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Foodborne transmission of hepatitis A and hepatitis E viruses: a literature review

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Abstract

Foodborne viruses have been recognized as a growing concern to the food industry and a serious public health problem. Hepatitis A virus (HAV) is responsible for the majority of viral outbreaks of food origin worldwide, while hepatitis E virus (HEV) has also been gaining prominence as a foodborne viral agent in the last years, due to its zoonotic transmission through the consumption of uncooked or undercooked infected meat or derivatives. However, there is a lack of scientific reports that gather all the updated information about HAV and HEV as foodborne viruses. A search of all scientific articles about HAV and HEV in food until March 2020 was carried out, using the keywords "HAV", "HEV", "foodborne", "outbreak" and "detection in food". Foodborne outbreaks due to HAV have been reported since 1956, mainly in the USA, and in Europe in recent years, where the number of outbreaks has been increasing throughout time, and nowadays it has become the continent with the highest foodborne HAV outbreak report. Investigation and detection of HAV in food is more recent, and

the first detections were performed in the 1990's decade, most of them carried out on seafood, first, and frozen food, later. On the other hand, HEV has been mainly looked for and detected in food derived from reservoir animals, such as meat, sausages and pate of pigs and wild boars. For this virus, only isolated cases and small outbreaks of foodborne transmission have been recorded, most of them in industrialized countries, due to HEV genotype 3 or 4. Virus detection in food matrices requires special processing of the food matrix, followed by RNA detection by molecular techniques. For HAV, a real-time PCR has been agreed as the standard method for virus detection in food; in the case of HEV, a consensus assay for its detection in food has not been reached yet.

Our investigation shows that there is still little data about HAV and HEV prevalence and frequency of contamination in food, prevalent viral strains, and sources of contamination, mainly in developing countries, where there is no research and legislation in this regard. Studies on these issues are needed to get a better understanding of foodborne viruses, their maintenance and their potential to cause diseases.

Keywords: foodborne viruses; food; foodborne outbreak; detection in food.

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Author contributions: Guadalupe Di Cola and Anabella Fantilli performed the literature search, the analyses of the results, and wrote of the original draft. María Belén Pisano and Viviana E. Ré carried out the conceptualization, the supervision of all the search process, and reviewed and edited the manuscript.

1. Introduction

Each year, unsafe food causes 600 million cases of foodborne diseases and 420000 deaths worldwide (WHO, 2019). Human pathogenic viruses are among the most frequent causative agents of foodborne diseases. These viruses are released into the environment by various routes, including water run-offs, sewage and aerosols. The main foods contaminated with viruses correspond to fruits, salads of raw vegetables, oysters and raw fish. Foodstuffs of animal origin, such as sausages, salami or pate can be contaminated with viruses and their consumption may cause human infection if the viral particles are not inactivated during food processing (Rodríguez-Lázaro et al., 2012).

In 1999 the Codex Alimentarius Commission started to concern about the importance of enteric virus transmission by food. A European group proposed that Codex Committee on Food Hygiene should take into serious consideration viral hazard for food safety to develop recommendations for their control, as the foodborne transmission of viruses can be attributed to the extreme stability of these viruses outside their host, and to the their highly infectious nature (CAC, 1999; Koopmans et al., 2002). In 2008, a FAO/WHO meeting was carried out and, as a result, a Meeting Report entitled *Viruses in Food: Scientific advice to support risk management activities* was published. This document underlines the significance to evaluate the state of knowledge on viruses in foods and their public health and trade impacts (FAO/WHO, 2008). Later, during the FAO/WHO Expert Meeting on Food Viruses in 2012, it was agreed that hepatitis A virus (HAV) is one of the greatest concerns regarding food safety, being responsible of numerous outbreaks in the world, and it was drafted a Proposed Draft Guidelines for the Control of Food Viruses. The document also notes that, even though the transmission of zoonotic viruses through food is not commonly reported, it does occur, as demonstrated in the case of hepatitis E virus (HEV) (FAO/WHO, 2012), which has acquired greater prominence in recent years as a possible threat of food transmission.

HAV is a causative agent of acute self-limited hepatitis, which in 0.6% of the cases can lead to fulminant hepatitis. It is a small non-enveloped single-stranded RNA virus, belonging to the *Picornaviridae* family. There are six HAV genotypes (I to VI), all of them belong to only one HAV serotype. Genotypes I, II and III, divided into subtypes A and B, infect humans. Genotype I, followed by III, are the most commonly reported, while genotype II is hardly ever isolated and its genetic diversity is unknown. On the other hand, genotypes IV, V, and VI have been found in infected non-human primates (Desbois et al., 2010; Vaughan et al., 2013).

HAV infection is frequent and endemic in developing countries, where infections are most commonly acquired during early childhood, usually asymptomatic or mild, resulting in a high proportion of adults immune to HAV (Mohd Hanafiah et al., 2011). On the other hand, in developed regions, the incidence of HAV infections is low. Due to a decrease in HAV circulation among population, large proportions of young adults might have never been exposed or vaccinated against HAV and are susceptible to infection. Thus, hepatitis A virus could re-emerge through outbreaks in regions where it is not endemic (Mariojoules et al., 2019; Ndumbi et al., 2018).

HEV (family *Hepeviridae*, genus *Orthohepevirus*, specie *Orthohepevirus* A) is a non-enveloped, positive-sense, single-stranded RNA virus. It has been classified into 8 genotypes (HEV-1 to HEV-8), genotypes 1 to 4 and 7 have been shown to infect humans (Smith and Simmonds, 2018; Sridhar et al., 2017). Only HEV-3 and HEV-4 are considered zoonotic and have been observed in different animal species and in sporadic human cases. HEV-3 has a worldwide distribution, while HEV-4 is mainly found in Asia and to a lesser extent in Europe. The main reservoirs for these genotypes are pigs, wild boars and deers, and the virus can be transmitted through zoonotic and foodborne pathways, mostly by consumption of uncooked or undercooked infected pork or game meat (Di Bartolo et al., 2012; Geng and Wang, 2016). Besides, HEV-7 has been identified in camels and in a man who regularly consumed camel meat and milk (Cook et al., 2017; Lee et al., 2015). Despite the virus causes acute infections (most of the cases are asymptomatic), HEV may also cause fulminant hepatitis in those

individuals with other underlying liver diseases and in pregnant women (up to 30% of fatal hepatic failure when the infecting genotype is 1). Moreover, immunosuppressed subjects might develop chronic hepatitis, mainly associated with HEV-3 and HEV-4 (Doceul et al., 2016; Gupta and Agarwala, 2018).

Foodborne viruses, including HAV and HEV, can persist for months in food products or in the environment (soil, water, sediments, bivalve mollusks, inanimate surfaces), and most of them are more resistant than bacteria to commonly used control measures (refrigeration, freezing, pH, drying, ultraviolet radiation, heat, pressure, disinfection). Three main sources of viral contamination of food have been identified: 1) wastewater/human feces, 2) infected people handling food, and 3) animals infected with zoonotic viruses. The combinations of viruses and food products with greater concern for public health are: a) HAV in prepared foods (ready for consumption), bivalve mollusks and fresh products (many times with the joint presence of norovirus); b) HEV contaminating drinking water, raw deer, semi-raw pork liver, wild boar meat and raw products derived from animals (such as salami) (RSA, 2019). For HEV, there are alternative transmission routes that do not involve foods or water, such as blood transfusions and vertical transmission, which are becoming increasingly relevant (Perez-Gracia et al., 2015). Figure 1 shows possible routes of introduction of HAV and HEV in the food chain and sources of infection to humans.

HAV and HEV outbreaks involving a food item are particularly challenging to identify because of: a) a long incubation period of these viruses (2-10 weeks, approximately), b) the difficulty for patients to remember food consumption history before illness, c) some asymptomatic cases may not be reported, d) viral contamination levels of a food item may be low and focal and, therefore, hard to detect (Sánchez et al., 2007) and e) a low level of knowledge of the health care team about foodborne viral diseases. The latter has probably led to an underestimation of the food transmission of these viruses, especially HEV.

With this background, we aimed to collect updated information about outbreaks and detections of HAV and HEV in food, in order to elucidate the impact of these viruses on

foodborne diseases and human health all over the world. For that purpose, we searched published scientific articles regarding HAV and HEV outbreaks related to food transmission, and viral detections in food, until March 2020, by assessment of PubMed (NCBI) using the following keywords: HAV, HEV, foodborne, outbreak and detection in food. Additional relevant publications were identified from articles found in PubMed. From 919 abstracts, 231 were considered pertinent since they met at least one of the following conditions: a) include HAV and/or HEV detections in food matrices, b) contain information about foodborne hepatitis outbreaks associated with these viruses (those related to contaminated water were dismissed), and c) comprise the current methodology used to detect them. Specific requirements taken into account for the article writing are detailed in each section.

2. HAV and HEV detections in food

HAV is considered one of the most serious foodborne viruses, and it has been the most extensively studied with regard to virus detections in foods. The first detections of HAV in food matrices were performed in the 1990's decade, and most of the studies focused their search and detection on seafood. HAV findings in foodstuffs are summarized in Supplementary Table 1 (those linked to outbreaks were not considered in this section). It is widely documented that bivalves are one of the riskiest foods when eaten raw or undercooked (Rizzo et al., 2007), not only to HAV transmission but also to other enteric viruses, because of their filter-feeding nature. In recent years, frozen foods have been investigated more deeply for the presence of HAV (Bozkurt et al., 2020; Nasheri et al., 2019; Tavoschi et al., 2015). HAV genotype does not appear to be related to the route of transmission, and it is rarely determined, only for epidemiological (and non-diagnostic) purposes.

On the other hand, HEV has been recognized as an emerging pathogen in the last years in industrialized countries and, since it was first associated with food transmission in 2003 (Heldt et al., 2016), it has also been looked for in food products derived from reservoir animals. Most HEV detections performed in meat or derivatives

of pork and wild boar, belong to the zoonotic genotypes 3 and 4. It is assumed that these products could play an important role in the transmission and maintenance of HEV, reaching positive values of viral RNA up to 70% (Boxman et al., 2019). Besides, in the last years, HEV has been detected in milk of many animals, which could be a source of infection for consumers, especially in rural areas, where handmade food products are not subjected to decontamination processes and/or control of microorganisms. HEV genotype 3 has also been found (detected by PCR techniques) in shellfish, evidencing the need for the implementation of control measures in seafood too (Chan et al., 2017; Crossan et al., 2012; O'Hara et al., 2018). Supplementary Table 2 summarizes all HEV detections in food published up to date. We considered only food or products obtained in retails, markets and grocery stores. We did not contemplate pork or wild boar samples obtained in slaughters, abattoirs or farms, since it was not clear if they were going to be destined for consumption.

Leafy green vegetables, frozen fruits and ready-to-eat salads are accompanied by new food safety threats, since they are eaten raw, and usually without any further washing/decontamination procedures (Little and Gillespie, 2008). HAV and HEV have rarely been detected in raw vegetables and fruits worldwide, which could probably be due to that these foods would not be the main route of transmission, or to the low number of research studies carried out on them up to date (Brassard et al., 2012; Khan et al., 2014; Martí et al., 2017; Maunula et al., 2013; Parada-Fabián et al., 2016; Purpari et al., 2019; Randazzo et al., 2018c; Shin et al., 2019; Terio et al., 2017). Figure 2 shows the main matrices in which viruses have been detected worldwide (Abad et al., 1997; Amri et al., 2011; Banks et al., 2010; Bazzardi et al., 2014; Benabbes et al., 2013; Berto et al., 2012; Bigoraj et al., 2014; Bouwknegt et al., 2007; Boxman et al., 2019; Brassard et al., 2012; Chan et al., 2017; Chironna et al., 2002; Cioffi et al., 2018; Coelho et al., 2003; Colson et al., 2010; Cossaboom et al., 2016; Croci et al., 2007, 2000; Crossan et al., 2012; De Medici et al., 2001; Demirci et al., 2019; DePaola et al., 2010; Di Bartolo et al., 2015, 2012; Di Pasquale et al., 2019; Diez-Valcarce et al., 2012; Elamri et al., 2006; Fang et al., 2016; Feagins et al., 2007;

Formiga-Cruz et al., 2002; Fusco et al., 2019, 2017; Geng et al., 2019; Gharbi-Khelifi et al., 2007; Giannini et al., 2018; Gutiérrez-Vergara et al., 2015; Hansman et al., 2008; Heldt et al., 2016; Iaconelli et al., 2015; Intharasongkroh et al., 2017; Khan et al., 2014; Kingsley et al., 2002; Kitahashi et al., 1999; Kittigul et al., 2010; Korsman et al., 2019; La Rosa et al., 2018, 2012; Le Guyader et al., 2000, 1994; Li et al., 2007; Macaluso et al., 2006; Manso et al., 2010; Manso and Romalde, 2013; Marti et al., 2017; Martin-Latil et al., 2014; Maunula et al., 2013; Mesquita et al., 2016; Monge and Arias, 1996; Montone et al., 2019; Moor et al., 2018; Muniain-Mujika et al., 2003; Mykytczuk et al., 2017; Namsai et al., 2011; Nenonen et al., 2006; O'Hara et al., 2018; Parada-Fabián et al., 2016; Pavio et al., 2017; Pereira et al., 2018; Polo et al., 2015; Purpari et al., 2019; Randazzo et al., 2018c; Roldán et al., 2013; Romalde et al., 2002; Shin et al., 2019; Sincero et al., 2006; Suffredini et al., 2017; Szabo et al., 2015; Terio et al., 2017; Wang et al., 2008; Wilhelm et al., 2014; Wong et al., 2019; Yazaki et al., 2003).

3. Main characteristics of the foodborne HAV and HEV outbreaks

Transmission of HAV by contaminated food or water is a well-recognized phenomenon, and the first records of outbreaks involving food date from the 1950's decade (Roos, 1956). About 118 foodborne HAV outbreaks from 1956 up to date (2019) were identified in the published literature, and they are represented in Figure 3, according to the region in which they occurred. Supplementary Table 3 shows the outbreaks organized according to the date of the event, the number of people involved, the implicated food or food handler, the HAV genotype responsible for the outbreak, the location, and the possible source of food contamination. We contemplated outbreaks whose implicated source was confirmed or not by PCR (Amon et al., 2005; Apaire-Marchais et al., 1995; Becker et al., 1996; Beller, 1992; Bialek et al., 2007; Bosch et al., 2001; Boxman et al., 2016; Bozkurt et al., 2020; Butt et al., 2004; Calder et al., 2003; Cao et al., 2009; Carvalho et al., 2012; CDC, 2019, 1993; Chironna et al., 2004, 2002; Collier et al., 2014; Conaty et al., 2000; Costa-Mattioli et al., 2001; Dalton et al., 1996; Denes et al., 1977; Dentinger et al., 2001; Desenclos et al., 1991; Dismukes et al.,

1969; Donnan et al., 2012; Dougherty and Altman, 1962; Enkirch et al., 2018; Fitzgerald et al., 2014; Fournet et al., 2012; Frank et al., 2007; Franklin et al., 2019; Fujiyama et al., 1985; Furuta et al., 2003; Gallot et al., 2011; Goh et al., 1984; Gossner and Severi, 2014; Guillois-Bécel et al., 2007; Gurav et al., 2019; Gustafson et al., 1983; Guzman-Herrador et al., 2015; Halliday et al., 1991; Hanrahan et al., 1984; Harries et al., 2014; Hasegawa et al., 2007; Hernández et al., 2019; Hooper et al., 1977; Hu et al., 2020; Hutin et al., 1999; Istre and Hopkins, 1985; Joseph et al., 1965; Kosatsky and JP, 1986; LaPorte et al., 2003; Latham and Schable, 1982; Lee et al., 2004; Leoni et al., 1998; Levy et al., 1975; Lopalco et al., 1997; Lowry et al., 1989; Mackowiak et al., 1976; Marosevic et al., 2019; Mason and McLean, 1962; Massoudi et al., 1999; Mele et al., 1989; Meyers et al., 1975; Mishu et al., 1990; Mollers et al., 2018; Niu et al., 1992; Nordic Outbreak Investigation Team C, 2013; O'Mahony et al., 1983; Ohara et al., 1983; Osterholm et al., 1980; Parker et al., 2014; Pebody et al., 1998; Petrignani et al., 2014, 2010; Pintó et al., 2009; Pontrelli et al., 2008; Portnoy et al., 1975; Reid and Robinson, 1987; Robesyn et al., 2009; Roels et al., 1998; Roos, 1956; Rosenblum et al., 1990; Rowe et al., 2009; Ruddy et al., 1969; Sánchez et al., 2002; Sane et al., 2015; Scavia et al., 2017; Schenker et al., 2006; Schmid et al., 2009; Schoenbaum et al., 1976; Schwarz et al., 2008; Severi et al., 2015; Shieh et al., 2007; Smith et al., 2019; Snydman et al., 1981; Stroffolini et al., 1990; Swinkels et al., 2014; Tang et al., 1991; Tavoschi et al., 2015; Viray et al., 2019; Wang et al., 2014; Warburton et al., 1991; Weltman et al., 1996; Wheeler et al., 2005; Yoon et al., 2009).

Since its first detection, HAV outbreaks by food consumption were recorded mainly in the USA (America), probably due to the further study of the virus and the cases. Then, an increase in the number of foodborne hepatitis A outbreaks associated with infected travelers and imported frozen produce items from endemic regions to developed countries occurred (Nasheri et al., 2019; Sánchez et al., 2007), such as to Europe. In this continent, the number of outbreaks has been growing through time, and nowadays it has become the region with the highest number of foodborne outbreaks registered.

Transnational outbreaks of foodborne infections are currently reported with increasing frequency as a consequence of globalization and international food trade (Hu et al., 2020). Thus, HAV has been considered a reemerging major public health concern, especially in high-income regions (Sprenger, 2014).

The fact that the vast majority of foodborne HAV outbreaks have been recorded in developed countries would reflect two things: 1) a higher number of studies of viruses in food and, as a consequence, better surveillance systems for foodborne diseases and a higher number of outbreak reports; 2) better sanitary conditions, which leads to less unsafe water and person to person transmission; therefore, foodborne transmission in these scenarios would be relevant. The most common items involved in foodborne HAV outbreaks in the last years have been frozen berries, semi-dried tomatoes and ready-to-eat foods (Fiore, 2004), compared to the predominance of seafood as the principal cause of HAV outbreaks in the past (Figure 3). This could be a consequence of more effective food safety control measures during the processing and handling of seafood.

Regarding foodborne cases and outbreaks related to HEV, we only took into account those with positive detection of HEV RNA by PCR. Isolated cases and small foodborne outbreaks have been recorded, all related to zoonotic genotypes 3, 4 and 7 (Table 1). This could be due to insufficient virus surveillance in food, which could lead to underreports on food transmission cases, especially in developing countries. In some regions, such as Europe, foodborne transmission linked to consumption of pork and game meat is considered the main source of autochthonous infection, and small outbreaks have been reported linked to the consumption of pork liver sausages and wild boar meat (Montone et al., 2019). Seafood has also been linked, though to a lesser extent, to outbreaks due to HEV.

4. Methods used for HAV and HEV detection in food.

Virus detection in food matrices can be problematic due to low virus concentrations in food samples and to the presence of significant inhibitors in food that prevent methods

from working properly (Sánchez et al., 2007). Therefore, the development of standard, efficient, accurate and highly sensible methods for virus isolation in food (either the viral genome or the intact viral particle) has been a subject of study in recent years (Papafragkou and Kulka, 2016).

Although special processing is required according to the wide variety of food matrices, virus detection in food generally includes a step of virus extraction from the food matrix, the viral genomic material purification phase and the molecular detection, especially RNA detection, which is commonly carried out by real-time reverse transcription PCR (RT-qPCR) techniques (Stals et al., 2012).

Viral extraction, for subsequent recovery of the viral genomes or for infectivity-based assays, is one of the most critical steps, and it includes separation and concentration of viruses from food matrices. There are three main approaches described in the literature for this procedure: a) elution (using a neutral or basic elution buffer)–concentration protocol; b) direct genomic material extraction from food with the use of stronger denaturants/detergents (Papafragkou and Kulka, 2016); and c) proteinase K treatment (Stals et al., 2012). After viral extraction from food, RNA extraction is carried out; most of the protocols are based in commercial kits that use columns of silica. Then, virus detection is performed by PCR, nested-PCR or real-time PCR, depending on the virus and the protocol used. Due to the particularity of food matrices, which are challenging due to the physical and chemical properties of foods, a virus process control is generally added, to measure the efficiency of the different steps that are considered critical for a correct detection (Bosch et al., 2018; Stals et al., 2012). Ideally, process controls should be: 1) genetically related to the tested virus, 2) easy to cultivate, and 3) unlikely to naturally contaminate the tested food sample. Some of them are: murine norovirus 1 (MNV-1), the feline calicivirus (FCV), a genetically modified mengovirus (vMC0), the MS2 bacteriophage and PP7 bacteriophage (Stals et al., 2012).

4.1. Methodology for HAV

Since the number of protocols described for the detection of HAV in food is extremely high, and with numerous small variations (which could not be fully described in detail), in this review we took into account the most frequently used and the most current ones. Because of this reason, in 2013 the European Committee for Standardization and the International Standards Organization (ISO) published a standard methodology for quantitative and qualitative determination of HAV in food (together with norovirus), using real-time PCR (ISO 15216, 2017). This protocol has allowed an increasing number of HAV infections to be definitively linked to contaminated food consumption (Bosch et al., 2018), and it is the preferred one to be used currently. This international method has been validated in seven food matrices: bottled water, food surfaces (bell pepper pieces), oysters (*Crassostrea gigas*), common mussels (*Mytilus edulis*), raspberries, lettuce and green onions. After obtaining the appropriate quantity of food to be assayed, subsequent steps include concentration and virus detection/identification.

According to the ISO standard 15216, viruses are concentrated and removed with different methods depending on the matrix: for food surfaces viruses are extracted by swabbing; for soft fruit, leaf, stem and bulb vegetables, the process consists of an elution step with agitation and it includes precipitation with PEG/NaCl; for bottled water, it is done by adsorption and elution using positively charged membranes followed by concentration by ultrafiltration; and for bivalve molluscan shellfish, with a proteinase K solution that disintegrates tissues of the digestive glands.

Apart from precipitation with PEG/NaCl or ultrafiltration (described in the ISO), there are other common concentration methods, for instance: immunomagnetic separation (based on magnetic beads coated with different kinds of ligands, such as specific antibodies against HAV) or general cationic particles to capture the viral agent. In recent studies, as an alternative to antibodies, carboxyl beads (Zheng and Hu, 2017), Ricin A (Ko et al., 2015) and Concanavalin A (Ko et al., 2018) were used for HAV concentration, showing a significantly higher binding affinity to HAV than other molecules.

The next step includes RNA extraction, and according to the international standard, it is carried out based on viral lysis with guanidine thiocyanate, a chaotropic reagent, and adsorption to silica particles. After RNA is purified, detection is carried out by RT-qPCR. Some authors have used primers targeted to VP1 capsid region (Brooks et al., 2005), but other primers targeting the highly conserved 5'-noncoding region are also well-known (Abd El Galil et al., 2005; Costa-Mattioli et al., 2002; Costafreda et al., 2006; Hewitt and Greening, 2004; Jothikumar et al., 2005; Silberstein et al., 2003; Villar et al., 2006). In the ISO standard, 5'-noncoding region is amplified.

The ISO norm includes some controls throughout the procedure: the process control virus to determine the level of recovery (mengovirus), an external amplification control to monitor the possible RT-PCR inhibition (purified single stranded RNA carrying the target sequence for the target virus) and a double stranded DNA (dsDNA) control to make a standard curve (ISO 15216, 2017).

4.2. Methodology for HEV

In the case of HEV RNA detection in food, mainly of animal origin, no standardized methods have been described. Detection rates vary according to the type of samples processed and the method used. Due to that HEV replicates within pork liver tissues, virus extraction procedure in some pork food products is a crucial step that requires an efficient and accurate disruption for releasing HEV from food (Hennechart-Collette et al., 2019). Several techniques of sample homogenization, virus concentration and nucleic acid extraction, followed by RT-PCR or real-time RT-PCR, have been tried in pork products, using artificially contaminated matrices and several internal controls, which have led into different recovery rates. Table 2 summarizes the methods proposed up to date to concentrate and eluate HEV from meat and other animal products. Briefly, most of them use a homogenization buffer to eluate viruses, followed by mechanical disruption and/or centrifugation for clarification. Numerous groups base their techniques on the protocol described by Szabo et al. (2015) and checked by Althof et al. (2019).

Even though most of the published protocols are capable of detecting HEV in food matrices (with greater or lesser recovery), and all of them are used by different research groups, we consider it is necessary and important to achieve a consensus standardized protocol for this virus, which would lead to more reliable detections and allow virus surveillance in food, as well as comparisons between laboratories.

4.3. Viral quantification and typing

After a positive detection for HAV or HEV in food, viral quantification and typing is frequently performed. Quantification of viruses in food matrices represents an advance in outbreak investigations and routine monitoring, as it can provide data to establish acceptance levels in food commodities and development of quantitative risk assessments (Bosch et al., 2018; Pintó et al., 2009). However, there are still discrepancies about the protocol and the internal control to be used, which makes comparisons and the adoption of unified decision criteria very difficult. Therefore, there are no current regulations related to acceptable levels of viruses (e.g. standards, guidelines or specifications). Consequently, most food companies and authorities which perform food testing mainly ask for qualitative results as part of production hygiene analyses or outbreak investigations (Bosch et al., 2018; Müller et al., 2015). Real-time PCR is the most commonly used method for quantification of viruses in food, and the standardized one (ISO 15216, 2017), although viral quantification (and particularly HAV and HEV) from food matrices using digital PCR has been reported as an efficient methodology for this purpose (Fraisse et al., 2017; Martin-Latil et al., 2016).

Most foodborne viral outbreaks cannot be prevented or intervened because the explicit links between contaminated food and infected individuals cannot often be identified. Molecular epidemiologic techniques in the area of food safety, such as genomic methods, hold promise for identifying and typing the viral strain, which allows to know the possible source of foodborne outbreaks (Papafragkou and Kulka, 2016). In order to collect epidemiological information, apart from obtaining more detailed exposure

histories during case investigations, it is also recommended to perform systematic typing of strains from serum specimens obtained from infected persons involved in outbreaks and to carry out surveillance of viruses in food commodities related to outbreaks; thus, food can be linked to outbreaks that have occurred to assess the magnitude of the problem, to study possible routes of transmission and to inform the population to prevent further infections (EFSA, 2011; Sarvikivi et al., 2012). For this purpose, it might be useful to carry out conventional RT-PCRs targeting longer and more variable regions for sequencing, able to provide more phylogenetically relevant information (Bosch et al., 2018). Moreover, the convenient exchange of typing information and circulating strains between laboratories and countries should be encouraged (Shukla et al., 2018).

4.4. Detection of infectious viral particles

Although PCR detection is a reliable and accurate method, it has also generated reasoned debates among the scientific community about the interpretation of a positive test result in foods, as there is little information on distinguishing between the presence of amplifiable viral fragments and infectious viral particles. However, due to the fecal-oral route is the primary mode of HAV and HEV transmission, its presence typically suggests that fecal contamination has occurred somewhere along the supply chain from farm to fork.

This has left regulators and industry alike wondering how best to respond and react to positive findings (Bosch et al., 2018). Because of this, it would be recommendable to determine the presence of infective viral particles using cell culture. However, enteric viruses most commonly involved in outbreaks are difficult to culture *in vitro* because of the lack of efficient and robust cell culture systems (Martin-Latil et al., 2014; Papafragkou and Kulka, 2016; Prez et al., 2018), so integrated methods, using cell culture and RT-PCR assay, have been reported in some studies, and are considered a valid solution. Integrated methods were proved mostly in HAV studies and they consist of subjecting all positive samples by PCR screening to a cell culture assay and

detecting the presence of viruses in culture supernatant by RT-PCR. This integrated method is useful since even viruses not capable of producing the cytopathic effect, because present in very low concentration, can be detected (Jiang et al., 2004; Prato et al., 2006).

For HEV, no cell culture system has been shown to be applicable to all strains, none has been standardized, and not many studies have demonstrated their use for measurement of HEV infectivity in food samples (Cook et al., 2017). There are few reports which consider cell culture as a valid option for meat products, and only three studies have reported the successful isolation of HEV from pork products by cell culture, concluding that zoonotic transmission should be considered (Berto et al., 2013a, 2013b; Takahashi et al., 2012).

Other strategies to enable the differentiation between infectious and non-infectious viral particles, based on using viability markers to determine the viral capsid integrity, have been reported (Randazzo et al., 2018b): a) treatments with nucleases and/or proteolytic enzymes in order to remove any signal from damaged capsids (Lamhoujeb et al., 2008; Nowak et al., 2011; Schielke et al., 2011); b) treatments with intercalating dyes before extraction with a photoactivation step, e.g., propidium and ethidium monoazide (PMA and EMA) (Elizaquível et al., 2014) or without, e.g., platinum and palladium compounds (Fraise et al., 2018). These viability markers are used to pretreat samples before RNA extraction, combining with the RT-qPCR. Randazzo et al. (2018b, 2018a) studied the efficacy of intercalating dyes to distinguishing between infectious and inactivated HAV and HEV in environmental and food samples. Their results show that PMA–Triton pretreatment is suitable for the analysis of infectious HAV in complex food samples, such as vegetables and shellfish, and the platinum chloride ($PtCl_4$) pretreatment represents progress for more accurate interpretations of intact HEV quantification.

5. Control and prevention

Early and accurate identification of HAV and HEV in foods is of great importance to the successful handling of an outbreak, as well as to implement preventive measures and carry out public health interventions. Vaccination is the most efficient and safe preventive action to be performed. Many countries have included HAV vaccine to national immunization programs, leading to a decrease in disease morbidity rates and viral circulation; in the case of outbreaks, vaccination campaigns to mitigate HAV dissemination should be done (Sattar et al., 2000). At present, one hepatitis E vaccine has been commercially developed and licensed in China (HEV 239 vaccine, Hecolin®) and has shown a high degree of efficacy against hepatitis E (WHO, 2015).

Food handlers have been a major source of many reported foodborne virus outbreaks worldwide. A single infected food handler can transmit virus to dozens or hundreds of individuals during food preparation or serving. Hence, adequate sanitation and personal hygiene at this stage are important means of controlling transmission of hepatitis viruses (Tricco et al., 2006). Viral contamination may also occur during growing, harvesting, processing, distribution and storage of food by HAV or HEV infected workers or by contact with viral contaminated water during irrigation, handling and washing (Fiore, 2004; Koopmans and Duizer, 2004). Sewage discharge from several sources into the water that feeds shellfish beds can be another source of contamination (Conaty et al., 2000; Crossan et al., 2012; Halliday et al., 1991). In this sense, measures aimed at improving sanitary and living standards, such as adequate supplies of safe drinking water, proper disposal of sewage within communities and appropriate wastewater treatment, combined with personal hygiene practices, like regular hand washing, will contribute to decreasing viral propagation (Franco et al., 2012).

It is well known that HAV and HEV survive and remain infectious for long periods of time on a wide variety of animate and inanimate surfaces, such as dried feces, human hands, food superficies, environmental surfaces indoors, fresh or salt water, soil and roots (Chancellor et al., 2006; Petrignani et al., 2014); and they resist adverse environment conditions, which can be attributed to their non-enveloped viral structures.

For example, according to some experimental investigations, HAV transfer occurs with a 10 seconds casual contact between contaminated and clean surfaces, resulting in the transfer of nearly 10% of the infectious virus (Mbithi et al., 1992). Another investigation demonstrated that incubation of homogenates of contaminated pig livers in a 56°C bath for 1 hour did not entirely inactivate HEV (Feagins et al., 2008), supporting the idea that undercooked products may still transmit the virus (Emerson et al., 2005). This combination of high resistance to different environmental conditions and physical agents confers these viruses a strong potential to spread via foods. Therefore, sanitation systems that provide a hygienic environment, together with good food cooking (at high temperatures and for adequate periods of time), will reduce viral contamination in food and prevent disease transmission (Bae et al., 2014).

Finally, the establishment of food safety standards and control regulations to intercept unsafe food commodities, as well as the development of effective washing and sanitization processes by food industry, will help to prevent diseases by HAV and HEV.

6. Conclusion and future perspectives

In the last 20 years, reports of foodborne virus outbreaks have been increasing, evidencing that these viruses are a serious threat to overall global health (Bosch et al., 2018). The high impact on food matrices contaminated with viruses, both at the health and economic level, has led to devoted efforts and resources worldwide to reduce the risk of foodborne viral transmission, through improved monitoring and control of viruses in food. However, there is still little data about virus prevalence and frequency of contamination in food, prevalent viral strains, or sources of contamination, mainly in developing countries, where there is no investigation and legislation in this regard (this could probably be the reason why there are no reports of foodborne viral outbreaks in these regions).

As far as HAV detections in food is concerned, they started in the 1990's decade and the majority of them have been focused on seafood. In the recent years, vegetables and fresh fruits also began to be taken into account as an important source of infection.

HAV outbreaks have been recognized for 6 decades. At the beginning, they were reported mainly in North America associated to shellfish. Nevertheless, the number of reported outbreaks has been increasing worldwide, particularly linked to imported frozen produce items (such as berries) and vegetables.

Considering HEV, most of food detections have been performed in pork products, especially in Europe, the USA and Canada, since 2003, notably increasing in the last years. No big scale foodborne HEV outbreaks have been documented, and only isolated cases have been reported, connected to meat products, principally pork foodstuffs.

The development of a standardized methodology for the detection of HAV in food (ISO) has allowed the early detection of outbreaks and the improvement in food quality. Thus, in several countries, such as the USA and countries from Europe, there is already regulation that requires the detection of HAV as part of the routine quality control (RSA, 2019). The experience and legislation of these regions could help other areas of the world (such as South America) to implement more efficient viral quality control in food, both for consumption and for exportation. For HEV, although there is still no standardized protocol for its detection in food, many groups are currently working on a reliable agreed methodology that combines all criteria.

The implementation of improved standard methods of viral detection (partially performed), in combination with increased surveillance programs and reinforcement of strategies to prevent food contamination, represents a challenge in the near future to reduce the health risk associated with the consumption of virus-contaminated food.

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Figure 1. Possible routes of introduction of HAV and HEV in the food chain and sources of human infection.

Figure 2. Main detections of HAV (green) and HEV (blue) in food worldwide.

Figure 3. Foodborne HAV outbreaks registered up to date (from 1956 to 2019) in different regions and involving different foods (seafood, vegetables, frozen berries and multiple foods, including sandwiches, drinks, meat, ice cream, cheese, bakery products, etc.).

Note: America includes mainly outbreaks in the USA.

Table 1. Foodborne cases and outbreaks related to HEV published up to date worldwide.

Year	Number of cases	Source	Genotype	Country	Reference
2003	4	Deer meat [1]	3	Japan	(Tei et al., 2003)
2005	1	Wild boar meat [1]	3	Japan	(Li et al., 2005)
2006	1	Wild boar meat [1]	3	Japan	(Inoue et al., 2006)
2006	3	Pork meat and entrails [2]	4	Japan	(Miyashita et al., 2012)
2007	2	Pork meat [2]	3	France	(Deest et al., 2007)
2007	3	Figatelli [1]	3f	France	(Colson et al., 2010)
2008	2	Figatelli [1]	3f	France	
2009	1	Figatelli [1]	3f	France	
2009	1	Raw bile juice from a wild boar [1]	4	South Korea	(Kim et al., 2011)
2011	1	Pork meat [1]	3f	Spain	(Riveiro-Barciela et al., 2015)
2012	1 (chronic infection)	Camel milk [1]	7	United Arab Emirates	(Lee et al., 2015)
2013	2	Figatelli [1]	3f	France	(Renou et al., 2014)
2013	3	Spit-roasted piglet [1]	3f	France	(Guillois et al., 2015)
2013	1 (chronic infection)	Shellfish [2]	3	Argentina	(Gruz et al., 2016)
2015	3	Tap water [1]	4d	China	(Chen et al., 2016)
2015	8	Wild boar meat [1]	3	Spain	(Rivero-Juarez et al., 2017)
2018	27	Pork liver [2]	4	China	(Yin et al., 2019)

[1]Confirmed cases linked to the contaminated food product; [2]Epidemiologically related.

Table 2. Characteristics of the methods for HEV detection in food matrices.

Food matrices	Sample tested [1]	Preanalytical processing [1]	RNA extraction method [1]	Detection method	Process control	Recovery rate	Reference
Pork liver	250 mg	Disruption with lysis buffer, proteinase K and beads in a Hybaid Ribolyser Cell Disrupter.	In-house procedure with size fractionated silica beads.	RT-PCR (OFR2)	n.d.	n.d.	(Bouwknegt et al., 2007)
Pork liver, meat and sausages	1 cm^3	Homogenization with RLT (lysis buffer) and β-mercaptoethanol, followed by mechanical disruption and centrifugation.	RNeasy Midi Kit (Qiagen)	RT-qPCR (ORF2/ORF3) [2]	MNV-1	n.d.	(Di Bartolo et al., 2012)
Pork liver	312 mg	Homogenization with ceramic beads and RLT buffer using FastPrep®-24 homogenizer and centrifugation.	RNeasy Midi Kit (Qiagen)	RT-PCR (OFR2) and RT-qPCR (ORF2/ORF3) [2]	FCV	n.d.	(Wilhelm et al., 2014)
Pork chops	262 mg						
Sausages	3 g	Homogenization in distilled water using a stomacher. After clarification, a solution of PEG/NaCl was added to concentrate the virus by centrifugation.	NucliSens easyMAG (BioMérieux)	RT-qPCR (ORF2/ORF3) [2]	MNV-1	3.9% (HEV) and 2.9% (MNV-1)	(Martin-Latil et al., 2014)
Figatelli					MNV-1	18.4% (HEV) and 13.1% (MNV-1)	
Raw sausage (salami)	5 g	Homogenization with TRI Reagent solution in a stomacher, followed by filtration and centrifugation, addition of chloroform to clarify and a final centrifugation.	NucliSens easyMAG (BioMérieux)	RT-qPCR (ORF2/ORF3) [2]	MS2	1.92% (MS2)	(Szabo et al., 2015)
Pork liver and meat	250 mg	Disruption with TRI reagent and beads, followed by treatment with chloroform and centrifugation. The RNA in the supernatant was precipitated with 70% ethanol.	QIAamp viral RNA minikit (Qiagen)	RT-qPCR (ORF2/ORF3) [2]	TATAA Universal RNA Spike I	n.d.	(Chan et al., 2017)
Oysters	2 g						

Pork liver, pate and sausages	25 g	Homogenization with a probe in glycine buffer, followed by filtration, precipitation with PEG and centrifugation.	TRI Reagent (Invitrogen)	RT-PCR (ORF2)	FCV	From 0.06 to 14.4% (FCV)	(Mykytczuk et al., 2017)
Pork liver	0.1 g	Mechanical disruption with TGBE buffer in FastPrep®-24, followed by centrifugation, addition of TGBE and clarification.	NucliSens easyMAG (BioMérieux)	RT-qPCR (ORF2/ORF3) [2]	MNV-1	1.5 – 6.6% [3]	(Boxman et al., 2019)
Liverwurst	0.3 g					n.d.	
Liver pate						18.4 – 49.8% [3]	
Sausages						13.5 – 52.9% [3]	
Wild boar meat						n.d.	
Figatelli and sausages	3 g	Homogenization in distilled water with the FastPrep®-24 homogenizer, transference to a tube containing ceramic beads, incubation, filtration and centrifugation.	NucliSens easyMAG (BioMérieux)	RT-qPCR (ORF2/ORF3) [2]	n.d.	Better HEV recovery comparing with Martin-Latil et al., 2014.	(Hennechart-Collette et al., 2019)

[1] Most efficient procedure chosen by the authors; [2] Protocol of Jothikumar et al., 2006; [3] Variation according HEV inoculated copies.

FCV: feline Calcivirus; **MNV-1:** Murine norovirus 1; **MS2:** bacteriophage MS2; **PBS:** phosphate-buffered saline; **PEG:** polyethylene glycol; **TGBE:** Tris glycine beef extract; **TRI:** TRIzol® Reagent (Invitrogen); **n.d.:** no data.

Highlights

- A review about foodborne transmission of HAV and HEV worldwide was performed.
- Most foodborne HAV outbreaks occur in developed countries, related to frozen products
- Foodborne HEV cases occur by ingestion of contaminated animal meat or derivatives.
- Standardized methodology for HAV detection in food is available.
- For HEV detection in food, standardized methodology should be implemented.

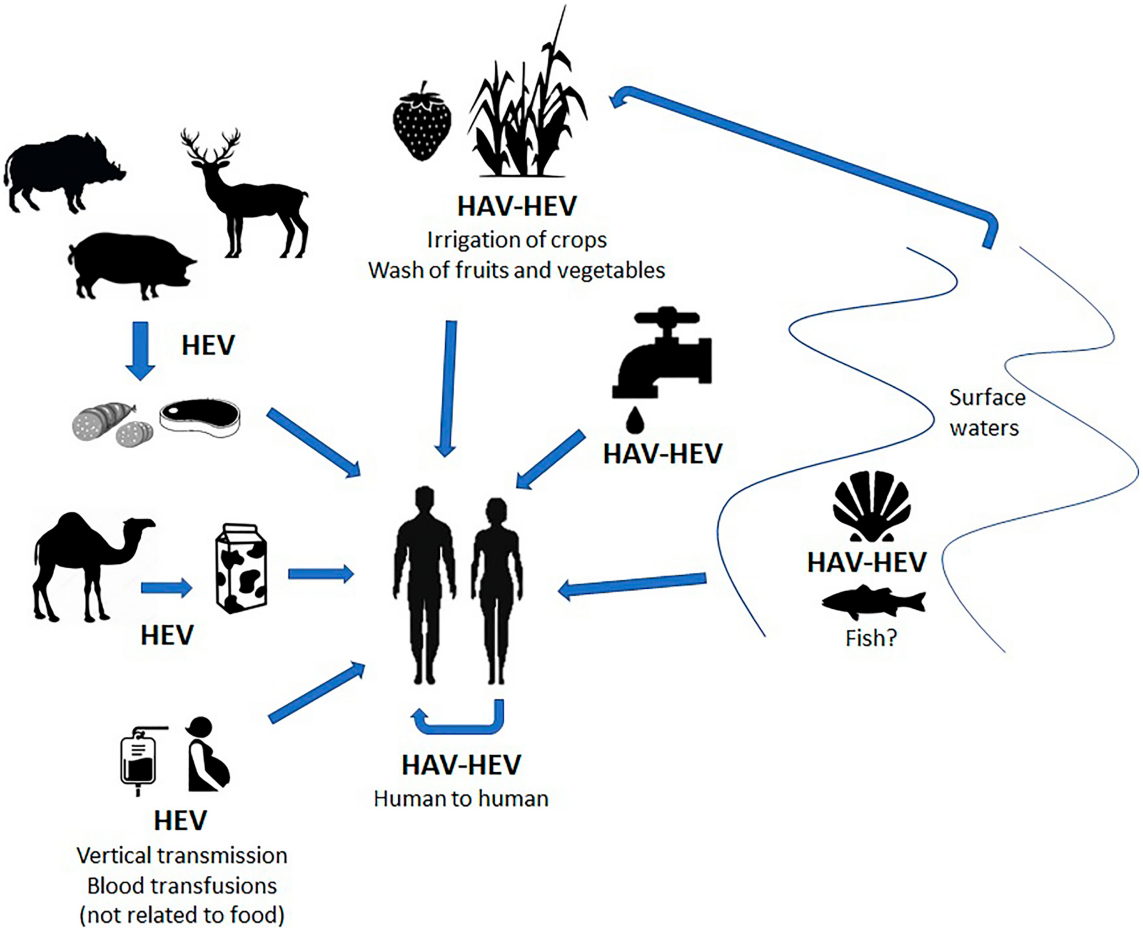
HAV-HEV
Irrigation of crops
Wash of fruits and vegetables
HEV
HAV-HEV
Surface waters
HAV-HEV
HEV
HAV-HEV
Fish?
HAV-HEV
Human to human
HEV
Vertical transmission
Blood transfusions
(not related to food)

Figure 1

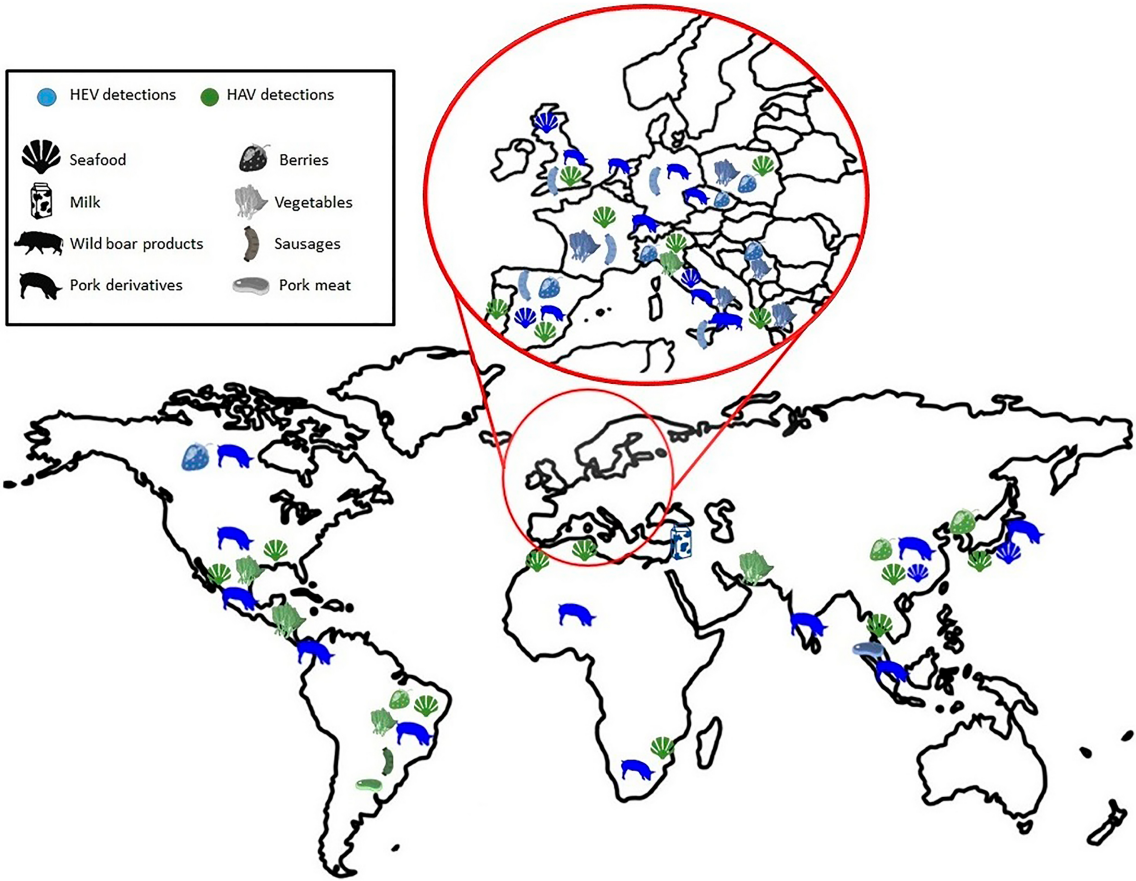
HEV detections
HAV detections
Seafood
Berries
Milk
Vegetables
Wild boar products
Sausages
Pork derivatives
Pork meat

Figure 2

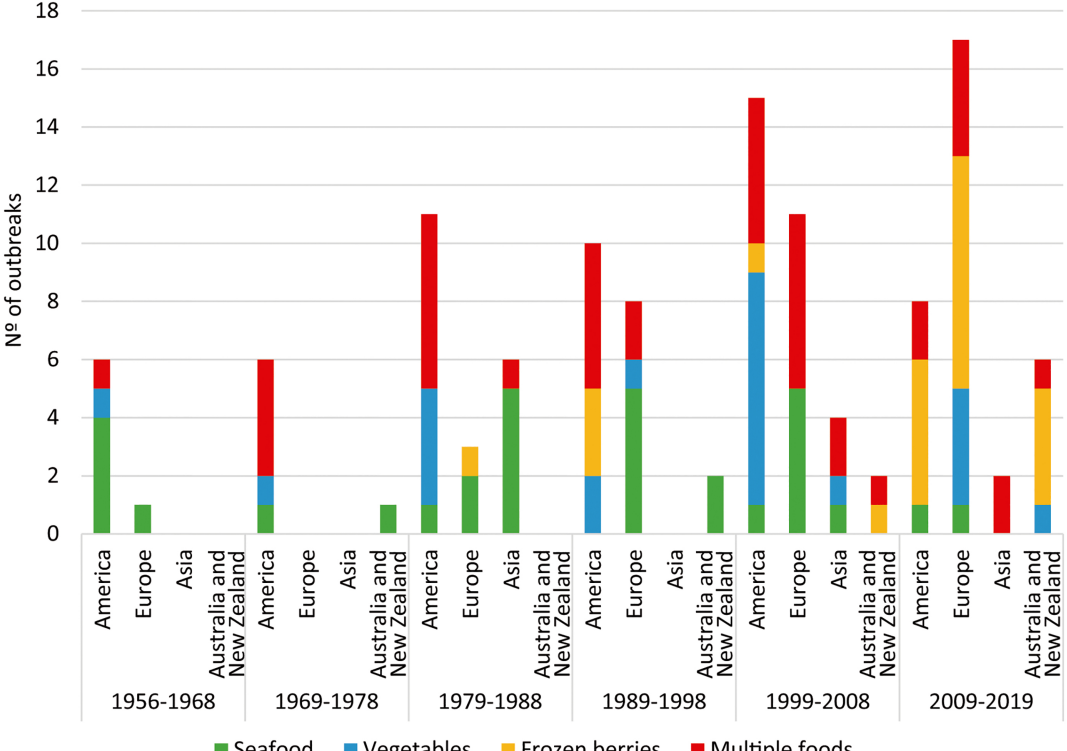
Nº of outbreaks
18
16
14
12
10
8
6
4
2
0
America
Europe
Asia
Australia and New Zealand
1956-1968
1969-1978
1979-1988
1989-1998
1999-2008
2009-2019
Seafood
Vegetables
Frozen berries
Multiple foods

Figure 3