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Chapter 5

Viral Contamination of Food

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5.1 INTRODUCTION

Transmission routes for enteric viruses may be diverse such as via person-to-person, fomites, and food or waterborne pathways associated with insufficient hygiene and sanitation (Wyn-Jones and Sellwood, 2001; Koopmans et al., 2002). It was reported that over 100 types of pathogenic viruses are excreted in human and animal wastes (Melnick, 1984). Usually, enteric viruses are transmitted via the fecal-oral route and primarily infect and replicate in the gastrointestinal tract of the host and shed in extremely high numbers in the feces of infected individuals, typically between 10^5 and 10^{11} virus particles per gram of stool (Farthing, 1989). In addition to causing acute diseases, they are of public health concern due to their low infectious dose (Haas et al., 1993).

Unlike bacteria, viruses do not multiply or produce toxins in food, so food items merely act as vehicles for their transfer (EFSA, 2011). The viruses most frequently involved in foodborne infections are human *Norovirus* (NoV) and hepatitis A virus (HAV), but other viruses such as *Enterovirus* (EV), human *Rotavirus* (HRV), hepatitis E virus (HEV), astrovirus (AstV), Aichi virus (AiV), *Sapovirus*, *Coronavirus*, *Parvovirus*, and human adenovirus (HAdV) can also be transmitted by food (Greening, 2006; FAO/WHO, 2008; EFSA, 2011). Besides the above-mentioned viruses, evidence suggests the list of foodborne viruses may be even longer (Koopmans and Duizer, 2004; FAO/WHO, 2008). Most of these viruses are very small, with a single-stranded positive-sense RNA genome and without a lipid envelope; are stable outside the host and consequently remain infectious in the environment or on food (Seymour and Appleton, 2001; Newell et al., 2010; EFSA, 2011). The exceptions are dsRNA rotaviruses, coronaviruses, which contain an envelope, and the adenoviruses and parvoviruses, which are DNA viruses (FAO/WHO, 2008).

According to Newell et al. (2010), some general characteristics of foodborne viral infections that represent important differences from bacterial infections are these. (1) Viruses do not grow in food, because they need living cells to replicate. This means that the transmission via food reflects mostly fecal contamination, with the persistence of viruses on or in the food, but without replication. (2) Just a few particles are needed to produce disease. Most foodborne viruses are very infectious, and for the majority of these, only a few infectious particles (10-100) are required to cause infection (Greening, 2006). (3) Foodborne viruses are usually very stable outside the host and are acid-resistant. (4) High numbers of viral particles are shed in the stools from infected persons (e.g., up to 10^{11} particles per gram of stool was reported for *Rotavirus* (Koopmans and Duizer, 2004)). Zoonotic viruses like HEV or tick-borne encephalitis virus may be present in animal products such as pig liver or cow's milk without fecal contamination, but these viruses also do not replicate outside living cells (Newell et al., 2010).

Looking back through history, the first report of a small, raw milk-associated outbreak of poliomyelitis that occurred in 1914 in the United Kingdom was reported by Jubb (1915). Additional milkborne outbreaks were recognized after this time, but with the development of a vaccine for poliovirus and with the pasteurization of milk, no outbreaks were reported in the developed world after the early 1950s (Sattar and Tetro, 2001). Cliver (2010) summarized a total of 36 foodborne outbreaks of HAV and 10 foodborne outbreaks of poliomyelitis reported until 1967. The predominant vehicle for HAV was shellfish, and the predominant vehicle for polio was raw milk. In the 1990s, molecular methods became available for the detection of hardly cultivable or noncultivable viruses, which led to the understanding that viruses are the leading cause of foodborne illness in the developed world (Koopmans and Duizer, 2004). Mead et al. (1999) estimated that 76 million cases of foodborne illness occur in the United States each year and viruses were estimated to cause 67% of these outbreaks. Increased consumption of foods traditionally eaten raw and globalization of international trade have increased the risks of viral contamination of foods, because a significant proportion of the produce consumed in the developed world now originates from less developed countries where sanitation and hygiene are not adequate (Gerba, 2006). Sometimes outbreaks due to food were sudden and huge. For example, over 100,000 persons contracted HAV from contaminated clams in China

Antimicrobial Food Packaging. http://dx.doi.org/10.1016/B978-0-12-800723-5.00005-X

(Halliday et al., 1991), and over 4700 persons in Japan contracted foodborne gastroenteritis due to AstV (Oishi et al., 1994). More recently, there was an outbreak in Germany, predominantly in schools and childcare settings, linked to NoV in frozen strawberries that were imported from China (Mäde et al., 2013).

Outbreaks have been documented to be caused by different kind of food items (e.g., deli meat, vegetables, berries, shellfish, and a great variety of RTE foods like sandwiches, bread rolls, bakery products, cold meat, pastries, and ice cubes) (EFSA, 2011). The food types that are at highest risk of contamination are foods requiring either intensive manual handling, including manual handling under poor hygienic conditions, or close-to-fork and final-product manual handling. Dishes containing fresh (or freshly frozen) fruits and vegetables have been the source of numerous outbreaks of foodborne illness (Koopmans and Duizer, 2004; EFSA, 2011). Filter-feeding shellfish are a particular risk, as they concentrate viruses present in water during their growth, and numerous outbreaks linked to the consumption of shellfish have been reported (Koopmans and Duizer, 2004; EFSA, 2011). Foods at greatest risk of virus contamination at the preharvest stage are shellfish, soft berry fruits, herbs, and salad vegetables. Preharvest contamination of fruits and vegetables, including strawberries (Niu et al., 1992), raspberries (Reid and Robinson, 1987; Ramsay and Upton, 1989), blueberries (Calder et al., 2003), lettuce (Pebody et al., 1998), and green onions (CDC, 2003) were reported and have resulted in outbreaks of disease in countries such as Finland and New Zealand, where populations have low or no immunity to the disease (Pebody et al., 1998; Calder et al., 2003). The source of contamination in these outbreaks was reported to be either infected fruitpickers or contaminated irrigation waters (Greening, 2006). Postharvest contamination of raw food may occur as a result of human handling by workers and consumers, contaminated harvesting equipment, transport boxes, contaminated aerosols, wash and rinsing water, or cross-contamination during transportation and storage (Harris et al., 2006). Recontamination after cooking or processing and inadequate sanitation has also been associated with outbreaks of enteric virus infections (Richards, 2001). Foods at risk from contamination by food handlers include a wide range of foods that are subjected to too much handling and are subsequently consumed cold or uncooked. These include bread and bakery goods (Kuritsky et al., 1984), lightly cooked or raw shellfish, delicatessen meats, sandwiches (Parashar et al., 1998; Daniels et al., 2000), salads, herbs, fresh fruits, and cold desserts. Poor food handling was shown to be a key risk factor in the transmission of noroviruses and rotaviruses in the Netherlands (de Wit et al., 2003).

5.2 MOST IMPORTANT FOODBORNE VIRUSES

An expert meeting convened under the auspices of the Food and Agriculture Organization (FAO) of the United Nations and the World Health Organization (WHO) reviewed available evidence and grouped viruses according to their ability to cause high morbidity, severe disease, or a significant ability to cause foodborne outbreaks (FAO/WHO, 2008). In the FAO/WHO document, the common pathogens such as NoV, group A HRV, and HAV were ranked as priority hazards. In the category of emerging hazards, HEV, Nipah viruses, H5N1 avian influenza viruses, and SARS coronavirus were considered to be of greatest concern. The meeting discussion resulted in several virus-commodity combinations for which prevention and control measures should be considered. Those combinations are: for NoV and HAV in bivalve molluscan shellfish; for NoV and HAV in fresh produce; for NoV and HAV in prepared foods; for rotaviruses in water for food preparation; and emerging viruses in selected commodities.

NoV is one of the most widely recognized viral agents associated with foodborne outbreaks of nonbacterial and often epidemic gastroenteritis and is considered to be the most common cause of foodborne disease worldwide (Greening, 2006; EFSA, 2011). NoV is shed in huge quantities in the stool and vomit of infected persons, and it has been estimated that the infectious dose may be as few as 18 virus particles (Teunis et al., 2008). NoVs are primarily transmitted through the fecal-oral route, by consumption of fecally contaminated food or water, or by direct person-to-person spread that is still the major mode for NoV transmission. Secondary spread is person-to-person spread, but may also occur by airborne transmission. According to EFSA (2010) caliciviruses (including NoV) cause approximately 90% of epidemic nonbacterial outbreaks of gastroenteritis around the world and are responsible for many foodborne outbreaks of gastroenteritis. The majority of viral gastroenteritis outbreaks in Europe have been attributed to NoVs, where they were reported to be responsible for more than 85% of nonbacterial gastroenteritis outbreaks between 1995 and 2000 (Lopman et al., 2003; Koopmans et al., 2003). Estimations based upon analysis of questionnaire data suggested that in the Netherlands approximately 12-15% of community cases of NoV gastroenteritis were attributed to foodborne consumption (EFSA, 2011). Also, European data from the beginning of this century show that about 12% of the NoV outbreaks are foodborne (ECDC, 2006). This makes NoV as common a cause of foodborne gastroenteritis as *Campylobacter* and a more common cause than *Salmonella* (de Wit et al., 2003). A European-wide surveillance network for Nov outbreaks, DIVINE-Net, has noted that Europe has been faced with an increased NoV activity during the second half of the first decade of the twenty-first century. The new NoV variants of GII.4-2006 had most likely been the dominating circulating strains. The role of foods, such as oysters and imported

raspberries, as vectors for NoV transmission, had been stressed, because both food commodities have been associated in several NoV outbreaks in many countries (Petrović, 2013).

HAV is the etiological agent of one of the most common types of hepatitis worldwide, and HAV as a serious foodborne infection is a notifiable disease in most developed countries. Approximately 1.4 million people worldwide become infected with HAV annually (Issa and Mourad, 2001). The incidence of infection varies among regions of the world, with the highest rate in developing countries where sewage treatment and hygiene practices are poor (Rodrıguez-Lazaro et al., 2012) and where more than 90% of children have been reported to be infected, usually asymptomatically, by 6 years of age (Cliver, 1997; Greening, 2006). Conversely, the number of reported cases of HAV infection has declined substantially in countries with effective vaccination. The major mode of transmission for HAV is directly or indirectly from the human reservoir, mainly as a consequence of traveling to endemic regions, engaging in risky sexual practices, or consuming contaminated water or food (EFSA, 2011). Food (Pebody et al., 1998; Lees, 2000; Greening, 2006) and drinking water (Tallon et al., 2008) are considered major vehicles of HAV transmission to humans. HAV can, via sewage discharge, contaminate watercourses, soil, and consequently food crops (Bosch, 1998; Cook and Rzeźutka, 2006). The other main source of produce-associated HAV infection is from food handlers and food processors. HAV is distinguished from other viral agents by its prolonged (2-6-week) incubation period. Since HAV is shed before symptoms become apparent and there are often more than 10^6 infectious virus particles excreted per gram of feces, HAV-infected produce harvesters and food handlers can become a source of contamination without their knowledge. In areas with poor hygiene practices, this can present a high risk to human health. Foodborne outbreaks of HAV are relatively uncommon in developing countries where there are high levels of immunity in the local population, but foreigners in these regions can be susceptible if they are not vaccinated (Greening, 2006).

HEV is usually the result of a waterborne infection in developing countries and is suspected to be spread zoonotically in industrialized countries (Bosch et al., 2008). The disease is endemic in many parts of the world, mostly in the Indian subcontinent, northwest China, and Central Asia. In these regions, HEV is transmitted mainly through the fecal-oral route, especially by the consumption of fecally contaminated drinking water, and sewage is a major source for contamination of surface water (Greening, 2006; FAO/WHO, 2008). Foodborne outbreaks of HEV are most common in developing countries as a consequence of inadequate environmental sanitation (Greening, 2006). HEV is unusually reported in industrialized countries and when it is reported, it is mostly as sporadic cases in humans who have traveled to endemic countries. Recently, some human HEV infection in nonendemic countries could not be explained by the contact of those patients with the virus in the endemic regions. Although originally it was believed that HEV did not occur in industrialized countries, in recent years it has been identified in Europe, Asia, Australia, and the United States; however, it rarely is a cause of overt disease in these countries (Clemente-Casares et al., 2003; Emerson and Purcell, 2003). In contrast to NoV and HAV, HEV has been identified also as a zoonosis (EFSA, 2011). HEV has been detected in the feces of a wide range of domestic animals (Meng et al., 1997; Vasickova et al., 2005; Greening, 2006; Petrović et al., 2010). It has been found to be highly prevalent in pigs in several countries where HEV in humans is rare, including Spain, New Zealand, the Netherlands, Serbia, Japan, and Canada (Emerson and Purcell, 2003; Lupulović et al., 2010; Petrović et al., 2014). Also, recent studies have revealed quite variable seroprevalence rates among Europe's population and a possible porcine zoonotic transmission has been postulated (Meng, 2011; Petrović et al., 2014). Moreover, the human HEV strains described in industrialized countries appear to be closely related to the swine HEV strains found in the same countries. Although rare, the importance of HEV transmission via food is increasingly being recognized in the European Union (EU) (EFSA, 2011).

HRV is the leading cause of severe diarrhea among infants and young children. In adults, the disease caused by HRV is considered to be mild (Greening, 2006). It is estimated that HRV causes more than 130 million cases of diarrhea in children less than 5 years of age annually worldwide (Glass and Kilgore, 1997). HRV infection is a particularly serious problem in developing countries where up to 600,000 deaths occur annually among children. In the United States, HRV had been estimated to cause about four million infections per year, resulting in almost 70,000 hospitalizations and more than 100 deaths annually (Sattar et al., 2001). It was estimated that only 1% of HRV cases was foodborne (Mead et al., 1999). HRV causes disease in both humans and animals, especially domestic animals (Greening, 2006). Outbreaks associated with food and water have been reported in a number of countries (Sattar et al., 2001). In countries with a seasonal climate change, HRV is more common during the winter months. In tropical regions, outbreaks can occur both in the cooler and drier months and throughout the year, especially where transmission is related to contaminated water supplies and where no sewage treatment systems exist (Ansari et al., 1991). HRV is stable in the environment, so infection can occur through consumption of contaminated water or food and contact with contaminated surfaces (Greening, 2006).

EVs of concern for water and foodborne spread include polioviruses, Coxsackie A and B viruses, and ECHO (enteric cytopathic human orphan) viruses. They are transmitted by the fecal-oral route and are excreted in feces, but generally do not cause gastroenteritis. They can cause a range of other diseases, including viral meningitis, myocarditis and poliomyelitis

(Greening, 2006). Polioviruses were the first viruses that have been confirmed to be foodborne (Jubb, 1915; Sattar and Tetro, 2001), but virulent wild-type strains are now very rare because of global immunization campaigns. Outbreaks of foodborne illness associated with Coxsackie viruses and ECHO viruses have been reported (Cliver, 1997; Sattar and Tetro, 2001). Enteroviral infection is most common in summer and early autumn, and many infections are asymptomatic. Although EVs are regularly detected in the environment, there have been very few recorded foodborne outbreaks associated with these viruses. EVs, including ECHO viruses and Coxsackie A and B viruses, have been isolated from shellfish, but no outbreaks associated with the consumption of shellfish have been reported (Greening, 2006).

AstVs are distributed worldwide and they have been isolated from different animal species like cats, dogs, pigs, sheep, cattle, and birds, as well as from humans. The main feature of AstV infection in both humans and animals is a self-limiting gastroenteritis (Greening, 2006). AstVs are a common cause of human gastroenteritis, with most cases of infection detected in young children less than 1 year of age (Appleton, 2001). Although AstVs cause a mild infection in adults, they have been associated with gastroenteritis in immunocompromised persons. Transmission is through the fecal-oral route via water, food, and person-to-person contact (Appleton, 2001).

HAdVs are widespread within nature, infecting birds and mammals, including humans. They commonly cause respiratory disease but may also cause other illnesses such as gastroenteritis and conjunctivitis. In children under 4 years of age, the enteric HAdVs are the second most prevalent cause of gastroenteritis (after HRV) (Allard et al., 1990). HAdVs can be transmitted from person to person by direct contact, or via fecal-oral, respiratory, or environmental routes. Most HAdV infections in normally healthy individuals are mild or subclinical, but can be associated with respiratory, ocular, and gastrointestinal disease. All virus serotypes are shed enterically in feces, but of the many types of HAdVs, only HAdV serotypes 40 and 41 are generally associated with fecal-oral spread and cause gastroenteritis (Greening, 2006). The virus is shed in large numbers in feces and respiratory secretions for long period, even for months or years after the infection. Enteric HAdV infections are common all year round. These viruses have been identified in a variety of environmental samples, including wastewater, sludge, in marine, surface, and drinking waters, and shellfish, but no foodborne or waterborne outbreaks associated with the enteric HAdV have been reported (Greening, 2006).

5.3 PREVALENCE OF VIRUSES IN FOOD—RESULTS OF SOME SURVEYS AND OUTBREAK OCCASIONS

5.3.1 Viruses in Food—Viruses in Fresh Food

Food may be contaminated by viruses during all stages of the food supply chain. The presence of viruses in food can be the result and consequence of the environmental contamination during primary production—contaminated irrigation waters by sewage as well as manure, which in turn contaminate produce on the field, during the processing and storage phases—by water contaminated with viruses, and from contact virus transmission from humans, such as infected food handlers (involving fecal-oral and aerosol spread of fecal material and vomit). Transmission of zoonotic viruses (e.g., HEV) can also occur by consumption of products of animal origin (EFSA, 2011). The relative contribution of different sources (shellfish, fresh produce, food handler including asymptomatic shedders, food-handling environment) to foodborne illness has not yet been determined (EFSA, 2011). Food handlers are very often the reason for virus transmission. Transmission could occur via infected food handlers with clinical symptoms, but also from infected food handlers who have recovered from illness and no longer display any symptoms, but may still be shedding high numbers of NoV. In addition, transmission could occur via infected food handlers with asymptomatic infections and food handlers who come in contact with sick people (Koopmans and Duizer, 2004). Although most outbreaks can be traced to infected food handlers at the end of the food chain, the food contamination could occur anywhere (e.g., seasonal workers during berry harvesting or people on recreational boats near shellfish harvesting areas). Fresh fruits and vegetables can become contaminated by enteric viruses, possibly through the use of contaminated fertilizers or irrigation water supplies (Grohmann and Lee, 2003).

An increased number of foodborne viral outbreaks are being recorded in several countries. Reasons for this include the improved diagnostic methods for virus detection and the increased marketing of fresh and frozen foods that have led to a worldwide availability of high-risk foods (EFSA, 2011). In 2009, a total of 5550 foodborne outbreaks were reported in the EU, and it was at the same level as in 2008. Overall, 48,964 human cases, 4356 hospitalizations, and 46 deaths were recorded. The largest number of reported foodborne outbreaks was caused by *Salmonella* (31.0% of all outbreaks), followed by viruses (18.8%), bacterial toxins (10.1%), and *Campylobacter* (6.0%). During 2009, 21 EU member states reported a total of 1043 foodborne outbreaks caused by viruses (EFSA and ECDC, 2011). Overall, the number of reported viral foodborne outbreaks increased by more than 40% compared to 2007 and 2008. Only a few (6.7%) reported viral outbreaks were verified (EFSA and ECDC, 2011); however, the number of verified viral outbreaks also increased

by 84.2%, from 38 outbreaks in 2008 to 70 in 2009. For 22 out of the total of 70 verified foodborne virus outbreaks, the implicated foods were fruit/berries and juices, and products thereof. These outbreaks were reported by Finland and Sweden and involved 1223 human cases (EFSA and ECDC, 2011).

The Panel on Biological Hazards (BIOHAZ) identified NoV, HAV, and HEV as viruses of significance for foodborne transmission (EFSA, 2011). Data from systemic virus surveillance in foods are missing mainly because there are no systemic surveillances on national or wider levels, and the existing data were collected partly from research project-based studies and mainly from studies after the outbreak occasions. In the European Rapid Alert System for Food and Feed (RASFF) online database (http://ec.europa.eu/food/food/rapidalert/rasff_portal_database_en.htm) up to December 31, 2014, presence of enteric viruses in fruit and vegetables were found in a total of 36 cases (alerts). Mostly NoV was detected (23/36; 63.89%) in fruit (22/23), most often frozen raspberries (21/22), and just in one case in lettuce (from France). Out of 13 alerts of HAV presence in different kind of fruits, 2 HAV-positive fruit (dates) cases from 2010 to 2011 originated from Algeria, and 11 HAV fruit (different kinds of berries) alert cases from 2012 until April 2014 originated from different, mostly European countries. NoV-positive raspberries originated from Serbia (9/22), Poland (9/22), China (3/22), and Chile (1/22).

NoV outbreaks linked to fresh soft red fruits and leafy greens have been reported. Between 1992 and 2000, 1518 foodborne outbreaks of infectious enteric disease were reported in England and Wales. From that number, 83 (5.5%) were associated with the consumption of salad vegetables or fruit. The pathogens most frequently reported were salmonellas (41.0%) and NoV (15.7%) (Long et al., 2002). In Denmark, at least 11 linked outbreaks of gastroenteritis with a total of 260 cases were reported in January 2010. Lettuce of the Lollo Bionda type grown in France was found to be the vehicle of virus transmission (Ethelberg et al., 2010). Baert et al. (2009) reported that during 2007 from a total of 75 reported foodborne outbreaks in Belgium, 10 were caused by NoV, affecting 392 persons. The major implicated foods were sandwiches (4/10). Furthermore, Baert et al. (2009) summarized the data collected from international outbreaks between 2000 and 2007 reported by Eurosurveillance, Morbidity and Mortality Weekly Reports and from internationally available peer-reviewed scientific journals. As a result, 40 foodborne and waterborne outbreak events due to NoV, epidemiological and/or laboratory confirmed, from 2000 to 2007 have been reported. Further analysis revealed that in 42.5% of the cases, the food handler was responsible for the outbreak, followed by water (27.5%), bivalve shellfish (17.5%), and raspberries (10.0%).

Maunula et al. (2009) described the NoV outbreaks affecting about 200 people in Southern Finland in 2009. All outbreaks occurred after consumption of imported frozen raspberries. Recently, Sarvikivi et al. (2012) reviewed the data regarding all notified foodborne outbreaks in 2009 in Finland and found that 13 NoV outbreaks affecting about 900 people could be linked to imported frozen raspberries. Müller et al. (2014) described NoV outbreaks in Denmark at the end of 2010 and at the beginning of 2011. The NoV detected in patients' stool samples from six outbreaks were sequenced and epidemiologically linked to the single batch of frozen raspberries originating from Serbia. These molecular investigations showed that the apparently independent outbreaks were the result of one contamination event of frozen raspberries (Müller et al., 2014).

Out of 75 examined fruit products, despite a good bacteriological quality, Stals et al. (2011) found NoV GI and/or GII in 4/10, 7/30, 6/20, and 1/15 of the tested raspberries, cherry tomatoes, strawberries, and fruit salad samples, respectively. The level of detected NoV genomic copies ranged between 2.5 and 5.0 log per 10 g. Baert et al. (2011) reported the results of the study where in total, 867 samples of leafy greens, 180 samples of fresh soft red fruits, and 57 samples of other types of fresh produce (tomatoes, cucumber, and fruit salads) were analyzed in those three countries. NoV was detected in 28.2% ($N=641$), 33.3% ($N=6$), and 50% ($N=6$) of leafy greens tested in Canada, Belgium, and France, respectively. Soft red fruits were found positive in 34.5% ($N=29$) of the samples tested in Belgium and in 6.7% ($N=150$) of the samples tested in France. Also, 55.5% ($N=18$) of the other fresh produce types, analyzed in Belgium, were found to be NoV-positive.

HAV has often been associated with the consumption of contaminated fresh-cut vegetables and fruit (EFSA, 2010). At the beginning of 1988, 202 cases of HAV were reported in and around Jefferson County, Kentucky (Rosenblum et al., 1990). A case-control study found that eating green salad was strongly associated with acquiring hepatitis. Rosenblum et al. (1990) concluded that this outbreak of HAV was the first recorded outbreak in the United States apparently associated with fresh produce contaminated before distribution to restaurants. In 1997, a total of 213 cases of HAV were reported from 23 schools in Michigan and 29 cases from 13 schools in Maine. Most of the patients ate lunch in schools, and preliminary analysis established a strong association between illness and consumption of food items containing frozen strawberries originating from Mexico (Hutin et al., 1999). Forty-three cases of serologically confirmed HAV occurred among individuals who ate at a restaurant in Ohio in 1998. A case-control study was conducted that determined foods containing green onions, which were eaten by 38 (95%) of 40 case patients were associated with illness (Dentinger et al., 2001). In 2003, a large HAV outbreak connected to one restaurant in Pennsylvania was described by Wheeler et al. (2005). Out of 601 identified patients, 3 died and at least 124 were hospitalized. Identical sequences of HAV strains from all 170

tested patients were identified. Mild salsa, which contained green onions grown in Mexico, was identified as the source of the HAV (Wheeler et al., 2005). Petrignani et al. (2010) reported the connection between HAV infection with 66 cases in the Netherlands at the beginning of 2010, and that semi-dried tomatoes in oil was the source of the outbreak. All the examined patients were infected by an identical HAV strain not previously detected in the Netherlands. In October 2009, semi-dried tomatoes originating from Turkey were identified as the source of several HAV outbreaks in Australia (more than 200 cases) and France (55 cases) (EFSA, 2011). Gillesberg Lassen et al. (2013) described a foodborne outbreak of HAV in Denmark from October 2012 to April 2013. A case-control study identified frozen berries eaten in smoothies as the potential vehicle. In the following weeks, Finland, Norway, and Sweden also identified an increased number of HAV patients without travel history. Most cases reported having eaten frozen berries at the time of exposure. In total, 71 cases were notified in the four countries. According to information obtained in the case-control study, different kinds of berries were suspected to be the source of HAV, but no specific type of berry, brand, or origin of berries was identified. During 2013, more than 1300 cases of HAV were reported by 11 EU member states as potentially linked to an ongoing outbreak (Wenzel et al., 2014; ECDC, 2014). Epidemiological, microbiological, and environmental investigations indicate frozen berries as the vehicle of infection for this outbreak and suggested that it could be linked to a single source (ECDC, 2014).

Frequent zoonotic transmission of HEV has been suspected. Norder et al. (2009) sequenced the ORF2 genome region of 63 HEV strains originating from human blood sera collected between 1993 and 2007 and found that patients infected in Europe were infected by genotype 3. In order to find the connection between human and swine HEV, Norder et al. (2009) additionally sequenced the HEV strains originating from 18 piglets from 17 herds in Sweden and Denmark. Phylogenetic analyses of the genotype 3 strains showed geographical clades and high similarity between strains from patients and pigs from the same area, so the authors concluded that autochthonous HEV cases are present in Scandinavia. Also, Bouquet et al. (2011) assessed the genetic identity of HEV strains found in humans and pigs in France. HEV sequences identified in patients with autochthonous HEV infection were compared with sequences amplified from pig livers collected in slaughterhouses. A similarity of >99% was found between HEV sequences of human and swine origins, indicating that consumption of some pork products, such as raw liver, is a major source of exposure for autochthonous HEV infection (Bouquet et al., 2011). Recently, there has been increasing evidence of foodborne transmission of HEV. Tei et al. (2004) concluded that consumption of uncooked deer meat was a major epidemiological risk factor for HEV infection in the city of Kasai in Japan. In their study, from the total of 45 examined volunteer subjects with experience of eating raw deer meat, 8 (17.7%) of the subjects and only 1 (2.2%) of the controls had measurable serum anti-HEV IgG levels. In addition, the studies of Yazaki et al. (2003) and Tamada et al. (2004) suggest that consumption of undercooked pig liver and undercooked wild boar meat may have been the cause of some cases of HEV in Japan. Wild boar liver is often eaten raw in Japan, and this has also been linked to some HEV cases (Matsuda et al., 2003).

Numerous survey studies have estimated the prevalence of HEV RNA in marketed livers. HEV RNA was detected in 1.9% of 363 livers from supermarkets in Japan (Yazaki et al., 2003), and in 6% of 62 packages in the Netherlands (Bouwknegt et al., 2007). Feagins et al. (2007) examined 127 packages of commercial pig liver sold in local grocery stores in the United States for the presence of HEV RNA, and found 14 (11%) positive for HEV RNA. Subsequent experimental infection of pigs inoculated with positive pig livers homogenates demonstrated that HEV in pig livers was infective. Leblanc et al. (2010) examined the presence of HEV in the tissues of 43 adult pigs, randomly selected from an experimental herd at slaughter in Canada. HEV RNA was detected in 14 out of the 43 animals tested. Even although no HEV RNA was detected in any of the muscle tested, 20.9% of liver samples obtained at the slaughterhouse tested positive for HEV RNA. In a Chinese abattoir, Li et al. (2009) found that 3.5% of liver samples tested were positive for HEV RNA. During 2009, the Centre for Food Safety in Honk Kong obtained a total of 100 fresh pig liver samples from pigs slaughtered in a local slaughterhouse. Among the collected samples, 16 out of 51 (31%) roaster liver samples were found positive for HEV, while none of the 49 pork liver samples were found positive. Partial ORF2 sequences of some HEV isolates from roaster pigs were found to be the same as those from seven local human cases from 2009, as well as local cases recorded in the past. This study suggests the possibility that, apart from contaminated water or food such as raw or undercooked shellfish, pigs also could be one of the sources of human HEV in endemic regions (Anon, 2010).

Available data suggests that the consumption of raw/undercooked sausage meat is a potential route of HEV transmission. In the United Kingdom, Grierson et al. (2011) detected HEV in 6 out of 63 (9.5%) tested sausages, and the presence of HEV was found at all three points of the pork food supply chain: production, processing, and point of sale. In another study in the United Kingdom, Berto et al. (2012) detected HEV in 6 out of 63 (9.5%) and in 1 (3%) of 40 tested sausages and livers. HEV RNA was also detected at each of three sites (production, processing, and point of sale) in the pork food supply chain. An autochthonous HEV infection was recently described in Portugal in a patient who recalled eating traditional homemade pork sausages made of raw meat about 2 weeks prior to the development of the clinical manifestations of acute hepatitis (Duque et al., 2012). Renou et al. (2014) presented the case of the direct evidence of foodborne transmission

of HEV after consumption of uncooked "figatellu" sausage in France, with 100% identity between the sequences from the patient and the food product. Di Bartolo et al. (2012) evaluated the prevalence of HEV in the pork production chain in the Czech Republic, Italy, and Spain during 2010. HEV RNA was detected in at least one of the samples (feces, liver, or meat) from 36 (32%) out of 113 examined slaughtered pigs at slaughterhouses. Pig feces showed highest HEV RNA presence (27%), followed by liver (4%) and meat (3%). Out of 313 sausages sampled at the processing and point of sale (supermarkets) stages, HEV was detected only in Spain (6%, 6/93). HEV sequencing confirmed only G3 HEV strains.

The EFSA BIOHAZ has published a scientific opinion urging for measures to prevent HEV from entering the food chain (EFSA, 2011). The BIOHAZ opinion states that in contrast to NoV and HAV, HEV has been identified as a zoonotic virus that can be very effectively transmitted between pigs, and can be transmitted to humans through consumption of products of animal origin, especially through consumption of meat; however, there are no measures in place to control the spread of the virus (EFSA, 2011).

Eleven foodborne outbreaks consisting of 460 cases of rotaviral gastroenteritis were reported in New York between 1985 and 1990 (Greening, 2006). From that number, seven outbreaks have been associated with food-service premises, and the foods included salad, cold foods, shepherd's pie, and water or ice (Sattar et al., 2001). Large-scale outbreaks of rotaviral gastroenteritis have been reported in Japanese primary schools with more than 3000 cases recorded for one outbreak (Matsumoto et al., 1989). School lunches prepared at a central facility were suspected as the vehicle of infection, but no HRV was isolated from food or water. Lettuce at a market was found to be contaminated with HRV and HAV at a time when there was a high incidence of rotaviral diarrhea in the Costa Rican community (Hernandez et al., 1997). Recently, Mayr et al. (2009) described an HRV outbreak in a mother-and-child sanatorium. In total, 74 food samples from the sanatorium kitchen were taken and tested for HRV. HRV particles were isolated from potato stew. Out of 275 samples of packaged leafy greens, tested by Mattison et al. (2010), 40 (15%) were found and confirmed to be positive for NoV, and only 1 (0.4%) was found positive for HRV group A. Additionally, Brassard et al. (2012) described the presence of HRV as one of the detected pathogenic human and zoonotic viruses on strawberries.

5.3.2 Viruses in Shellfish and Other Bivalve Mollusks

Probably one of the most recognized routes of foodborne transmission of enteric viral infections is through the consumption of shellfish grown in sewage-polluted marine environments (Okoh et al., 2010). The most common route for transmission is accidental contamination after heavy rainfall, when extra loads cause an overflow and there is a release of untreated sewage into the aquatic environment. Current water treatment practices are unable to provide virus-free wastewater effluents. Consequently, human pathogenic viruses are routinely introduced into marine and estuarine waters (Bosch and Le Guyader, 2010). Shellfish, which includes mollusks such as oysters, mussels, cockles, clams, and crustaceans such as crabs, shrimps, and prawns are filter-feeders that result in the bioconcentration of environmentally stable, positive-stranded RNA viruses, such as NoV, HAV, and EV in their edible tissues, digestive glands, and gills (Le Guyader et al., 2006). Shellfish can filter some 10-201 of water per hour and in that process, they concentrate infectious agents that are present in the marine environment (Grohmann and Lee, 2003). By this process, oysters can concentrate viruses up to 99 times compared to the surrounding water (Burkhardt and Calci, 2000). A major public health concern posed by virus-contaminated bivalves is that shellfish are often eaten raw, like oysters and clams, or lightly cooked, like most other molluscan shellfish, just steamed for a few minutes (Bosch and Le Guyader, 2010).

HAV has contributed to numerous foodborne outbreaks that are often associated with raw or lightly cooked shellfish (Richards, 1985). Contamination generally occurs either preharvest or during food handling. The first recorded outbreak of shellfish-associated viral disease resulted from storing clean oysters in a fecally contaminated harbor while awaiting sale (Gard, 1957). That HAV outbreak resulted in more than 600 cases. The largest foodborne outbreak of HAV occurred in China in 1988 when approximately 300,000 people were infected during a 3-month period after consumption of partially cooked, HAV-contaminated clams harvested from a growing area contaminated by raw sewage (Halliday et al., 1991). A few of the documented shellfish-associated outbreaks include oysters in Australia (Conaty et al., 2000), oysters in Brazil (Coelho et al., 2003), mussels in Italy (Croci et al., 2000), and clams in Spain (Bosch et al., 2001). Sewage was generally the source of pollution in most of these outbreaks. Contamination of shellfish with HAV is still common in Italy, Spain, and other European countries (Greening, 2006).

Foodborne NoV outbreaks often result from preharvest contamination of foods such as shellfish (Christensen et al., 1998). Berg et al. (2000) described three oyster-related gastroenteritis outbreaks attributed to NoV that occurred in Louisiana between 1993 and 1996. Traceback and environmental investigations revealed that the overboard disposal of sewage by oyster harvesters into oysterbed waters was the most likely source of contamination in at least two of the outbreaks. Christensen et al. (1998) described the outbreak in which more than 350 people in Denmark became ill from consumption

of imported oysters during the New Year of 1996/1997. NoV and EV were identified from both oyster and patients' fecal samples. Bosch et al. (2006) provide examples of large outbreaks (with more than 100 cases) described in literature connected to the viruses in shellfish. In 10 presented outbreaks from 1976 to 1999, mostly NoV in oysters, cockles, and clams (5/10) was the causative agent followed by HAV in cockles and clams (3/10).

In recently conducted studies, NoV has been detected in 5-55% of oyster samples collected from Europe and the United States by random sampling at market places and oyster farms (Boxman et al., 2006; Costantini et al., 2006). Boxman (2010) published a detailed review about human enteric virus presence and prevalence in bivalve mollusks that were collected from European waters or markets from 1990 to 2006. RNA of enteric viruses have been detected in shellfish from commercial and noncommercial harvesting areas, as well as in products available on the market for direct consumption and in shellfish associated with disease outbreaks. The presented data suggest a high prevalence of different human enteric viruses, but mostly NoV, HAV, EV, HAdV, and HRV were found in shellfish samples collected from growing areas, as well as from the market in different countries. The viruses were present in shellfish from polluted areas, in depurated shellfish and even in shellfish classified in category class A, as well as those ready for human consumption. The relation with the *E. coli* most probable number (MPN) that is in use for classification of growing areas and to determine whether shellfish products can be presented for human consumption could not be confirmed in this study.

Up to February 10, 2010, in RASFF online database notifications of enteric viruses in shellfish on the European market (http://ec.europa.eu/food/food/rapidalert/rasff_portal_database_en.htm), Boxman (2010) found 38 alerts on the (suspected) presence of viruses. Twenty-eight alerts have been reported on NoV in food notified by 10 different EU countries between 2001 and 2010, and 10 alerts have been reported on the (suspected) presence of HAV in food between 1999 and 2008. The majority of these alerts on NoV in food concerned oysters (18 times), followed by scallops (one report). Half of the notified batches of oysters were of French origin, followed by oysters derived from the United Kingdom, and Ireland. All 10 alerts on the (suspected) presence of HAV in food were reported by Italy and Spain and were only involving shellfish: oysters (five reports), small bivalve animals (four reports), and scallops (one report). Half these products were of French origin, whereas the other half was shellfish from Peru (Boxman, 2010). After this period and the data described by Boxman (2010) until December 31, 2014, 32 new NoV-positive shellfish alerts were published in the RASFF online database. Analyzing the alert reports on shellfish, NoV presence was mostly connected to oysters (25/32; 78.13% cases) from France (16/25), Ireland (4/25), the Netherlands (4/25), and Spain (1/25); in three cases connected to mussels from the Netherlands (1/3) and Spain (2/3); in three cases connected to clams from Portugal, United Kingdom, and Vietnam; and in one case connected to raw shell scallops from Chile.

In the EFSA report (2010), from a total of 697 foodborne outbreaks reported in 19 EU member states during 2008, crustaceans, shellfish, mollusks, and products thereof were the most frequently implicated food items. For those outbreaks that were verified, NoV was the most frequent cause, followed by HAV (EFSA, 2010). In the recent United Kingdom Food Safety Authority project-based study, NoV was detected in 76.2% oyster samples (643/844), with similar prevalence in the two species of oysters tested (76.1% (468/615) for *Crassostrea gigas* and 76.4% (175/229) for *Ostrea edulis*). Clear seasonality was observed with a positivity rate of 90.0% (379/421) for samples taken between October and March compared with 62.4% (264/423) for samples taken between April and September (Anon, 2011). In the first report on the presence of human enteric viruses in shellfish from Portugal, approximately 2000 different kinds of shellfish, organized in 49 batches, were collected between March 2008 and February 2009 (Mesquita et al., 2011). Viral contamination was detected throughout the year in all shellfish species and in all collection areas, independently of classification of their harvesting areas. NoV was detected in 37% of the batches, followed by EV in 35%, and HAV in 33%. Overall, 69% of all analyzed batches were found to be contaminated by at least one of the studied viruses, while the simultaneous presence of two and three viruses was detected in 22% and 6% batches, respectively. The special problem was the fact that viruses were detected in six of the eight shellfish batches from the A-class harvesting areas (one NoV, three EV, and two HAV) (Mesquita et al., 2011). Diez-Valcarce et al. (2012) examined the prevalence of different enteric viruses in commercial mussels at the retail level in three European countries (Finland, Greece, and Spain). A total of 153 mussel samples from different origins were analyzed for virus presence. Samples were positive in 41% of cases. HAdV was found to be the most prevalent virus detected (36%), and the prevalence of NoV GG II, HEV, and NoV GG I were 16%, 3%, and 0.7%, respectively. Presence of HAV was not detected.

Epidemiological evidence of AstV transmission by foods is limited, but infections via contaminated seafood like shellfish and water have been reported (Oishi et al., 1994; Appleton, 2001). One large outbreak of acute gastroenteritis was reported in Japan involving thousands of children and adults from 14 different schools in 1991 (Oishi et al., 1994). The outbreak was traced to food prepared by a common supplier for school lunches and AstV type 6 was identified as causative agent. There are several Japanese reports of AstV genomes identified in shellfish with the evidence of their contribution in foodborne outbreaks of gastroenteritis, mainly after the consumption of contaminated oysters

(Kitahashi et al., 1999). HAdVs have been identified in a variety of environmental samples, including wastewater, sludge, and in marine, surface, and drinking waters, as well as in shellfish, but no foodborne nor waterborne outbreaks associated with the enteric HAdVs have been reported (Greening, 2006). Swine manure could be a source of HEV contamination of coastal waters with subsequent contamination of shellfish (Smith, 2001). Said et al. (2009) reported that the small genotype 3 HEV outbreak on a cruise ship returning to the United Kingdom in 2008 was connected to the consumed shellfish.

5.3.3 Emerging Zoonotic Viruses with Concern for Foodborne Transmission

Zoonotic viral infections are generally not transmitted by food; however, there are a few reports on transmission of some emerging viruses via food. This transmission is likely to be rare, relative to other transmission routes, and will probably be restricted to a few food products or items and occasions. For example, highly pathogenic avian influenza (HPAI) virus in undercooked poultry or eggs, HEV in porcine organs, or muscle tissue and Nipah virus in date palm sap are postulated to be foodborne. Another emerging virus for which this mode of transmission may be relevant is severe acute respiratory syndrome coronavirus (SARS-CoV) (FAO/WHO, 2008; Newell et al., 2010). All mentioned viruses are zoonotic, and limited epidemiological data exist that support their transmission by the consumption of contaminated foods. Each of these viruses is capable of causing significant illness and mortality in humans. They are present in the intestinal tracts of infected humans and animals, and are shed into the environment through feces that can contain high levels of virus (Newell et al., 2010). SARS-CoV was spread into the human population through the preparation and consumption of food animals that appear to be infected from another reservoir, probably bats (Lau et al., 2005). Infectious H5N1 avian influenza virus has been found in duck meat, and the consumption of duck blood has resulted in the infection of humans (Tumpe et al., 2002). Almost all reported cases of avian influenza (AI) virus infection in humans that have been recently caused by HPAI viruses belonging to the H5 or H7 subtypes were transmitted directly from infected birds to humans. Other routes of infection, such as consumption of edible tissues from infected avian species or contact with contaminated water, have been suggested as possible sources of infection, but have not yet been proven (EFSA, 2011). Transmission of HEV through food of animal origin is already documented (Yazaki et al., 2003; Tei et al., 2003; Li et al., 2009; Meng, 2011; Said et al., 2014) and explained in detail previously. Nipah virus was shown to affect people slaughtering pigs. Whether eating produce from infected pigs can transmit the Nipah virus is not known (FAO/WHO, 2008). Nipah virus was shown to affect children eating fruits contaminated with urine from bats shedding the virus, and three outbreaks in Bangladesh have been linked to consumption of fresh local sweet delicacy, which had been contaminated by bats (Luby et al., 2006). Besides those mentioned, there is evidence of transmission of the Ebola virus through bushmeat mainly by ingesting the meat of fruit bats. This mode of Ebola virus transmission has been found as a route of virus transmission from wildlife to human population (Leroy et al., 2009). It is important to stress that, for most of the aforementioned emerging foodborne pathogens, contaminated foods is not a usual or even a likely vehicle of transmission, but the potential for foodborne transmission should be considered in epidemiological studies (FAO/WHO, 2008; Newell et al., 2010). Recently, the European Food Safety Authority (EFSA) BIOHAZ stressed that except for tick-borne encephalitis virus, which can be shed by infected dairy animals and subsequently infect humans via milk; and HEV, which can be transmitted through consumption of undercooked meat, viral foodborne infections are limited to the recycling of human viruses back to humans (EFSA, 2011).

5.4 KNOWLEDGE GAPS AND FUTURE TRENDS AND EXPECTATIONS

Food and environmental virology is a relatively young scientific discipline and consequently there is little published data on virus presence and prevalence in different matrices. There are just a few existing data on virus presence and prevalence in different foods. The data available originates mainly from research project-based studies, and in most cases were from studies conducted after the outbreak occurred. Data from systemic virus surveillance in foods are missing mainly because there is no systemic surveillance either on a national or wider level (Petrović, 2013).

Another important data gap relates to the lack of knowledge regarding the prevalence of disease caused by viruses in foods in comparison with other possible transmission routes. Also, the relative contribution of different sources (shellfish, fresh produce, food handler including asymptomatic shedders, and food handling environment) to foodborne illness has not been determined. Most countries have some level of reporting of foodborne illness outbreaks, but few of these systems include viral foodborne illness (Greening, 2006; Newell et al., 2010). Due to the high rate of secondary transmissions, small initial foodborne events may rapidly present person-to-person outbreaks, if the initial introduction event was not recognized (EFSA, 2011). Some case-based surveillance exists for HAV and EVs, but usually it is not focused on detecting foodborne

transmission as a source of the infection (Newell et al., 2010; EFSA, 2011). As a result, national statistics on foodborne viral disease are not readily available and, where present, it likely reflects significant underreporting (Mead et al., 1999; Greening, 2006; FAO/WHO, 2008). Routine harmonized surveillance of viral outbreaks and of virus occurrence in different foods would be recommended to aid source attribution studies. Estimates of the proportion of illness caused by foodborne viruses that can be connected to consumption of contaminated food are based upon very few studies, and according to the EFSA BIOHAZ (EFSA, 2011) would require the addition of systematic strain typing to routine surveillance, or more systematic studies to provide more reliable data for burden estimates.

Testing for viruses in food products is difficult, and there is considerable debate over interpretation of findings. As a consequence, data from food-product monitoring are at the least inconsistent (EFSA, 2011). A problem for the detection, study, as well as for the control of most of the foodborne viruses is that some enteric viruses replicate poorly (HAV) or not at all (NoV) in cultured cells (Atmar and Estes, 2001). In addition, there are no laboratory animal models available for experimental studies of virus inactivation. For these reasons, detection methods currently rely on virus genome detection by molecular techniques such as reverse transcription polymerase chain reaction (RT-PCR). The application of molecular techniques such as real-time (RT)-PCR has enabled relatively rapid, sensitive, and specific detection of viral genome sequences. The problem of this methodology is the fact that the positive signal does not provide information on virus infectivity; rather it indicates the presence of the viral genomic segment. So, inactivated virus particles that pose no threat to public health may still contain intact RNA and give a positive result (Koopmans and Duizer, 2004; Stals et al., 2011). The positive results of NoV presence in food are of special concern in the absence of linked outbreaks. Consequently, a potential risk for infection cannot be excluded, but the actual risk from RT-PCR NoV-positive produce remains unknown. For this reason, studies should be designed determining the probability of infection related to the presence or levels of NoV genomic copies (Baert et al., 2011).

A lack of appropriate detection methods for confirmation of viruses as the etiological agent in food is also the reason for underreporting of foodborne virus outbreaks (Baert et al., 2009). Although protocols are available for the detection of HAV and NoV as the viruses that are most frequently associated with foodborne outbreaks, few laboratories use them when investigating the causes of foodborne diseases, because the methods are considered to be too expensive and too time-consuming for the routine screening of foods (Lopman et al., 2002). From 2013, an International Organization for Standardization (ISO) methods (technical specifications) for the detection of HAV and NoV in foods exists: "Horizontal methods for determination of hepatitis A virus and norovirus in food using real-time RT-PCR (ISO TS 15216-1, 2013 and ISO TS 15216-2, 2013)," but still they are very expensive and time-consuming and not adequate for wide surveillance studies. Currently, methods used for monitoring of foods using *E. coli* as microbiological criteria do not correlate consistently with presence or absence of viruses in foods. Also, current safety standards for determining food quality typically do not specify what level of viruses should be considered acceptable (Okoh et al., 2010). As a consequence, the food industry and food safety authorities, at present, lack the tools that enable them to monitor virological quality control in contrast with the situation that exists for bacteriological contamination (EFSA, 2011).

Despite the fact that viruses are one of the most common pathogens transmitted via food, no systematic inspection and legislation exist regarding the presence of viruses in the food chain that would set up virological criteria for food safety (Koopmans and Duizer, 2004; Okoh et al., 2010). Accordingly, the education of food-industry managers, producers, distributors, and consumers about hygienic regulations and conditions of food production and processing are essential (Vasickova et al., 2005). Commission Regulation (EC) 2073/2005 on microbiological criteria for foodstuffs lays down food safety criteria; however, no specific criteria are set for viruses.

At the time of this writing, no routine monitoring of viruses in foodstuffs is performed; however, it would be highly beneficial to have such surveillance, including a system where data from food and environmental monitoring could be epidemiologically compared with data from outbreaks in the population (Petrović, 2013). Molecular epidemiology and surveillance of food samples are necessary to elucidate the public health hazards associated with exposure to foodborne viruses and for the estimation of the true size of food-related cases (ECDC, 2006). Thus, fast, reliable, and standardized methodologies for the detection of pathogen viruses in different kinds of foods are necessary and it is one of the major future demands and expectations. These methods will most probably be based upon molecular (RT) PCR with the inclusion of all necessary external and internal controls needed to control the steps in detection (Petrović, 2013). Many studies were recently performed on this subject (D'Agostino et al., 2011, 2012; Diez-Valcarce et al., 2011a,b). Multiplex formats may be based upon real-time amplification or PCR-microarray systems (Bosch et al., 2008). The established, previously mentioned ISO technical specifications (ISO TS 15216-1, 2013 and ISO TS 15216-2, 2013) are the first steps in that direction.

ACKNOWLEDGMENT

The authors would like to acknowledge funding from the project No. TR31084 of Ministry of Education, Science, and Technological Development of the Republic of Serbia. Special thanks go to Dr. Nigel Cook, FERA, United Kingdom, who introduced the research interest for food and environmental virology to the authors of this book chapter.

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