

Three simultaneous, food-borne, multi-country outbreaks of hepatitis A virus infection reported in EPIS-FWD in 2013: what does it mean for the European Union?

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Between March and May 2013, three multi-country outbreaks of hepatitis A virus (HAV) infection were reported through the Epidemic Intelligence Information System for Food- and Water-borne diseases (EPIS-FWD) of the European Centre for Disease Prevention and Control (ECDC). The aim of this work is to put these outbreaks into a European Union (EU) and European Economic Area (EEA) perspective and highlight opportunities for improving detection and investigation of such outbreaks. Although HAV outbreaks are not unusual in the EU/EEA, having three large food-borne multi-country outbreaks declared within three months is an unexpected event, particularly when at least two of these outbreaks are associated with frozen berries. Factors influencing the occurrence of these events include the increased number of susceptible Europeans, the limited coverage of HAV vaccination, the global trade of potentially contaminated products introduced in the EU/EEA, and the 'awareness chain effect' leading to a wave of notifications. Further studies should be conducted to understand the risk posed by frozen berries. Laboratory capacity and surveillance of viral infections in the EU/EEA, as well as HAV vaccination recommendations to travellers to endemic countries should be strengthened. Finally, timely reporting food-borne events through EPIS-FWD, to ensure timely response.

Surveillance and early warning for hepatitis A virus infection in the European Union and countries of the European Economic Area

Hepatitis A is a self-limiting viral disease caused by hepatitis A virus (HAV). HAV has low to very low endemicity in northern and western Europe and intermediate to low endemicity in eastern and southern Europe [1]. Infection takes place mainly via the faecal-oral route through person-to-person contact but food- and waterborne transmission is also common. Groups at increased risk for HAV infection include travellers to

endemic areas, men who have sex with men, people who inject drugs, recipients of blood and blood product and close contacts of infected individuals [1].

Hepatitis A is a notifiable disease at the European Union (EU)/European Economic Area (EEA) level. In 2011, the overall annual disease incidence in EU/EEA was 3 per 100,000 inhabitants; of 28 countries for which incidence is available, 19 reported HAV incidence below one per 100,000 inhabitants and three reported more than ten per 100,000 inhabitants, the highest incidence being 74 per 100,000 inhabitants in Bulgaria [2]. Cases are usually confirmed through serological analysis. Only a few EU countries perform routine molecular characterisation of the viral isolates of the cases. Timely collection and analysis of surveillance information is essential to monitor hepatitis A trends over time and early detect increases in disease incidence. Molecular characterisation of the collected HAV isolates is then helpful to understand whether reported cases are linked. While EU/EEA countries report individual cases of HAV infection on an annual basis to The European Surveillance System (TESSy) of the European Centre for Disease Prevention and Control (ECDC), outbreaks with a potential international dimension are reported in real time through ECDC Epidemic Intelligence Information System for Food- and Water-borne Diseases [3]. EPIS-FWD was established in March 2010 and is a communication platform for early detection and assessment of food- and waterborne threats with potential international dimension. The system gathers epidemiologists and microbiologists from all EU/EEA countries, plus Australia, Canada, Japan, New Zealand, South Africa, Switzerland, Turkey and the United States. In 2010 and 2011, three outbreaks of HAV infections were reported via EPIS-FWD. Two of these outbreaks, involving Australia, France, the Netherlands and the United Kingdom, were due to the consumption of semi-dried tomatoes [4–6]; the source of infection of the third outbreak in Estonia was not identified, but a food-borne

TABLE

Description of the food-borne multi-country hepatitis A outbreaks in the European Union/European Economic Area, 2013

	1 March 2013 Denmark reports a national outbreak in EPIS-FWD	17 April 2013 Norway reports an outbreak in travellers returning from Egypt in EPIS-FWD	8 May 2013 Germany reports an outbreak in travellers returning from Italy in EPIS-FWD
Countries reporting associated cases	Denmark, Finland, Norway and Sweden.	Denmark, Estonia, Finland, France, Germany, Ireland, Latvia, Lithuania, Norway, Slovakia, Sweden, Switzerland, the Netherlands and the United Kingdom.	Italy, Ireland, Germany, the Netherlands and Poland.
Epidemiological investigations	As of 6 August 2013, there were 106 cases reported since 1 October 2012. 61% female, median age 23 years old. Trawling questionnaire and case control studies in the affected countries pointed towards frozen strawberries as vehicle of infection.	As of 20 August 2013, there were 107 cases reported since 1 November 2012. 50% female, median age 36 years old. Trawling questionnaire and case control study in the affected countries pointed to foodborne transmission. Strawberries were suspected among other fruits.	As of 27 July, there were more than 200 reported cases in 2013, the majority in Italy. Trawling questionnaire and case-control study in the affected countries pointed towards frozen mixed berries.
Microbiological information	Subgenotype 1B. Two RNA sequences (sequence 1 and sequence 2) which differed by 1.7% over 847 bp.	Subgenotype 1B. One RNA sequence which differed by 1.22% over 1,233 bp and by 1.26% over 397 bp from sequence 1 and 2 of the Nordic countries outbreak.	Subgenotype 1A. One RNA sequence.
Food investigations	Trace-back analysis pointed to strawberries from Egypt and Morocco. No food sample was found positive. One RASFF notification issued.	No information available about possible food investigations in Egypt.	HAV isolated in frozen mixed berries of various origins, mostly from Eastern European countries. One isolate from the food samples had an identical sequence to the outbreak strain. Eleven RASFF notifications issued.

EPIS-FWD: Epidemic Intelligence Information System for Food- and Water-borne diseases; RASFF: Rapid Alert System for Food and Feed

origin was suspected. No HAV outbreak was reported in EPIS-FWD in 2012.

Between March and May 2013, three multi-country outbreaks of hepatitis A virus infection were reported through EPIS-FWD. Prompt analysis of surveillance information and timely reports triggered rapid and coordinated response among affected countries and ECDC.

The aim of this work is to put these recent outbreaks into an EU perspective and highlight opportunities for improving detection and investigation of future multi-national HAV outbreaks.

The three outbreaks of HAV infection reported on EPIS-FWD between March and May 2013 involved over 400 cases from 15 EU/EEA countries and Switzerland. The first outbreak was initially reported by Denmark on 1 March, with cases subsequently reported by Finland, Norway and Sweden. As of 6 August, 106 cases had been reported by the four Nordic countries of Denmark, Sweden, Norway and Finland [7]. Two closely related strains with subgenotype 1B were associated to this outbreak [8]. Epidemiological investigations, including case interviews and case control study, and purchase history investigations pointed towards frozen strawberries from Egypt and Morocco as the most likely source of infection [9,10]. Although strawberries are

not botanical berries, they are treated as berries in this article. Despite extensive food sampling and testing of frozen strawberries, no HAV could be isolated.

The second outbreak was initially notified by Norway on 17 April and subsequently an additional 13 countries reported associated cases (see Table). As of 20 August, 107 travellers returning from different locations in the Red Sea region, Egypt, were reported infected. The outbreak strain was subgenotype 1B as well, but with a different sequence from the Nordic countries outbreak mentioned above. Multi-country epidemiological investigations, including case interviews and case control study, suggested that the implicated vehicle of infection was a food item distributed to different hotels in Egypt, with strawberries suspected among other fruits [11,12].

The third outbreak, reported on 8 May on EPIS-FWD, was thought to have affected about 200 Italian residents as of August 2013, although it was initially reported by Germany following identification of nine HAV infections in travellers returning from northern Italy [13]. A Dutch traveller and five Polish travellers to Italy were also part of this outbreak [14]. In addition, 21 people living in Ireland with no travel history to Italy were infected with an HAV strain with identical sequence [15]. The outbreak strain was subgenotype 1A. Case interviews and a case control study in Italy, including the Dutch

and Polish cases, identified imported frozen mixed berries as the vehicle of infection [14,16]. Subsequently, a case-control study in Ireland led to the same conclusion [15]. Isolation of HAV in frozen mixed berries in Italy led to eleven notifications through the Rapid Alert System for Food and Feed (RASFF), which is the EU notification system to exchange information on measures taken on risks related to food and feed. Berries forming the mix mentioned in the RASFF notifications originated mostly from east European countries [17]. Several isolates from the food samples had a sequence identical to the outbreak strain [16,18].

Is there a link between these outbreaks?

The epidemiological and microbiological information available suggests no direct link between these simultaneous HAV outbreaks. All outbreaks were caused by a different persistent source of exposure: two were confirmed to be associated with the consumption of berries, while strawberries were one of the suspected vehicles of infection in the third outbreak. In the Nordic countries outbreak, having two closely related sequences co-circulating may suggest an environmental contamination of the berries, most likely through sewage water [19,20], or that the berries have geographically close origins.

Three of the outbreaks strains belong to subgenotype IB (two from the Nordic countries outbreak, one from cases with travel history to Egypt). The fourth outbreak strain, associated with berries in Italy, belongs to subgenotype IA, which excludes any link between the Italian outbreak and the other two outbreaks. Based on overlapping RNA fragments in the VP1 2A region, it was established that the three subgenotype IB sequences differed from each other by less than 2% [8]. Considering that the rate of mutation of the HAV RNA sequence is low [21], a 2% difference between sequences is a marker of a relatively long phylogenetic evolution. This suggests that it is unlikely that it would be one strain that would have rapidly mutated and spread but rather that the strains involved in the two IB subgenotype outbreaks would have a common geographical origin.

Is this situation unusual or unexpected?

Having three multi-country outbreaks declared within three months is an unexpected situation. Several HAV outbreaks in European travellers returning from HAV endemic countries such as Egypt were described in the past decade [22,23]. Food-borne HAV outbreaks due to the consumption of fruit including berries have previously been reported. Such outbreaks have involved vehicles like raspberries [24], strawberries [25], blueberries [26] and semi-dried tomatoes [4]. Also the simultaneous occurrence of HAV outbreaks in the EU has been previously observed, as in 2008 when three outbreaks in the Czech Republic, Latvia and Slovakia occurred. However, for these later outbreaks, transmission was mostly human-to-human [27].

Several factors have most likely drove toward this peculiar situation: first, the decreased incidence of HAV infections in the past decade, coupled with the fact that HAV was not included in the vaccination schedule of most of the countries of the EU/EEA, led to an increase in the number of susceptible European citizens, leaving the opportunity for large outbreaks to occur [1]; second, the limited coverage of HAV vaccination among European travellers to HAV endemic countries, particularly when staying in all-inclusive resorts [22,28], together with the increase in the number of travellers [29], explains the pool of cases among travellers to endemic areas; third, the large amount of fruit and vegetables and other food items imported into the EU and their extensive redistribution within the EU [30] may facilitate the introduction of HAV-contaminated products, leading to multi-country outbreaks. Contamination of the berries early in the food production chain seems most likely for the outbreaks in the Nordic countries and in Italy, allowing wide distribution of the contaminated fruit. Several pathways of contamination of berries can be suggested: irrigation with faecally-contaminated water prior to harvesting, infected field workers during the harvest or processing at the factory, and spraying with contaminated water before distribution [31].

Since the first RASFF notification in 1979, and as of 15 September 2013, over 37,100 notifications have been issued, and in the past five years, there has been an average of 3,400 notifications per year. So far, 35 notifications related to food-borne viruses and berries have been issued, which represents 7.4% (35/474) of the notifications related to pathogenic microorganisms in fruits and vegetables. Both notifications related to berries contaminated with food-borne viruses and notifications of food-borne virus outbreaks implicating berries have increased in recent years. Thirty-nine notifications related to berries, of which 30 (77%) were reported since 2009 and twelve (31%) between 1 January and 15 September 2013. The most frequently reported pathogenic microorganism in berries was norovirus (23 notifications, 59%) and HAV (nine notifications, 23%). All nine HAV notifications in berries are since November 2012, which suggests that more berries have been found to be contaminated recently than in previous years. In addition, there were 30 notifications about food items contaminated with HAV, of which 16 (53%) were made between 1 January 2012 and 15 September 2013. While notifications before 2012 on HAV findings in food and HAV outbreaks were mostly related to crustaceans and bivalve molluscs (10/14), since January 2012, the majority of HAV notifications have been related to fruit and vegetables (12/16), among which 9/12 are berries. This may indicate that fruit and vegetables, particularly berries, have become more frequently contaminated in the recent years. It should be emphasised that these could also be an effect of increased frequency of samplings and improvement of the sensitivity of analytical methods.

Finally, the first outbreak in the Nordic countries, initially reported by Denmark, may have indirectly facilitated the reporting of the following two outbreaks. In fact, the investigation of the Nordic countries outbreak may have encouraged Norway to increase the sequencing of HAV isolates from reported cases and therefore to detect and report the second outbreak through EPIS-FWD. In the same way, these first two outbreaks may have facilitated the detection of the cases related to travel to Italy and prompted Germany to report the outbreak through EPIS-FWD. Finally, the Italian public health authorities were alerted to the travel-related cases and immediately acknowledged the occurrence of a local outbreak. In the absence of a direct link between the outbreaks, the hypothesis of an 'awareness chain effect' might explain the quasi-simultaneous notifications of these outbreaks.

Avenues to prevent recurrence of similar HAV outbreaks

The outbreaks described have shown that frozen berries are efficient vehicles of HAV infection; to this extent, the risk posed by berries should be studied further. Such study could include the analysis of the pathways of berry contamination and the likelihood of being exposed to HAV-contaminated berries in the EU considering the intensive intra- and extra-EU trade of berries.

EPIS-FWD allowed the early detection of the multinational dimension of these outbreaks. The system supported the rapid exchange of information among the network's experts and easy access to up-to-date epidemiological and microbiological results. EPIS-FWD was also used as a document repository for the line listings, questionnaires and protocols, and rapid risk assessments prepared by ECDC. Although the system currently extends beyond EU/EEA borders, it is limited to very few non-EU/EEA countries. To fill the gap, the new version of EPIS-FWD, launched in July 2013, allows inviting non-network countries to participate in a discussion if the need arises, aiming to facilitate the exchange of information.

The development of molecular characterisation, and particularly RNA sequencing, has allowed the three simultaneous outbreaks to be identified and defined, and has allowed dispersed cases to be either linked or individuated within the outbreaks. ECDC and the European Commission should play a role in ensuring that adequate capacity to isolate and sequence HAV in food and human samples is available at the EU level, through promoting common protocols and sharing expertise.

The ECDC food- and waterborne toolbox for outbreak investigation [32] could be further developed beyond the standard trawling questionnaires already present to include the necessary protocols for HAV detection and sequencing.

Timely coordination of the control actions by the European Commission, including coordination of the trace-back and trace-forward activities at the EU/EEA level, is crucial during multi-country investigations. To minimise the risk of contamination of berries at farm and processing plant level, and therefore to minimise the risk of importing contaminated berries into the EU, food safety agencies and private food industries in the importing and exporting countries should work closely together, ensuring that best practices are applied. Good intersectoral cooperation is paramount during outbreak investigation to timely receive information about distribution of the product and eventual breaches in production practices.

These outbreaks have shown the complexity of viral epidemiology and microbiology. ECDC has initiated in 2013 the nomination of food-borne viral infections experts (microbiologists and epidemiologists) from the EU/EEA countries to contribute in providing data and expertise through TESSy and EPIS-FWD. Strong collaboration with existing international networks such as the International HAV laboratory network, HAVNET (www.havnet.nl), managed by the Dutch National Institute for Public Health and the Environment (RIVM) should be ensured.

The outbreak in travellers to Egypt also highlights the importance of vaccination in travellers to endemic areas in a time of increasing tourism to endemic destinations.

More HAV outbreaks are expected to occur in the EU. The 2013 experience demonstrates the absolute necessity for extensive collaboration between countries and between the public health and food sectors to identify as quickly as possible the vehicle of infection and, ideally, to control the outbreak in a timely fashion.

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Conflict of interest

None declared.

Authors' contributions

Both authors worked on the EU coordination of these outbreaks and wrote this manuscript.

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