A large prolonged outbreak of hepatitis A associated with consumption of frozen berries, Italy, 2013–14

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Abstract

Purpose. In 2013/2014, Italy experienced one of the largest community-wide prolonged outbreaks of hepatitis A virus (HAV) throughout the country. The article provides a comprehensive description of the outbreak and the investigation carried out by a multidisciplinary National Task Force, in collaboration with regional and local public health authorities. Control strategies of food-borne HAV infection in both the human and food sectors are also described.

Methodology. Enhanced human epidemiological and microbiological surveillance together with microbiological monitoring of HAV in food and trace-back investigation were conducted.

Results. A total of 1803 HAV cases were identified from 1 January 2013 to 31 August 2014, in Italy. Sequencing was possible for 368 cases (20.4 %), mostly collected between 1 January 2013 and 28 February 2014, and 246 cases (66.8 %) harboured an HAV outbreak strain. Imported frozen berries contaminated with HAV were identified as the vehicle of the outbreak which also involved many other European countries in 2013 and 2014. Epidemiological evidence obtained through a case–control study was supported by the finding of a 100 % nucleotide similarity of the VP1/2A sequences of HAVs detected in human and food samples. Trace-back investigation revealed an extremely complex supplying network with no possibility for a point source potentially explaining the vast contamination of berries found in Italy.

Conclusion. The investigation benefited from an excellent collaboration among different sectors who shared proactively the available information. Our findings highlight the importance of considering frozen berries among the highest risk factors for HAV.

INTRODUCTION

Hepatitis A virus (HAV) is generally transmitted to humans through the faecal–oral route. Clinical infection by HAV is characterized by fever, diarrhoea and jaundice; in some cases, it can progress to liver failure. The average incubation period is 30 days (range is 15–50 days). The overall case fatality ratio is about 0.3 % but can be as high as 1.8 % in adults and immunocompromised patients [1].

Italy likely transitioned from intermediate to low endemicity in the 1980s and from low to very low endemicity in the late 1980s. It remains a very low endemicity country [2–4].

Despite the declining trend in the last 20 years (from 6 cases per 100 000 population in 1992 to 0.8 in 2012) [5, 6], the disease is still present in Italy, and in some Italian regions, it is endemic-epidemic, associated with raw shellfish consumption where it is a typical local dish [7–9]. There is no universal hepatitis A vaccination programme in Italy. The National Vaccination Plan recommends vaccination against HAV only for specific risk subgroups [10].

In April 2013, through the international alert systems, platforms called ‘Early Warning and Response System of the European Commission (EC)’ and the ‘Epidemic Intelligence...
Information System of the European Centre for Disease Prevention and Control, Germany, The Netherlands and Poland reported 15 cases of HAV infection associated with a skiing holiday in Northern Italy. Concurrently, the specific sentinel surveillance system for acute viral hepatitis [(Sistema Epidemiologico Integrato Epatiti Virali Acute (SEIEVA)) at the National Institute of Public Health [Istituto Superiore di Sanità (ISS)] noted an increase in cases of HAV. Once the existence of an outbreak was established, the Italian Health Authorities immediately undertook a series of actions in order to manage and control it [11].

We present here a comprehensive description of the outbreak and the investigation activities carried out in Italy by a multidisciplinary National Task Force in collaboration with regional and local public health authorities. Evidence obtained is discussed to support the adoption of control strategies of food-borne HAV infection in both human and food sectors.

METHODS

Case finding

Hepatitis A is a mandatory notifiable disease in Italy. In addition, to support the official notification system in better profiling cases, a dedicated surveillance programme (SEIEVA) is also in place [12]. Once the national outbreak was declared, for case finding, the two systems were combined together, also adding microbiological data. Moreover, in order to enhance hepatitis A surveillance and facilitate the investigation, on 23 May 2013, the Ministry of Health published a note to alert regional and local health authorities and general practitioners and to inform them on the ongoing outbreak, improve awareness of HAV, remind them to promptly notify all HAV cases and collect serum samples from all new cases for virus molecular tests. Standardized questionnaires were used to systematically collect information on risk factors associated with HAV infection.

In Italy, a hepatitis A case was routinely defined as any person, resident in Italy, with discrete onset of symptoms (e.g. fatigue, abdominal pain, loss of appetite, intermittent nausea and vomiting) and at least one of the following three (fever, jaundice and elevated serum aminotransferase levels) and HAV-specific antibody response and/or detection of HAV antigen in stool.

Outbreak case definition

For the outbreak investigation, the cases were classified as probable, confirmed and non-cases.

A probable case was any HAV routinely notified case (as above described) with date of symptom onset (or date of testing if onset date not available) from 1 January 2013 to 31 August 2014.

For defining confirmed cases, the following laboratory criteria were set: detection of HAV nucleic acid genotype IA in serum or stool with with at least one of the following (i) identical sequence (i.e. 100.0 %) to the 2013 HAV genotype IA outbreak strain (GenBank accession number KF182323) based on a fragment of 460 nt in the region VP1-2A, (ii) 99.8 % similarity to this sequence (i.e. 1 nt difference in 460 nt) from nt 2915 to 3374 on NC_001489 and (iii) identical sequence (i.e. 100.0 %) on a shorter fragment of at least 174 nt in the region VP1-2Aa from nt 2967 to 3191 on NC_001489.

Cases were classified as non-cases if a sequence of different type from those reported in (i), (ii) and (iii) could be detected.

A case was defined as a secondary case if there was person-to-person contact with a confirmed case within 15–50 days before onset.

Epidemiological investigation

Cases were described by time (date of symptoms onset), person (demographic characteristics regarding age and sex, severity of symptoms and hospitalization rate were also provided), place (incidence rate by residence area) and exposure to the investigated risk factors. Moreover, we also compared confirmed and probable cases notified, using the chi-squared test and Fisher’s exact test when necessary, with P<0.05 being considered statistically significant. All statistical analyses were carried out in Stata version 11.2 (StataCorp).

In addition, we conducted in July 2013 a matched case-control study to test the hypothesis of an association of illness with consumption of frozen berries in the five most affected Italian regions (Apulia, Province of Bolzano, Emilia-Romagna, Friuli-Venezia Giulia and Province of Trento). The potential risk factors explored were the consumption of mixed berries and other food items described as potential sources of HAV infection, and history of travel. We compared each case with four age- and neighbourhood-matched controls. Potential controls, which had not presented with hepatitis A symptoms during the period from 1 January to 31 May 2013, were selected from the general population residing in the five Italian regions and matched with each case by age (±3 years) and place of residence (individual matching). Details on methods are reported in [13].

Molecular characterization of HAV isolates

The molecular characterization of the viral isolates from human cases serum samples collected was performed by the National Reference Laboratory for Viral Hepatitis at ISS by nested PCR and sequencing of the VP1/2A genomic region of HAV. Amplification, sequencing and phylogenetic analysis were carried out according to Bruni et al. [14]. Briefly, sequencing of the nested PCR products resulted in a 460 nt sequence. ISS also collected and analysed VP1/2A sequences transmitted by five regional reference laboratories, which used different protocols providing both ‘long’ sequences overlapping the 460 nt region (samples positive at first round of PCR) and ‘short’ sequences (samples positive only at second round of PCR). A 174 nt region common to all sequences was used for analysis of the ‘short’ sequence group, according to the outbreak case definition above described.
Enhanced food investigation

Samples of frozen berries belonging to the lots consumed by outbreak cases or epidemiologically related with cases were sampled in various settings by the local competent authorities and analysed. Frozen berries were also sampled by food business operators as part of their own Hazard Analysis and Critical Control Point (HACCP) procedures.

Samples were mainly tested for HAV at the Istituto Zooprofilattico Sperimentale della Lombardia ed Emilia-Romagna (IZSLER) using a PCR-based method described in Le Guyader et al. IZSLER also performed HAV genome analysis as described in Chiapponi et al.

The supplying chain of the ingredients included in the implicated lots was traced back, up to the primary production level (fruit farmer or picker) whenever possible. Data were obtained by the local health authorities for the Italian suppliers and via the EC’s Rapid Alert System for Food and Feed (RASFF) for suppliers located abroad. Trace-back and food investigation started after the confirmation of the first sample of frozen berries contaminated with HAV identified during the outbreak investigation in April 2013 and were conducted until 31 August 2014.

A food monitoring plan based on sampling and testing was primarily dedicated to assess which frozen berry products were implicated in HAV transmission, to trace the origin of HAV contamination.

Frozen berry products connected with the HAV outbreak were classified as follows:

- **Confirmed lot:** any lot of frozen berries for which microbiological evidence of HAV contamination was available.
- **Suspect lot:** any lot of frozen berries consumed by one or more outbreak case in the 15–50 days before the onset of symptoms, for which no microbiological evidence of HAV contamination was available.
- **Possible product:** any brand of frozen berries consumed by one or more outbreak case, for which the lot number could not be identified.

Suspect lots of frozen berries were identified from cases’ interviews and/or traceability data from shops or restaurants where they had been purchased or consumed.

Traceability information on suppliers and origin of frozen berries was collected for both confirmed and suspect lots starting from each ingredient used to make up the lot by the packing company. Transactions of frozen or fresh berries along the supplying chain were investigated backwards up to the primary production level (fruit farmer or picker) in order to unravel the architecture of the network of suppliers behind each ingredient and lot. Tracing-back data were encoded and stored in a dedicated database and analysed after validation by ISS. For each ingredient, transactions and suppliers were analysed in terms of type of berry supplied, type of activity and location of supplier, lot number, amount and date of delivery and date of production. For each lot comparative analysis of traceability data was carried out in order to identify suppliers and transactions in common to different types of berry, lots and packing companies so as to uncover the potential point in the berry-supplying chain where HAV contamination could have occurred. Criteria that drove the data collection and the analyses considered the hypotheses of either fresh berries pre-harvest contamination at the primary production level or during harvesting or frozen berries post-harvest contamination, including cross-contamination, during any processing of berries including freezing, sorting and re-packing.

RESULTS

Description of the outbreak

Through the enhanced surveillance (from 1 January 2013 to 31 August 2014), a total of 1803 cases of HAV were identified in Italy. Sequencing was possible for some of these cases (n=368, 20.4%), mostly those sampled between 1 January 2013 and 28 February 2014. Consequently and applying the case definition, 246 (66.8%) cases were confirmed as harbouring an HAV outbreak strain and 122 were classified as not outbreak cases: of those 93 (25.3%) harboured genotype IA sequences unrelated to the outbreak, 27 (7.3%) were genotype IB and 2 (0.5%) were genotype IIA [14]. The residual 1435 cases were not sequenced and classified as probable.

The epidemic curve in Fig. 1 shows the distribution of all HAV cases notified in Italy from January 2013 to August 2014 classified according to the outbreak case definition above described. The median age of probable cases was 32 years (mean: 31.8; range: 1–89) and 775 cases (54.0%) were males; more than 20 % of probable cases (n=309) were between 25 and 44 years old; the attack rate among this group was 2.7 per 100 000 person-years. The median age of confirmed cases was 38 years (mean: 38.5; range: 9–67) and 133 cases (54.0%) were males. The gender distribution was similar among confirmed, probable and not outbreak cases. Age, geographical area and the rate of hospital admission showed significant differences among groups. A total of 86.3 % among confirmed and 84.7 % among probable cases were admitted to hospital, with a median duration of hospitalization of 7 days (range: 1–60 days); the median age of hospitalized cases was 34 years (mean: 34; range: 1–89) and 55.3 % were males. One death among probable cases was reported. According to the case definition, 2.6 % (21/1026) were secondary cases (4 confirmed and 17 probable).

Consumption of frozen berries was a very frequent risk factor reported by probable cases (296/638; 46.4%). In confirmed cases, 78.2% reported the consumption of frozen berries (Table 1).

Information on the place of consumption of frozen berries was available for 214 cases: 117 were exposed at home and 97 were exposed in public settings (e.g. restaurant, canteen, coffee and pastry shops). The type of consumed frozen berries was reported by 221 cases: 212 patients ate mixed frozen berries, and 9 ate single berry products. Brand and lot number of
frozen berry products consumed by patients could be identified in 83 cases while 53 patients could only remember the brand.

**Trace-back and food investigation**

From April 2013 to August 2014, 1982 samples of mixed or single-ingredient frozen berries were sampled all over the country and tested for HAV. HAV was detected in 15 samples belonging to different lots of production. HAV sequence obtained from one positive sample proved to be 100% similar to the genotype IA outbreak strain.

In addition, 47 lots epidemiologically related with outbreak cases were identified based on cases’ interviews. The lots had been packaged by 13 different companies between February 2012 and November 2013 (Table 2 and Fig. 2). Thirty-four lots, including 14 HAV confirmed lots, could be traced back. They included six types of berries, mainly blackberries, blueberries, raspberries and redcurrants. A total of 1691 transactions from 406 different suppliers located in 19 different European Union (EU) and extra-EU countries could be traced back, as of 30 September 2014. However, completeness of the tracing back up to primary level varied importantly among lots and types of berry. Redcurrants and raspberries had the highest completeness with 77.4% and 43.3% of the lots containing these types of berry being traced back up to the primary level, respectively. In contrast, blackberries and blueberries had the lowest level of completeness with only 9.1% and 12.1% of total lots having the information on primary production available, respectively. To overcome this lack of data, the country where the freezing process of the fresh berries took place was assumed as the country of origin of the ingredient. Ingredients originated from 10 different countries but mostly from Poland, Bulgaria, Canada and Republic of Serbia (Table 3). Many suppliers linked to several lots or packing companies that had processed the lots could be identified but none was connected with all the lots or packing companies. In particular, 175 and 15 suppliers were connected to

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**Table 1. Risk factor distribution among cases of hepatitis A, by case definition, in Italy, 2013–2014**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Probable cases, no. (%)</th>
<th>Confirmed cases, no. (%)</th>
<th>Non-cases, no. (%)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Shellfish consumption</td>
<td>500 (49.5)</td>
<td>107 (54.3)</td>
<td>66 (63.5)</td>
<td>0.017</td>
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<tr>
<td>Consumption of well water</td>
<td>121 (12.4)</td>
<td>12 (6.4)</td>
<td>15 (15.3)</td>
<td>0.034</td>
</tr>
<tr>
<td>Consumption of frozen berries*</td>
<td>296 (46.4)</td>
<td>133 (78.2)</td>
<td>13 (39.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Travel outside Italy</td>
<td>296 (20.6)</td>
<td>22 (8.9)</td>
<td>34 (27.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Contact with HAV case in the previous 15–50 days</td>
<td>17 (2.2)</td>
<td>4 (2.4)</td>
<td>2 (2.3)</td>
<td>0.935</td>
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</table>

*The information on frozen berries was collected only since May 2013.*
more than one lot and more than one packing company, respectively. The highest number of lots and packing companies connected with the same supplier was 19 (55.8 % of the traced-back lots) and 4 (40.0 % of the companies), respectively.

Blackberries and redcurrants were the fruits with the highest number of lots sharing the same supplier. Tracing-back data show that only one single type of berry (i.e. redcurrants) originated from the same country for all the lots implicated in Italy.

Control measures
A range of public health actions were undertaken at national and regional levels, based on the outcomes of the investigations. All the contaminated frozen berry lots placed on the market were withdrawn and recalled as soon as the HAV contamination was detected and communicated by the Ministry of Health via RASFF (https://ec.europa.eu/food/safety/rasff_en). Thus, a total of 13 lots were continuously withdrawn and recalled from May 2013 to December 2013 (3 lots in May, 1 lot in June, 1 lot in August, 4 lots in September, 3 lots in October 2013 and 1 lot in December).

Vaccination of close contacts of all HAV cases was recommended by the Ministry of Health. Communication campaigns using the Ministry of Health and ISS websites, leaflet, press releases and engaging stakeholders were aimed at warning the general public, restaurants and catering companies about the risk of eating raw frozen berries and giving advice on the need of boiling frozen berries for at least 2 min before consumption [17]. Guidelines to support food business operators processing frozen berries in improving HACCP were also developed and disseminated [18]. A guideline was also prepared to reinforce, at national level, the detection of HAV in frozen berries imported from outside the EU [19]. Four packing companies manufacturing contaminated lots were inspected soon after the detection of HAV in frozen berries, starting from June 2013. Inspections were aimed at verifying any possible failures with the documentary requirements, hygiene conditions of the equipment, facilities and processing environment, manufacturing and hygiene procedures and the health status of the employees. Implementation of HACCP was also checked. All the companies adopted strictly Good Manufacture Process and own HACCP systems. Laboratory testing to assess bacteriological contamination of the food supply was correctly applied. The disinfection procedures used by three out of the four companies were effective to eliminate any possible HAV contamination of the fomites. In the plant where disinfection procedures had proved ineffective, 5 samples of frozen berries and 18 surface swabs were collected and

Table 2. Distribution of frozen berry lots (n=61) linked to the HAV outbreak in Italy, 2013/2014, by packing company

<table>
<thead>
<tr>
<th>Packing company</th>
<th>No. frozen berry lots contaminated with HAV (confirmed lots)</th>
<th>No. frozen berry lots with suspected contamination with HAV (suspect lots)</th>
<th>No. confirmed cases</th>
<th>No. probable cases</th>
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<tr>
<td>ID Country</td>
<td>Total (no.)</td>
<td>Traced-back (no.)</td>
<td>Total</td>
<td>Traced-back</td>
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<tr>
<td>a Italy</td>
<td>6</td>
<td>6</td>
<td>24</td>
<td>5</td>
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<tr>
<td>b Italy</td>
<td>1</td>
<td>1</td>
<td>12</td>
<td>12</td>
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<td>c Italy</td>
<td>1</td>
<td>1</td>
<td>4</td>
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<td>d Italy</td>
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Fig. 2. Distribution of confirmed and suspect lots (n=61) of frozen berries connected with the HAV outbreak in Italy, 2013 and 2014, by month of production. For one suspect lot, the information was not available. Black and grey boxes indicate confirmed and suspect lots, respectively.
submitted to the laboratory; all tested negative for HAV at IZSLER.

**Current situation and ongoing investigation**

After August 2014, the number of new cases slowed down and the outbreak appeared to be over. The epi-curve showed a decreasing trend over time and HAV cases returned within the expected number reported to the surveillance system over the years. However, in September 2015, a new confirmed case (with onset in August 2015) was notified by Veneto region in a patient that reported the consumption of frozen berries. It was a sporadic case; no more confirmed cases have been reported since then but the Ministry of Health decided to extend the enhanced surveillance for HAV, which is still ongoing. However, to date, no more confirmed cases have been identified.

**DISCUSSION**

In 2013–14, Italy experienced a large community-wide outbreak of HAV infection with approximately 1800 HAV reported cases, 1435 of which were probable and 246 were confirmed cases. Frozen mixed berries were identified as the main vehicle of infection through a complex and challenging outbreak investigation, conducted with an integrated approach using data from each point across the human and food chain. This approach has been described as the best practice in the surveillance of food-borne diseases at global level [20, 21].

Robust evidence that the outbreak was associated with the consumption of frozen berries was soon obtained after the national outbreak was declared in May 2013 [11]. Molecular characterization of HAV isolated from outbreak cases identified that a specific genotype IA strain was implicated in the outbreak. Results of the matched case–control study pointed out frozen berries as the main risk factor associated with the disease [Adjusted Odds Ratio (AOR), 4.2; 95 % confidence interval (CI), 2.5–7.0; Population Attributable Factor (PAF), 26 %]. The restricted statistical analysis conducted on the 24 cases with confirmed outbreak sequence identified berries as the highest associated risk factor for hepatitis A (AOR, 4.99; 95 % CI, 1.32–18.92; PAF, 63 %) followed by raw shellfish (AOR, 4.46; 95 % CI, 1.10–18.04; PAF, 43 %) [13]. These findings were definitely supported by the finding of a 100 % sequence similarity of HAV isolated in mixed frozen berries connected with outbreak cases [16].

The multi-country dimension of the outbreak was unveiled when autochthonous cases due to the same HAV outbreak strain were reported in other EU countries [22–24]. The source of contamination of frozen berries remains unknown and the route by which berries became contaminated could not be fully understood. The traceability investigation was very complex, but it ultimately seems not to exclude a contamination at pre-harvest stage. Circumstances of cross-contamination in the supply chain, distribution and packaging of frozen berries may have favoured the contamination of other positive batches. Berries are well-known vehicles of food-borne pathogens, including HAV [25, 26]. This type of food production is labour intensive and berries are often cultivated on small farms. Contamination and cross-contamination with HAV may occur in several ways at any point of the chain via equipment and water for irrigation and spraying of berry crops, particularly via food handlers and their excreta [26–28].

The pattern of contamination of frozen berries found in Italy appeared widespread and persistent, considering that
the 62 implicated lots had been packed by 13 companies located in 4 European countries during a 21 month period and all had 24 months shelf life. Our data indicate that only a limited proportion of the implicated lots were connected with the same supplier.

In 2011 and 2012, some Eastern European countries reported the highest number of hepatitis A cases across the EU; in particular, high rates were reported from Bulgaria, Romania and Estonia, suggesting a potential large HAV environmental contamination, as described in the European Centre for Disease Prevention and Control annual epidemiological report 2014 for food- and water-borne diseases [29].

Tracing-back data show that only one single type of berry (i.e. redcurrants) originated from the same country for all the lots implicated in Italy. At the EU level, redcurrants were also the only ingredient with the same country of origin present in both Italian and Norwegian products from which the HAV contamination could be attributed with certainty to the outbreak strain [30].

A traceability exercise coordinated by the European Food Safety Authority taking into account not only lots found in Italy but also the potential berries implicated in Ireland, Norway, France and The Netherlands has been conducted, but no single point source of contamination linking all 43 lots/cases could be identified [31, 32].

Evidence obtained in other EU countries involved in the same multi-country outbreak was fully consistent with our results, and it highlighted how large food-borne hepatitis A outbreaks may affect the increasingly susceptible EU/EEA (European Economic Area) general population and how, with the growing international food trade, frozen berries are a potential high-risk food [22].

Furthermore, results from our investigation suggest that several reasons exist for considering the risk profile of frozen berries for HAV among the highest. When consumed raw, frozen berries are ready-to-eat products. However, no points of mitigation of potential viral contamination exist from the farm to the consumer level whenever accidental contamination occurs. The intricate trading network of frozen berries implicates that, once frozen, berries could be delivered and processed worldwide creating the potential for cross-border prolonged international outbreaks to occur. Consequently, running molecular-based surveillance of HAV based on harmonized protocol should be highly encouraged, given that outbreaks associated with frozen berries consumption have increased in the last decade [33–35]. In the absence of any specific hygiene and microbiological standard for frozen berries, improvement of risk communication strategies should warn consumers and food services about the risks of consuming frozen berries uncooked.

Conclusions

In conclusion, to our knowledge, this is one of the largest food-borne hepatitis A outbreaks linked to frozen berries reported in the scientific literature in a single country. The successful investigation of this HAV outbreak demonstrates the importance of having strong management structures and coordination capability at national and international levels, which could only be obtained by sharing expertise in a multidisciplinary collaborative team and gathering information integrating epidemiological data, data from food and human laboratory investigations and data from trace-back activities. Moreover, since detecting community outbreaks from surveillance data can be extremely difficult, especially for diseases with long incubation periods such as hepatitis, collaboration among different sectors who share proactively the available information seems to be very important. While ideally integrated surveillance should be a routine, at least the molecular-based surveillance of HAV should be extended and maintained in Italy. However, some limitations that occurred at the very beginning and extended the time for operative control measures, probably resulting in a quite long-lasting outbreak should be mentioned: delays in notification, administrative hurdles and communication problems. However, as soon as the outbreak was declared, all efforts were put in place in order to identify the vehicle of the infection and the management and mitigation of the outbreak was possible through the combined efforts of epidemiologists, microbiologists and health and food safety authorities at national and regional levels.

APPENDIX

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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