>25</b>	<b>25</b>	<b>1</b>	<b>3</b>	<b>4</b>	<b>40</b>

<sup>a</sup> Date of testing was used when date of symptom onset was unavailable.

<sup>b</sup> The case went on a Nile cruise and to Sharm-El-Sheik.

<sup>c</sup> The case took part in a Red Sea cruise and traveled to Sharm-El-Sheik.

<sup>d</sup> One case participated in a Nile cruise, the other case went on a Nile Cruise, to Hurghada and to Cairo.

## Laboratory investigations

The genome sequence (N-terminal VP<sub>1</sub> and VP<sub>1</sub>/P<sub>2</sub>A) of HAV from four of the six Norwegian cases was identical (HAV genotype 1B); the remaining cases have not yet been sequenced. The outbreak sequence (provided at the end of the article), has been submitted to the Foodborne Viruses in Europe network (FBVE network), and is being submitted to Genbank. The Netherlands has acquired sequence data from six cases, of which all share an identical RNA sequence in the overlapping region of 440 nucleotides in the VP<sub>1</sub>/P<sub>2</sub>A region with the outbreak strain. England has identified identical sequences to those reported by Norway in five laboratory-confirmed cases. Denmark and England have excluded two and four cases, respectively, based on genotyping, which are not presented here, including several 1B HAV strains in cases with travel history to Egypt during the outbreak period. In Sweden and Germany, genotyping is being considered.

The Nordic countries, Germany, the Netherlands and England have relatively few cases of HAV reported annually. If an increase in cases is detected in several countries simultaneously, genotyping and sequencing potentially enables linking of cases internationally. However, many countries do not routinely type to this level, which may explain why so few countries have reported an increase following the messages sent through EPIS and EWRS. The response from specific countries in this outbreak may also have been attributable to the heightened awareness due to the concurrent outbreak of HAV in Nordic countries [13]. The initial response from the represented countries may also reflect travel patterns in people from colder climates during the winter months.

## Vaccination recommendations

Despite the explicit vaccination recommendations in all involved countries for travellers to Egypt, almost no cases were vaccinated prior to travel. In Denmark, England, the Netherlands, Norway and Sweden all cases with known vaccination status were unvaccinated. In Germany one case reported full course of vaccination and is being interpreted as a vaccination failure. All other cases from Germany with available information were unvaccinated. This increase in cases reported from European travellers returning from Egypt suggests that European public health authorities should consider reinforcing HAV vaccine recommendations for tourists travelling to endemic areas, especially Egypt. Although HAV vaccination is recommended, with the exception of England, none of the involved countries fund the vaccination of tourists or include the vaccine as part of the national vaccination plan. In England the hepatitis A vaccine is often provided free of charge by general practitioners.

The lack of vaccination may be partly explained by the perception among travellers that the risk of acquiring hepatitis A is low when engaging in organised holidays or activities. All interviewed cases in Norway and Denmark stayed in hotels that were either all-inclusive or had restaurants on-site. Information regarding participation of HAV cases in specific activities such as cruises, day trips, organised tours and recreational activities that may present a risk of exposure is unavailable at this time. Public health authorities may wish to engage travel companies in order to ensure travellers are informed about vaccination requirements prior to travel. Because of the increasing number of travellers booking tickets online, an automated reminder

when booking tickets has also been suggested as a means of increasing vaccination coverage [14]. Further investigation into the level of knowledge and attitudes among tourists visiting countries where hepatitis A is prevalent, particularly those joining chartered tours, could assist in targeting information about HAV vaccination. The collection of this information is being planned as part of the next stage of the multi-national investigation.

## Conclusions

This investigation into an outbreak of cases of hepatitis A in tourists to Egypt from several EU/EEA countries is ongoing and at this time the dynamics of the increase in cases are unclear. Although the background level in Egypt of the HAV strain involved in this outbreak is unknown at this time, a unique sequence among cases may indicate a common exposure. This hypothesis is potentially reinforced as confirmed cases appear to be temporally clustered between Week 5 and Week 10 of 2013. As of 25 April 2013 a total of 13 countries have responded to the EPIS urgent inquiry that they have at least one case which may match the probable case definition and are being investigated. The authors would like to invite other countries that have experienced an increase in hepatitis A in tourists returning from Egypt, or that have detected the sequences reported here, to share their data with the outbreak team. The National Institute for Public Health and the Environment in the Netherlands (RIVM) and Norwegian Institute of Public Health (depending on capacity) offer their sequence facilities to countries where sequencing is not among routine procedures. Please be aware that an actual rise may only be noted through typing. Sequences can be shared and compared in an international HAV database prepared by RIVM, for which access can be obtained by contacting fbve@rivm.nl.

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## Authors' contribution

EM contributed to the descriptive study in Norway, gathered information from other countries and drafted the manuscript as the lead writer. MF, CF and MG contributed with data from Germany and commented on the manuscript. SGL conducted the descriptive study in Denmark and commented on the manuscript, SEM contributed to the laboratory sequencing and analysis for Denmark and commented on the manuscript, LS contributed with data from Sweden and commented on the manuscript, AS and LVo contributed with data on the Norwegian cases and commented on the manuscript. LVo posted the initial message in EPIS for Norway,

gathered data from the different countries and took initiative to writing up the Eurosurveillance rapid communication. KSJ contributed to the laboratory sequencing and analysis for Norway and commented on the manuscript. MK, WvP, JS and LVe all contributed with data from the Netherlands and commented on the manuscript. SLN carried out the genotyping and sequencing of the cases from England and JL JC and KB contributed to collating epidemiological data and all commented on the manuscript.

## Outbreak sequence information

NOR-2013-V9-Egypt\_VP1/2PA:

```
CAATCACTCTGATGAATATTTGCTTTTTAGTTGCTA
TTTGTCTGTACAGAAACAATCAGAGTTTTATTTTCC
CAGAGCTCCATTGAATTCAAATGCCATGTTATCCAC
TGAATCAATGATGAGCAGAATTGCAGCTGGAGACT
TGGAGTCATCAGTGGATGATCCTAGATCAGAGGAG
GACAAAAGATTTGAGAGTCACATAGAATGCAGGAA
GCCATATAAAGAATTGAGATTAGAAGTTGGGAAAC
AAAGACTTAAGTATGCTCAGGAAGAATTGTCAAATG
AAGTACTTCCACCCCTAGGAAAATTAAGGACTGT
TTTCACAAGCCAAAATTTCTTTTTTATACTGAGGAG
CATGAAATAATGAAATTTCTTGGAGAGGAGTGACT
GCTGATACTAGAGCTTTAAGGAGTTTGATTCTCTT
TGGCTGCTGGG
```

NOR-2013-V9-Egypt\_VP1:

```
GATGTCACCACACAGGTTGGAGATGATTCTGGAGGT
TTTTCAACGACAGTTTCTACAGAGCAGAATGTTCCAG
ATCCACAAGTTGGCATAACAACCATGAAGGATTTAAA
GGGAAAAGCCAACAGAGGGAAAATGGATGTTTCAG
GAGTGCAAGCACCTGTGGGAGCTATTACAACAATTGA
GGATCCAGTTTTAGCAAAGAAAGTACCTGAGACTTT
CCTGAATTGAAACCTGGAGAATCCAGGCACACATCAG
ATCATATGTCCATTTACAAGTTTATGGGAAGGTCTCAC
TTTTTGTGCACTTTTACTTTCAATTCAAACAATAAGAA
TACACATTTTCTATAACCTTGCTTCAACCTCCAATCCTC
CTCATGGTTTGCCATCTACATTGAGGTGGTTTTTCAACT
TGTTTCAGTTGTATAGAGACCTTTGGATCTAACAAAT
ATAATTACAGGAGCAA
```

## Conflict of interest

None declared.

## \*Authors' correction:

The value of 46% in the sentence 'Overall, 46% of cases are male, and the ages of cases range from three to 76 years (Table 3)' was erroneously written as 49% in the original publication. In addition in Table 3, for England, the values of 4/11 for the proportion of males, and 36 for the respective percentage were originally 7/11 and 64. These mistakes were corrected on 26 April 2013.

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# Ongoing multi-strain food-borne hepatitis A outbreak with frozen berries as suspected vehicle: four Nordic countries affected, October 2012 to April 2013

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**A food-borne outbreak of hepatitis A in Denmark was notified to other countries on 1 March 2013. A case-control study identified frozen berries eaten in smoothies as potential vehicle. In the following weeks, Finland, Norway and Sweden also identified an increased number of hepatitis A patients without travel history. Most cases reported having eaten frozen berries at the time of exposure. By 17 April, 71 cases were notified in the four countries. No specific type of berry, brand or origin of berries has yet been identified.**

## Identification of the outbreak

In February 2013, Denmark registered a higher than usual number of notified patients with hepatitis A virus (HAV) infection who had no travel history 2–6 weeks before symptom onset or other known risk factors for HAV infection. Concurrently, viruses from six hepatitis A patients who had been notified since October 2012 were shown to be genotype 1B with the same sequence across 1,231 nucleotides of the capsid protein VP1 gene, including the VP3/VP1 and VP1/2A junctions (GenBank accession number KC876797). An outbreak investigation was initiated and an urgent enquiry was posted through the European Epidemic Intelligence Information System for food- and waterborne diseases (EPIS-FWD) on 1 March 2013, asking if any other countries had also seen an increase in the number of domestic patients with HAV infection. The sequence was also shared within the International HAV laboratory network managed in the Netherlands [1].

Following the urgent enquiry, Finland, Norway and Sweden also reported an increase in the number of patients with HAV infection who had no history of

foreign travel (Table 1). Each country identified one or more cases with HAV genotype 1B that had identical sequences to the HAV of the Danish cases. The outbreak is still ongoing.

The following outbreak case definition was defined in Denmark and applied in all four countries, except that Sweden only includes cases from 1 December 2012 onwards and Finland is not excluding cases with other potential risk factors.

- A *probable* case is defined as a person living in Denmark, Finland, Norway or Sweden with clinical illness compatible with HAV infection and positive for HAV IgM antibodies, no travel history outside of Nordic countries two to six weeks before onset of symptoms or having other known HAV risk factors, such as intravenous drug use, homelessness or male-to-male sexual contact and symptom onset on 1 October 2012 or later.
- A *confirmed* case is defined as a probable case typed with HAV genotype 1B with a sequence that differs by no more than 2% from sequence KC876797.
- We *exclude* all patients with HAV genotypes other than 1B, or patients with an HAV genotype 1B sequence that differs by more than 2% from sequence KC876797, or patients with an untyped HAV from the household of an excluded patient with HAV infection.
- A *secondary* case is defined as a probable or confirmed case with close contact to a probable or confirmed case and having symptom onset two or more weeks after that of the primary case.



**TABLE 1**

Hepatitis A patients by travel history, virus genotype and outbreak case type, Denmark, Sweden, Norway and Finland, 1 October 2011–17 April 2012 (n=53) and 1 October 2012–17 April 2013 (n=180)

Description	Number of patients							
	Denmark		Sweden		Norway		Finland	
	1 Oct 2011– 17 Apr 2012	1 Oct 2012– 17 Apr 2013	1 Dec 2011– 17 Apr 2012	1 Dec 2012– 17 Apr 2013	1 Oct 2011– 17 Apr 2012	1 Oct 2012– 17 Apr 2013	1 Oct 2011– 17 Apr 2012	1 Oct-2012– 17 Apr 2013
<b>Total</b>	<b>11</b>	<b>64</b>	<b>16</b>	<b>68</b>	<b>23</b>	<b>31</b>	<b>3</b>	<b>17</b>
<b>Travel history</b>								
Travel in foreign country	4	20	8	27	15	15	2	7
No foreign travel	7	43	7	34	7	16	1	10
Unknown	0	1	1	7	1	0	0	0
<b>Genotype</b>								
1A	0	2	4	3	0	6	0	0
1B	6	24	1	8	0	10	0	3
3A	3	2	0	1	0	3	0	0
Unknown <sup>a</sup>	2	36	11	56	23	12	3	14
<b>Outbreak cases<sup>b</sup></b>								
Confirmed	NA	13	NA	8	NA	4	NA	3
Probable	NA	22	NA	12	NA	2	NA	7

NA: not applicable.

<sup>a</sup> Typing is still ongoing on some of the patients for whom the viral genotype is currently unknown.

<sup>b</sup> The number of outbreak cases is a subset of the total number of hepatitis A patients in each country.

## Outbreak investigation in Denmark

HAV disease is notifiable in Denmark: physicians report patients directly to Statens Serum Institut (SSI). Diagnostic testing is performed at local laboratories and SSI using serology. Virus typing is carried out only at the SSI Microbiological Diagnostics and Virology Department, which receives IgM-positive diagnostic samples for confirmatory identification of virus RNA by PCR and further characterisation by genotyping and sequencing. Viral RNA is extracted, typed and sequenced at the VP1 region using a protocol supplied by H. Norder (personal communication, 21 December 2006), including some previously published primer sequences [2].

As of 17 April 2013, a total of 35 cases, including 13 confirmed, and two secondary cases have been identified in Denmark: 21 were female and the median age was 22 years (range: 4–66 years). Date of symptom onset ranged from 1 October 2012 to 27 March 2013 (Figure). Two families with two and three cases respectively, as well as a group of four friends exposed at the same time, were identified.

The HAV strain with GenBank accession number KC876797 (sequence 1) was identified in 10 cases. The HAV strain with GenBank accession numbers KC876798 and KC876799 (sequence 2), which differs by 1.7% over 847 base pairs from sequence 1, was identified in three of the four friends.

On 4 March 2013, the Netherlands and France reported via the EPIS-FWD and HAV laboratory network that sequence 1 resembles HAV sequences from hepatitis A cases returning from Egypt. Sequence 1 also showed 98.7% identity with HAV sequences from a Canadian outbreak associated with pomegranate seeds imported from Egypt in 2012 (Dr Anton Andonov, personal communication, 19 March 2013). Furthermore, the outbreak strains are closely related to the strain presently seen in European tourists returning from Egypt [1]. Sequence 1 also shows 99% homology with GenBank accession number HQ401265 from Spain in 2010 and 98% homology with EF190998 from Hungary in 2006.

## Epidemiological investigation

A total of 11 initial cases were interviewed using a trawling questionnaire to identify possible common exposures, such as common events or consumption of foods implicated in other food-borne hepatitis A outbreaks (e.g. shellfish, semi-dried tomatoes, dried fruit, berries and edamame beans). Based on the information obtained and the temporal distribution of cases, a case–control study was set up to test the hypothesis of an item on a list of long shelf-life food items being the source of infection.

The case–control study included 25 probable and confirmed cases and 50 controls and was carried out with questionnaires in telephone interviews from 6 to 13 March 2013. Secondary cases were not included. Controls were identified using the Danish population

registry, matched 1:2 by age, sex and municipality. Controls with a history of hepatitis A infection or vaccination were excluded at the interview phase. Cases were asked about exposures in the six weeks before onset of symptoms and controls six weeks before the interview. One case was later excluded from the analysis, as the person was found to have HAV genotype IA.

Of the 24 cases, 18 had eaten frozen berries used in freshly prepared smoothies (matched odds ratio (MOR): 12.5; 95% CI: 2.8–55) and 20 had eaten frozen strawberries (MOR: 15.8; 95% CI: 3.6–69). Statistically significant associations were found univariably with seven food items: frozen strawberries, frozen raspberries, frozen blueberries, other frozen berries, dates, figs and sun-dried tomatoes eaten in a dish other than salad or a sandwich (Table 2). Only six cases reported consuming sun-dried tomatoes, dates or figs. For the last two food items, a biased association may have arisen from the fact that the exposure period of cases – but not of controls – in a few instances included Christmas, at which dried dates and figs are traditionally eaten in Denmark. No specific supermarket chain was associated with illness of cases.

The results were communicated directly to the Danish Food and Veterinary Administration and to the public through a news item on the SSI website. The international community was informed through the European Early Warning and Response System (EWRS) on 14 March 2013. Concurrently, the Danish Veterinary and Food Administration recommended boiling all frozen berries for at least one minute before consumption.

### Outbreak investigation in Finland, Norway and Sweden

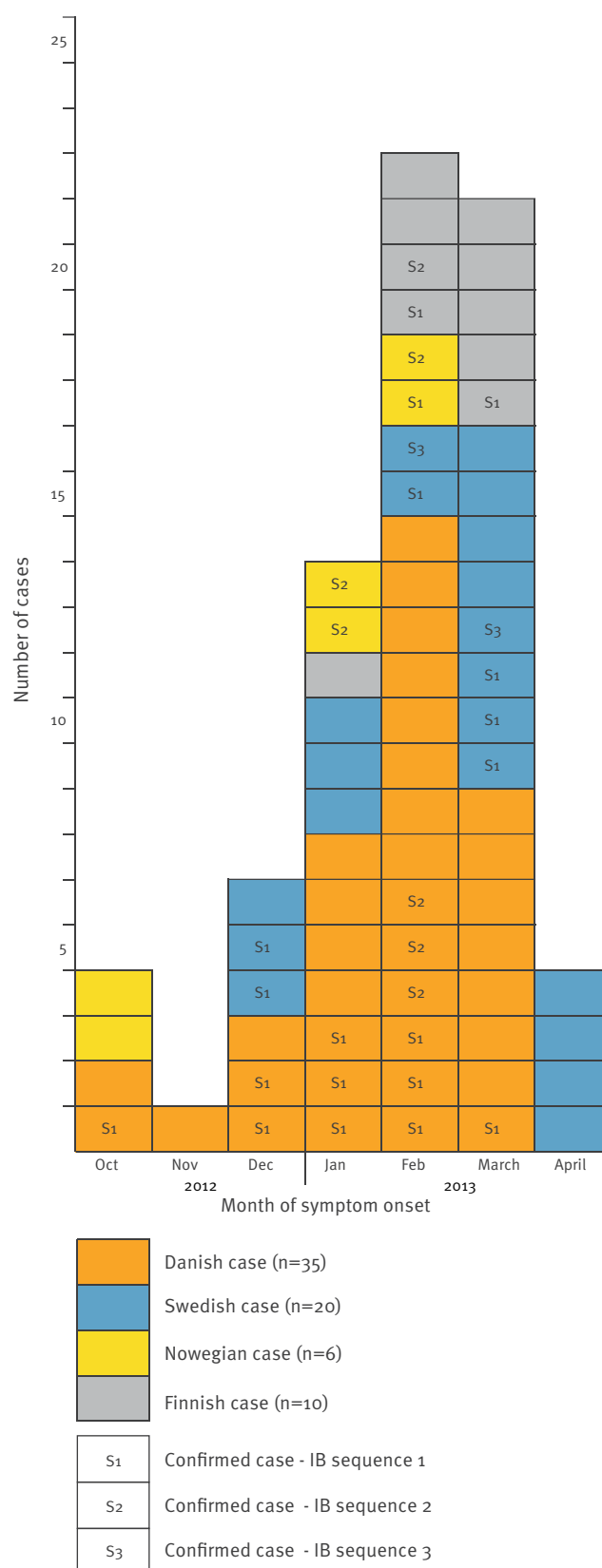
As of 17 April 2013, 36 cases, of whom 15 were confirmed, have been identified in Finland, Norway and Sweden, giving a total of 71 cases in the four countries (Table 1). Finland and Norway have reported confirmed cases with sequence 1 and 2. In Sweden, two of the eight confirmed cases have an HAV IB sequence with 2% difference to sequence 1 and 1% difference to sequence 2 (called sequence 3).

The overall median age for cases and the median age for confirmed cases is 25 years (range: 3–78 years); 43 cases are female. In Norway and Sweden (but not Finland), more women are affected than men. The distribution of cases by month and HAV sequence type is shown in Figure 1. As of 17 April 2013, Sweden is the only country with cases with symptom onset in April. An increased number of travel-related hepatitis A patients in the same time period (Table 1) may be explained in part by patients infected in Egypt [1].

Outbreak investigations are ongoing in Sweden, Finland and Norway. In Sweden, the Danish case questionnaire was sent to all cases. Of 12 cases, who answered the questionnaire as of 15 April, nine reported eating frozen berries at the possible time of infection. Among the seven confirmed cases who replied to the

**FIGURE**

Probable and confirmed hepatitis A cases by month of symptom onset<sup>a</sup>, country and sequence type, in Denmark, Sweden<sup>b</sup>, Norway and Finland, 1 October 2012–17 April 2013 (n=71)



<sup>a</sup> When date of symptom onset was unknown, date of diagnosis or date of sampling was used.

<sup>b</sup> Cases in Sweden notified from 1 December 2012 to 17 April 2013.

**TABLE 2**

Univariable matched analysis of association of hepatitis A and food consumption<sup>a</sup> in Denmark, 6–13 March 2013 (24 cases, 48 controls)

Exposure	Matched odds ratio	95% confidence interval	Number (%) of cases with exposure
Frozen berries in freshly prepared smoothie	12.5	2.8–55	18 (75)
Frozen berries eaten in dessert or ice cream	3.2	1.0–10	8 (33)
Frozen berries eaten in a different way	10.0	1.2–86	5 (21)
<b>Frozen berry type</b>			
Strawberry	15.8	3.6–69	20 (83)
Raspberry	5.6	1.8–17	14 (58)
Blueberry	4.3	1.3–14	11 (46)
Mixed berries <sup>b</sup>	–	–	11 (46)
Other berries	13.9	1.7–110	7 (29)
<b>Other exposures</b>			
Dates	12.8	1.5–110	6 (25)
Figs	4.0	1.0–16	6 (25)
Sun-dried tomatoes <sup>c</sup>	10.0	1.2–86	6 (25)

<sup>a</sup> Only statistically significantly associated food items are shown.

<sup>b</sup> No controls ate mixed berries.

<sup>c</sup> Eaten in dishes other than salads and sandwiches.

questionnaire, five reported having eaten frozen berries. Finland and Norway conducted trawling interviews with all patients with HAV infection. In Finland, seven cases had eaten frozen berries at the possible time of infection. All three confirmed cases in Finland had all eaten frozen strawberries; two had also eaten other types of berries (raspberries, blueberries and mixed berries). In Norway, all six cases reported having eaten frozen berries at the possible time of infection and all four confirmed cases reported having eaten frozen strawberries.

From 18 to 21 March 2013, Norway conducted a matched case–control study including 10 patients and 25 controls. Cases were patients with HAV infection or persons epidemiologically linked to a confirmed HAV case, and having similar symptoms with no travel history in the two months before symptom onset, assumed primary infection and symptom onset from 1 November 2012 to 21 February 2013. Controls were selected from the Norwegian population register and matched by age, sex and municipality. No food items were found to be statistically significantly associated with illness; however, this study suffered from limited power due to low case numbers. Eating frozen berries had a MOR of 2.7 (95% CI: 0.5–16); six of the cases reported having eaten frozen berries. MORs were also increased for blackberries (MOR: 8.5; 95% CI: 0.9–78), frozen strawberries (MOR: 7.4; 95% CI: 0.8–64) and frozen raspberries (MOR: 3.1; 95% CI: 0.5–18). Typing later showed that only four of the 11 ‘cases’ in the case–control study met the outbreak case definition. This may explain the lack of a significant association with frozen berries.

### Trace-back investigations and laboratory testing of food samples

Currently, trace-back investigations are being performed with the aim of identifying specific types or brands of frozen berries consumed by cases. Trace-back analysis is performed based on the information on the berries that were present in the freezers of the cases’ homes and in Denmark, use is also being made of purchase histories from supermarket till receipts. To date, laboratory testing of berries from the homes of seven confirmed cases from Denmark, Sweden and Norway has been negative for HAV. Results are still pending for berry samples from two confirmed cases in Finland.

### Public health action taken

As of 11 April, food authorities in Denmark, Finland and Sweden have issued a recommendation to heat treat all frozen berries or berries of non-domestic origin before consumption. On 12 April, the Norwegian Food Authorities and the Norwegian Institute of Public Health informed the public that the risk of contracting HAV through frozen imported berries can be reduced by boiling the berries before consumption. The European Centre for Disease Prevention and Control (ECDC) published a rapid outbreak assessment on 16 April 2013, informing other European countries as well as the European Commission about the outbreak [3].

### Discussion

This outbreak is the first Nordic food-borne outbreak of HAV infection. The results of the Danish case–control study clearly indicated frozen berries (particularly

strawberries) as the likely vehicle of the outbreak. Frozen berries have previously been identified as vehicles in outbreaks of HAV infection [4-6]. The epidemiological investigations in the three other Nordic countries, primarily case interviews, further support this notion. Sweden and Finland are considering conducting case–controls studies, to further test this main hypothesis.

As the available evidence has established consumption of frozen berries as the likely vehicle of the infections, the ongoing investigation is now mainly aimed at identifying the specific type and brand (or types and brands) of berries responsible for the outbreak. Comparison of information for trace-back on berries collected at cases' homes, as well as information obtained through purchase history from all four countries, is ongoing and the food authorities in the four countries are sharing information.

Three sequences of HAV genotype 1B with a maximum difference of 2% – corresponding to a difference of a few nucleotides – are implicated in the outbreak. One possible explanation for this would be that the berries are contaminated with several closely related strains. While outbreaks of HAV infection are often caused by a single viral genotype and sequence [7], food-borne outbreaks due to multiple HAV strains have been described previously [8,9] as has outbreaks of HAV infection due to food imported from HAV- endemic countries [10,11].

Given the long shelf life of frozen products, the long incubation time of HAV of 28–30 days (range: 15–50 days) [12] and the potential delay in notifications, more cases will probably still be notified in the four countries. The four national public health institutes and food authorities are therefore collaborating closely in order to confirm the source of the outbreak and stop further transmission. This is done in collaboration with ECDC and European Food Safety Authority (EFSA).

## Acknowledgements

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Prevention and Control for their collaboration during this outbreak investigation.

## Authors' contributions

SGL contributed to the study design collection and analysis of data and drafted the manuscript as the lead writer. BS contributed to the study design, collection and analysis of data and was lead in conducting the Danish case–control study. SEM and HTV contributed to the laboratory sequencing and analysis. AS and LV were in charge of the epidemiological investigations including the case–control study in Norway. KSJ were in charge of the laboratory typing and analysis in Norway. RRF was in charge of the epidemiological investigations in Finland. MK was in charge of the laboratory typing and analysis in Finland. ML and LE were in charge of the epidemiological investigations in Sweden. LS was in charge of the laboratory typing and analysis in Sweden. TKF contributed with interpretation of the virological data. TJ contributed to the trace-back. KM and SE contributed to the design of the Danish case–control study and to the epidemiological investigations. SE did the analysis of the Danish case–control study. BS, SEM, AS, LV, RRF, ML, ME, HTV, SE all critically reviewed the first draft of the paper. All authors approved the final version.

## Conflict of interest

None declared.

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# Severe Seoul hantavirus infection in a pregnant woman, France, October 2012

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**We report the first detection of Seoul virus (SEOV) in humans in Europe, causing severe disease in a pregnant woman in France in October 2012. The patient's laboratory test results mimicked that of pregnancy-induced liver pathologies such as acute fatty liver of pregnancy (AFLP) with severe renal failure. This led to an emergency delivery (at 27 weeks' gestation). On the basis of gene S (small) sequence analysis, the Seoul hantavirus strain detected was found to belong to the main SEOV phylogroup.**

## Case report

A primigravida woman in her mid-20s presented at 26 weeks of gestation in October 2012 with blurred vision, chills, headache, back pain and cough that had lasted two days. Her previous medical history was unremarkable. Physical examination revealed a high body temperature (39.1 °C). The fetal heart rate was normal and there was no uterine contraction. Antibiotics (ampicillin and gentamicin) were introduced systematically. Two days later (four days after symptom onset, day 4), she was transferred to the regional reference hospital because of abnormalities in test results from blood and urine sampled at day 3 (Table).

On admission to the department of obstetrics and gynaecology, she had no fever, hypertension or haemorrhagic symptoms. The admission laboratory results (day 4) showed an elevated C-reactive protein without lymphocytosis, elevated levels of liver enzymes, thrombocytopenia and mild coagulopathy (Table). Serological investigations were requested, to test for leptospirosis, toxoplasmosis, viral hepatitis, and herpes simplex viruses, cytomegalovirus, Epstein-Barr virus and hantavirus infection. Abdominal sonography showed no hepatobiliary pathology, but the presence of only one kidney. Obstetric examination and

ultrasound were normal, with normal fetal growth. The patient was closely monitored and antenatal prophylactic application of steroids (betamethasone, 12 mg per day for two days) for fetal pulmonary maturation was given. On day 7, the patient developed acute renal failure (creatininemia at 260 µmol/L) (norm: 53–115 µmol/L) (Table) with microscopic haemoglobinuria, proteinuria and anaemia. An emergency Caesarean section was performed on day 7 (at 27 weeks and two days' gestation) because of suspected acute fatty liver of pregnancy (AFLP) and to preserve maternal renal function in a patient with only one kidney. The preterm baby weighed 1,095 g when born and was intubated for respiratory distress syndrome.

After the birth, the mother was immediately transferred to a nephrology intensive care unit. Liver enzymes, blood count and coagulation normalised first, then renal function increased and was within the normal ranges within three weeks (Table), without the need for dialysis.

The newborn remained in a stable condition in the intensive care unit. Blood cultures and histological examination of placenta were normal. At five months of age, hypertonia and spasticity in the muscle of the lower extremities remained.

## Etiological investigation

The tests were negative for leptospirosis, toxoplasmosis, viral hepatitis, and herpes simplex viruses, cytomegalovirus, Epstein-Barr virus infection.

Tests for the detection of IgM and IgG against hantaviruses using Hantavirus IgG DxSelect and Hantavirus IgM DxSelect (Focus Diagnostics) were positive on a serum sample collected on day 7. As usual in France

TABLE

Blood and urine biochemical findings during hospitalisation of the Seoul hantavirus-infected patient, France, October 2012

Specimen	Parameters	Unit	Norm	Day of sampling <sup>a</sup>								
				Day 2	Day 3	Day 4	Day 5	Day 7	Day 8	Day 10	Day 15	Day 36
Blood	White blood cells	10 <sup>9</sup> /L	4–10	6.5	6.2	7.4	9.4	18	12.1	12	6.4	6.9
	Platelets	10 <sup>9</sup> /L	150–450	133	95	44	70	125	93	207	371	392
	Haemoglobin	g/dL	11.5–16.0	11.2	11.6	12.9	11.5	9.3	8.2	8.5	8.3	10.7
	C-reactive protein	mg/L	<3.2	17	59	133	114	49.9	ND	99.8	15.1	<2.9
	Lactate dehydrogenase	IU/L	120–228	ND	ND	965	913	407	329	ND	223	ND
	Aspartate aminotransferase	IU/L	15–37	ND	ND	785	792	259	169	98	17	ND
	Alanine transaminase	IU/L	9–52	ND	ND	333	347	178	128	94	31	ND
	Gamma-glutamyltransferase	IU/L	5–55	ND	ND	133	132	293	ND	221	131	ND
	Prothrombin ratio	%	70–100	ND	ND	74	89	94	94	97	100	ND
	Partial prothrombin time	s patient / s control	0.8–1.2	ND	ND	2.1	1.7	0.95	0.98	1.05	1.06	ND
	Creatinine	µmol/L	53–115	42	ND	61	67	260	328	648	295	63
mg/L		5–12	ND	1.17	ND	ND	ND	ND	ND	ND	ND	
Urine	Proteinuria	g/24 h	<0.3	ND	ND	ND	ND	3.35	ND	0.65	ND	ND

IU: international unit; ND: not done.

<sup>a</sup> The sampling day refers to the number of days after symptom onset.

for surveillance purposes, the positive sample was then transferred to the National Reference Centre for Hantavirus, where these positive results were confirmed by an enzyme-linked immunosorbent assay (ELISA) developed in-house using Hantaan virus (HTNV) and Puumala virus (PUUV) antigens [1].

The information sheet received with the sample reported that the place of residence of the patient was not in the north-east of France, where PUUV infection in humans are usually detected [2] and that the patient had not visited this endemic region in the previous month. Consequently, the emergence of PUUV at the patient's place of residence or the presence of another hantavirus was suspected. Therefore, the serum sample collected on day 4, which had been stored at –20 °C, was sent to the National Reference Centre for Hantavirus and tested for the presence of hantavirus RNA. The assay was positive using pan-hantavirus nested reverse transcription polymerase chain reaction (RT-PCR) targeting a part of L segment, Murinae-borne hantavirus nested RT-PCR targeting a part of S segment, and HTNV as positive control [3,4]. Amplicons were sequenced and a BLAST search indicated that the sequences were very close to those of Seoul (SEOV) strains (data not shown).

Then the complete S coding domain sequence was recovered via three nested RT-PCRs with in-house-designed primers (protocol available on request from the authors), producing three overlapping amplicons

(GenBank accession number KC902522). The amino acid sequence was identical to those of SEOV strains found in the United Kingdom, Vietnam, South Korea and China (GenBank accession numbers JX879769, AB618112, NC\_005236 and GU592947, respectively). It was also identical to the partial S coding domain sequence obtained from the SEOV strain detected in rodents in France [5]. Using MEGA version 5.1 [6], phylogenetic analysis based on S coding domain sequence confirmed that the strain – named REPLONGES/Hu/FRA/2012/12-0882 – belonged to SEOV species, especially to the main phylogroup, which includes strains from Asia and the rest of the world [7] (Figure).

## Background

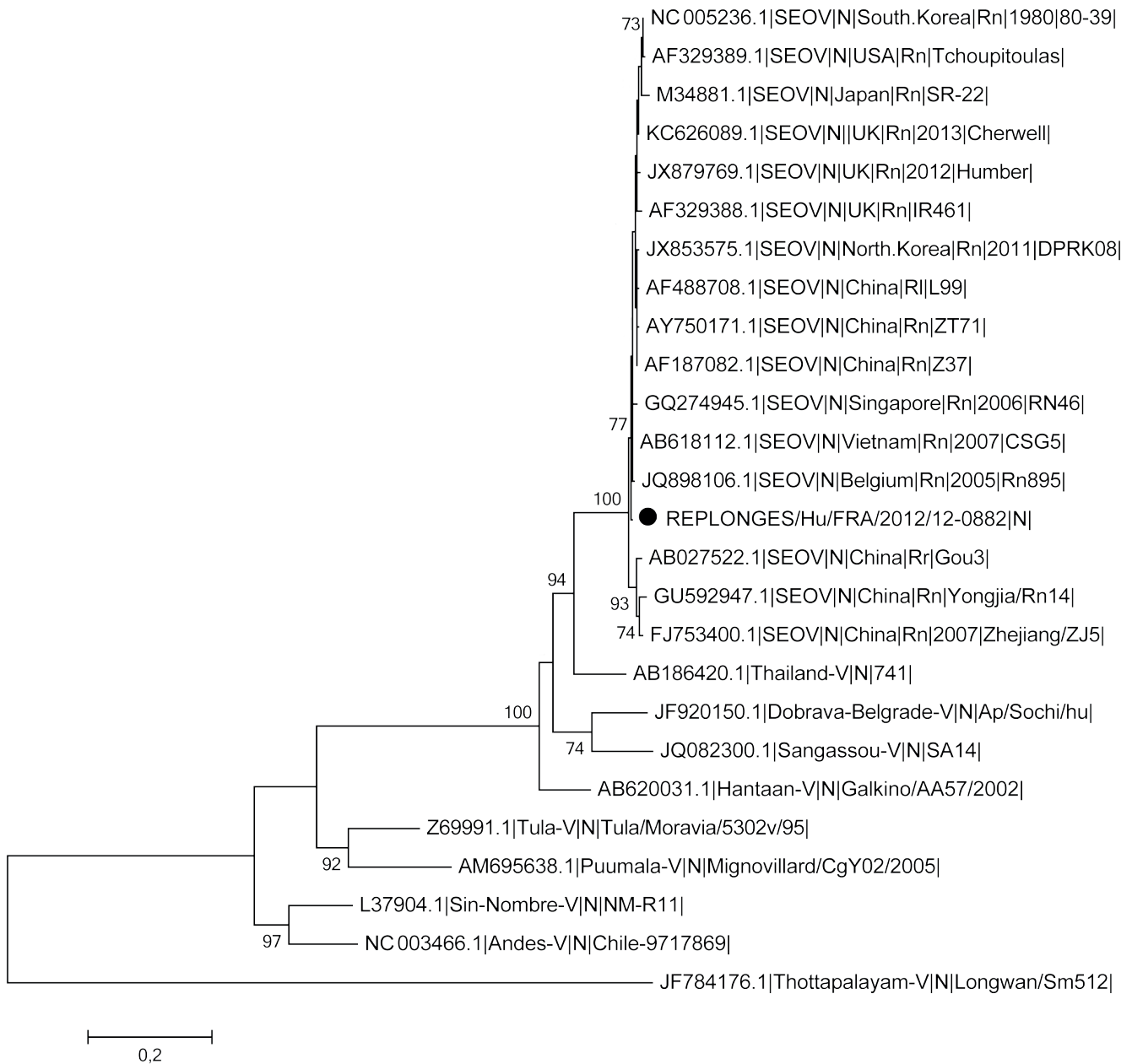
Five zoonotic hantaviruses have been described in Europe: PUUV, Dobrava-Belgrade (DOBV), Tula (TULV), Saaremaa (SAAV), and SEOV. These rodent-borne hantaviruses cause mild to severe haemorrhagic fever with renal syndrome. PUUV and DOBV are responsible for most human cases detected in Europe [8–10]. TULV and SAAV viruses have been only found in rodent samples; rare human cases have been serologically confirmed [8–10]. SEOV, a ubiquitous hantavirus, has been rarely detected in Europe in the brown rat, *Rattus norvegicus*, one of its rodent hosts. Few human cases have been suspected and serologically confirmed [8,11,12].

## Epidemiological investigation

The investigation was limited to an interview of the patient. The patient lived in a village near the Saône

**FIGURE**

Phylogenetic tree based on the entire gene S (small) nucleotide coding sequence from the patient with Seoul virus infection, France, October 2012, and representative strains of Seoul virus and other hantavirus species



The patient's strain, REPLONGES/Hu/FRA/2012/12-0882, is indicated by ●.

Bootstrap percentages  $\geq 70\%$  (from 1,000 resamplings) are indicated at each node. The scale bar indicates nucleotide substitution per site.

Using MEGA version 5.1, sequences were aligned by ClustalW and the maximum likelihood method was used: according to the best fit substitution model proposed, analysis was performed applying the generalised time reversible model using a Gamma distribution (+G) with five rate categories.



River in the Ain department (about 350 km south-east of Paris). She did not work during the six weeks before symptom onset and did not report apparent exposure to rodents at home or in her mother's house, which she visited several times during this period. The only indirect contact with rodents during that period was thought to have occurred when picking mushrooms in a forest close to a rural village in the Rhone department, about 25 km south-west from her home. Many unidentified rodents were observed by the patient in the forest, running at ground level. Investigation of rodents in the area is not yet planned.

## Discussion

To the best of our knowledge, that is the first report of SEOV infection in a pregnant woman, although we suppose such cases of infection may have been suspected or detected in Asia [13,14]. The clinical and biological picture of our case was confusing because distinguishing between this SEOV infection and certain liver pathologies of pregnancy, especially severe preeclampsia with haemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome and AFLP was problematic. Such syndromes have been suspected in pregnant women infected with hantaviruses [13-15]. In women with elevated levels of liver enzymes, thrombocytopenia and renal failure during pregnancy without hypertension, especially when laboratory test results are atypical and the symptoms begin with fever, practitioners should consider possible hantavirus infection instead of pregnancy-induced pathologies, which could potentially avoid emergency delivery and thus newborn prematurity.

As in the rest of Europe, data regarding SEOV in France are very scarce. The virus was detected in 2003 in reared brown rats in Lyon (about 60 km south of the patient's home), one human case was serologically confirmed (by neutralisation assay) and others suspected [2,5,8]. Routine serological tests do not allow discrimination between SEOV and PUUV infections and the demand for hantavirus testing in France, especially for mild cases, is limited because these tests are not free of charge. Therefore, the occurrence of SEOV infections in humans is probably underestimated. Large studies focusing on the epidemiology of SEOV infection should be conducted in France as well in the rest of Europe, as serologically confirmed cases have been recently described in the United Kingdom [11-12].

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## Authors' contributions

Guillaume Macé, Cécile Feyeux, Corinne Chantegret, Sylvain Audia, Jean-Michel Rebibou, Gilles Spagnolo, Jean-Baptiste Bour and Paul Sagot took care of the patient and her child. Gérard-Antoine Denoyel performed hantavirus serological

analysis. Nadège Mollard and Jean-Marc Reynes performed hantavirus serological analysis, SEOV detection and molecular analysis of the SEOV strain. Guillaume Macé and Jean-Marc Reynes wrote the manuscript. All co-authors reviewed the manuscript.

## Conflict of interest

None declared.

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# Virus-host interactions and the unusual age and sex distribution of human cases of influenza A(H7N9) in China, April 2013

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## To the editor:

Over the past two weeks, *Eurosurveillance* has published several timely papers related to the emergence of a new influenza A(H7N9) virus affecting humans in China [1-3]. Genetic studies by Kageyama et al. [1] and Jongens et al. [2] assessed evidence in the genome for virus origin, adaptation and virulence, and a paper by Corman et al. [3] described real-time reverse-transcription PCR assays for specific virus diagnosis. While these are important aspects of novel virus characterisation and detection, the accrual of over 100 human cases now also affords opportunity to consider evolving epidemiologic patterns as part of population risk assessment.

Perhaps the most intriguing impression to date from available surveillance findings has been the unexpected age/sex distribution of reported influenza A(H7N9) cases. The age range spans from 2 to 91 years but two thirds of influenza A(H7N9) cases have been 50 years of age or older and two thirds have been

male (Table) [4,5]. Illness severity, with a substantial case fatality of 20%, shows a similar age/sex profile (Table) [4,5]. Unlike the pattern observed for influenza A(H5N1), children, both boys and girls and notably the school-aged, are under-represented among influenza A(H7N9) detections. Among the first 100 adult influenza A(H7N9) cases, men and women were equally represented in the youngest age category 20–34 years, but men were 2–3-fold more frequent than women in older age groups (Table). Furthermore, compared with women 20–34 years of age, women 50–64 and 65–79 years were each twice as frequent among influenza A(H7N9) detections. Conversely, men 50–64 and 65–79 years are each 4–5-fold more frequent among influenza A(H7N9) detections than men 20–34 years of age. While being careful not to over-interpret early surveillance data, what hypotheses might be invoked to explain that pattern?

Disease occurrence is the result of the classic interaction triad of agent–host–environment. Environmental

## TABLE

Human cases of influenza A(H7N9) and deaths by age group and sex, China, as of 23 April 2013 (n=109)<sup>a</sup>

	Age (years)										
	<2	2–4	5–9	10–14	15–19	20–34	35–49	50–64	65–79	≥80	Unknown
Total cases	0	3	1	0	0	9	16	30	36	12	2
Female	0	0	1	0	0	4	5	9	9	4	0
Male	0	2	0	0	0	5	11	21	27	8	0
Unknown	0	1	0	0	0	0	0	0	0	0	2
Deaths	0	0	0	0	0	1	3	6	7	3	1
Female	0	0	0	0	0	0	1	2	2	0	0
Male	0	0	0	0	0	1	2	4	5	3	0
Unknown	0	0	0	0	0	0	0	0	0	0	1

<sup>a</sup> Data sources include the Chinese Center for Disease Control and Prevention and the World Health Organization.

factors such as differences in poultry exposure due to socio-cultural behaviours and host factors such as healthcare-seeking behaviour or underlying comorbid conditions have been postulated to explain these early influenza A(H7N9) surveillance signals [6,7]. However, hypotheses should also include the additional perspective of agent (i.e. virus)–host interactions. Immunological profiles by age likely reflect accumulated lifetime opportunities for influenza virus exposure, leaving intricate imprints that may positively or negatively modulate subsequent risk. We have illustrated this immunological complexity at the population level for influenza, showing variation in age-specific cross-reactive antibody levels to previously emerging influenza A(H1N1)pdm09 virus [8] and more recently to the emerging (swine-origin) influenza A(H3N2)v, probably reflecting complex cohort effects based on differential prime/boost exposures to influenza variants by age [9].

That pre-existing immunity can differentially modulate the infection process for novel pathogens may be relevant in understanding the differing age distributions of the emerging influenza A(H5N1) versus A(H7N9) viruses [6,7]. Anti-neuraminidase (N1) antibodies induced by cumulative influenza A(H1N1) lifetime exposures may have a role in mitigating risk and severity of influenza A(H5N1) infection [10–13] in older individuals accounting for its more youthful profile to date [4–7]. In contrast, for influenza A(H7N9) we may anticipate that anti-N9 antibodies would be less prevalent overall in the population. Other population immunological effects of the 2009 influenza A(H1N1) pandemic, which affected predominantly young people, such as cross-reactive T-cell responses to generally conserved internal virus proteins [14] or memory B cell responses to shared epitopes within group 1 (i.e. H1, H5) versus group 2 (i.e. H3, H7) subtypes [15] may also need to be considered as factors that influence influenza A(H5N1) and A(H7N9) age profiles.

At this stage, we should also stay open to the possibility that pre-existing cross-reactive antibodies may actually facilitate the viral infection process, a phenomenon best recognised for dengue through the mechanism of antibody dependent enhancement (ADE) [16,17]. ADE is thought to occur when low-levels of weakly heterotypic, cross-reactive but not cross-protective, antibodies generated by past exposure to virus antigen, e.g. through prior infection or immunisation, form bridging complexes to facilitate uptake and replication of related but non-identical variants [16–18]. The possibility of ADE in influenza has long been and remains the subject of intense interest among experts [19,20], for which there may recently be indirect evidence. Early during the 2009 influenza pandemic, we described a potentially important interaction between seasonal and novel emerging influenza virus, notably an approximate doubling of the likelihood of medically-attended pandemic influenza A(H1N1) illness among people previously administered seasonal influenza

vaccine that contained virus antigenically related but distant from the emerging influenza A(H1N1)pdm09 strain [18]. In a follow-up experiment, vaccinated ferrets showed higher lung virus titres and greater illness severity after influenza A(H1N1)pdm09 challenge than influenza-naïve animals [21]. In swine, disease exacerbation has also been observed following heterologous challenge [22–24]. ADE was one of the proposed (but unproven) hypotheses to explain the unexpected findings from Canada during the 2009 pandemic [18]. The possible relevance of weakly cross-reactive antibodies in facilitating infection due to other emerging influenza viruses with pandemic potential may therefore warrant further consideration.

In that regard, older Chinese men may not only have a greater likelihood of current poultry/bird exposure, to explain their disproportionate representation among influenza A(H7N9) cases, but also a greater total sum of lifetime avian influenza exposures potentially contributing to cross-reactive H7 antibody. Few serosurveys to assess H7 antibodies in the population of China are available in the English language, and none has yet been sufficiently powered to compare this by age or sex [25–28]. In a serosurvey conducted 20 years ago in central China (Nanchang), 25% of 100 samples collected from women who raised pigs were found by ELISA to have antibodies to purified H7 antigen [25]. In a more recent serosurvey conducted in 2006–08 in northern China, 5–10% of ca. 1,000 farmer families and poultry workers aged 5–87 years had detectable but low-level antibodies (titre of at least 1:20 but not exceeding 1:40) to influenza (H7N1) in a modified haemagglutination inhibition (HI) assay using horse erythrocytes [26]. In 2011, none of >1,500 duck-related workers in Beijing aged 14–71 years had influenza (H7N2) or (H5N1) titres exceeding 1:40 by modified HI, although seropositivity to influenza (H9N2) was more prevalent, particularly among adults older than 50 years of age in whom the rate of seropositivity was four-fold higher than among younger participants [28].

Although the detection of antibodies to H7 subtype viruses has proved challenging even among culture-confirmed cases [29–35], serosurveys to compare cross-reactive antibodies and neutralising effects by multiple assays and by age group could be important, not only to inform possible protection, but also to explore patterns of enhanced risk in influenza A(H7N9) affected areas and more broadly elsewhere to inform risk assessment. Certain immunological effects, including ADE as it pertains to influenza, may yet be speculative. At this early stage of trying to understand the unexpected epidemiological patterns of an emerging pathogen, however, it is prudent for the global scientific and public health community to consider all possibilities within the full virus–host–environment paradigm.

## Authors' contributions

All authors contributed to the writing, review and final approval of this letter.

## Conflict of interest

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# European Immunization Week 2013 and new ECDC tools to support routine vaccination programmes

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The eighth European Immunization Week (EIW) takes place between 22 and 27 April 2013 [1].

EIW promotes the core message that the immunisation of every child is vital to prevent diseases and protect life. This initiative is led and coordinated by the World Health Organization Regional Office for Europe (WHO/Europe) and implemented by the countries of the European Region. For one week in April, countries across the Region unite under the EIW slogan – Prevent. Protect. Immunize. – and carry out activities to inform and engage target audiences and to address challenges regarding immunisation. These activities include training sessions for healthcare workers, dissemination of informational materials, workshops, press conferences, among other things.

More information on the activities around the EIW is available on the campaign site at: <http://eiw.euro.who.int/>.

To mark the EIW, the European Centre for Disease Prevention and Control (ECDC) has launched a variety of new resources to support routine vaccination programmes. The tools are meant to support frontline healthcare workers and public health professionals working on routine vaccination programmes.

The ‘Vaccine Scheduler’ is a new platform of vaccination schedules for individual European countries and specific age groups. It displays vaccination schedules in the European Union Member States and makes it possible to compare national schedules against each other [2].

The ‘Measles Atlas’, an interactive map based on surveillance data available to ECDC, offers an easy to understand visualisation of the progress towards measles elimination in each European country. It displays four series of data maps cover vaccination coverage - one and two doses, and incidence rates - by age groups, for the years 2006 to 2012 [3].

‘Let’s talk about protection’ is a package of practical resources that offers healthcare workers guidance on how to best communicate with parents about vaccinating their children. It includes examples of letters to parents together with a ‘vaccine policy statement’ as well as Questions and Answers to use with parents. ‘Let’s talk about protection’ puts forward the thoughts, knowledge and insights of parents, social marketers and other health workers in their own words [4].

## References

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# Joint ECDC CNRL and WHO/Europe briefing note on diagnostic preparedness in Europe for detection of avian influenza A(H7N9) viruses

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To assist European laboratories in verifying and ensuring their diagnostic capability to detect and identify this virus, the European Centre for Disease Prevention and Control (ECDC) jointly with the Community Network of Reference Laboratories for Human Influenza in Europe (CNRL) and the World Health Organization Regional Office for Europe (WHO/Europe) has released a technical briefing note on diagnostic preparedness in Europe for detection of avian influenza A(H7N9) viruses [1].

The briefing note provides:

- a list of laboratory preparedness considerations to ensure European-wide diagnostic capability;
- an update on current methods used for molecular detection of human infection with avian influenza A(H7N9) virus by RT-PCR;
- a table of H7 HA RT-PCR assay validation criteria;
- information on options for positive controls for RT-PCR assays.

The document includes the following considerations on H7 detection capabilities:

- Laboratories testing for H7 will require a molecular detection capability allowing specific detection ability in response to clinical queries or case scenarios.
- A two-step approach for detection and confirmation of avian influenza A(H7N9) virus infection should be followed.
- Laboratories require: (i) a generic influenza A virus testing capability which will assuredly detect an avian influenza A(H7N9) virus and (ii) a specific H7 HA detection capability to confirm the presence of an avian influenza A(H7N9) virus in a sample which is positive for influenza A, but negative for H1, H3 and H5.

This document is intended for use in the area of human influenza surveillance, investigation, risk assessment and control, encouraging cooperation between expert and reference laboratories.

## References

1. European Centre for Disease Prevention and Control (ECDC). ECDC Technical Document. Diagnostic preparedness in Europe for detection of avian influenza A(H7N9) viruses. Technical briefing note. Stockholm: ECDC. 23 Apr 2013. Available from: <http://www.ecdc.europa.eu/en/publications/Publications/avian-influenza-H7N9-microbiology-diagnostic-preparedness-for-detection.pdf>