CHAPTER 1

# Norovirus as a Foodborne Disease Hazard

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Contents



Abstract

Norovirus (NoV) is the most common cause of infectious gastroenteritis in the world. Gastroenteritis caused by bacterial and parasitic pathogens is commonly linked to food sources, but the link between NoV and contaminated foods has been more difficult to establish. Even when epidemiological information indicates that an outbreak originated with food, the presence of NoV in the suspect product may not be confirmed. If food is found to contain a common strain of NoV that circulates widely in the community, it is not possible to use strain typing to link the contamination to patient cases. Although food is certainly implicated in NoV spread, there are additional person-to-person and fomite transmission routes that have been shown to be important. NoV has an extremely low infectious dose, is stable in the environment, and resists disinfection. Cell culture methods are not available, so viability cannot be determined. Finally, many NoV outbreaks

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originate with when an infected food handler contaminates ready-to-eat food, which can be interpreted as foodborne or person-to-person transmission. This review will discuss both the physical characteristics of NoVs and the available epidemiological information with particular reference to the role of foods in NoV transmission.

## I. INTRODUCTION TO NOROVIRUS

*Norovirus* is a genus of the *Caliciviridae* family, named for the cup-shaped depressions visible in the capsid by electron microscopy (Fauquet *et al.*, 2005). Other genera within *Caliciviridae* are *Lagovirus* that infects rabbits and hares, *Vesivirus*, infecting multiple animal species including cats and sea lions, and *Sapovirus* that infects humans.

The human caliciviruses, norovirus (NoV) and sapovirus, have also been described as small round structured viruses, for their 27–30 nm capsids. The NoV capsid consists of 180 copies of the VP1 major capsid protein packed as an icosahedron (Prasad *et al.*, 1999) and the VP2 minor capsid protein, which may contribute to stability (Bertolotti-Ciarlet *et al.*, 2002). The S domain of VP1 forms the inner shell of the capsid, while the P domain protrudes from the capsid surface and contributes to binding the histoblood group antigen receptor (Cao *et al.*, 2007) and antigenicity (Donaldson *et al.*, 2008; Lindesmith *et al.*, 2010).

The NoV genome is approximately 7.5 kb in length and contains three open reading frames ( Jiang *et al.*, 1993). ORF1 codes for a polyprotein that is cleaved by the viral protease into at least six nonstructural proteins including the viral Vpg, protease, and RNA-dependent RNA polymerase (Sosnovtsev *et al.*, 2006). ORF2 codes for the major capsid protein VP1, and ORF3 codes for the minor capsid protein VP2 (Green, 2007). The P domain of VP1, in particular the P2 subdomain, is the most variable region of the NoV genome, while the 5′ untranslated region (UTR) and the junction between ORF1 and ORF2 are the most highly conserved regions of the genome (Kageyama *et al.*, 2003). The P2 subdomain is associated with NoV antigenic variation (Lindesmith *et al.*, 2008; Siebenga *et al.*, 2007b), while the highly conserved regions are the sites of initiation for transcription of the viral genomic and subgenomic RNAs (Asanaka *et al.*, 2005; Bull *et al.*, 2005; Lambden *et al.*, 1995).

Sequence analysis of the major capsid protein, VP1, groups NoV into five genogroups that contain at least 29 genetic clusters (Zheng *et al.*, 2006). Most of the strains associated with human infection belong to genogroup I (GI) or GII, while GIII viruses infect cattle, GIV viruses infect humans and canines, and GV viruses infect mice.

NoV infection causes acute vomiting, diarrhea, and abdominal cramps (Koopmans, 2008). Fever is reported in approximately 40% of NoV cases (Kaplan *et al.*, 1982; Wyatt *et al.*, 1974). Cases typically become symptomatic 24–48 h after infection, and the illness typically resolves after 48–72 h (Teunis *et al.*, 2008; Wyatt *et al.*, 1974). Both symptomatic illness and asymptomatic shedding have been shown to last longer in children, as well as hospitalized or immunocompromised patients (Kirkwood and Streitberg, 2008; Lopman *et al.*, 2004; Rockx *et al.*, 2002; Simon *et al.*, 2006). Attempts have been made to correlate levels of NoV shedding with a particular genogroup or with disease severity, but to date, no clear picture has emerged (Ajami *et al.*, 2010; Barreira *et al.*, 2010; Chan *et al.*, 2006; Lee *et al.*, 2007). Deaths have been associated with NoV infection due to severe dehydration in sensitive populations (Chadwick *et al.*, 2000; Dedman *et al.*, 1998; Stuart *et al.*, 2010).

NoVs infect all age groups and are the most common cause of infectious gastroenteritis in both community and healthcare settings (de Wit *et al.*, 2001b; Estes *et al.*, 2006; Green *et al.*, 2002; Lopman *et al.*, 2003, 2004). See Table 1.1 for a summary of some published NoV outbreak reports. Although outbreaks occur throughout the year (Alain and Denis, 2007), there seems to be increased NoV activity in the colder months in temperate climates (Dey *et al.*, 2010; Greer *et al.*, 2009; Lopman *et al.*, 2009; Rohayem, 2009). A precise description of NoV prevalence worldwide is not possible, due to differences in surveillance systems and in detection methods, but reports suggest that anywhere from 5% to 30% of tested cases of gastroenteritis are caused by NoV (Amar *et al.*, 2007; Bon *et al.*, 1999; de Wit *et al.*, 2001a; Monica *et al.*, 2007; Oh *et al.*, 2003; O'Ryan *et al.*, 2000; Pang *et al.*, 1999; Parashar *et al.*, 2004). Repeated infection with the same NoV strain is possible, as natural infection does not appear to confer long-lasting immunity ( Johnson *et al.*, 1990; Parrino *et al.*, 1977).

## II. NOROVIRUS GENETIC TYPES AND OUTBREAK ASSOCIATION

Of all the NoV genetic clusters, the GII.4 cluster represents the majority of NoV detected by public health testing laboratories (Adamson *et al.*, 2007; Ho *et al.*, 2006; Ike *et al.*, 2006; Kearney *et al.*, 2007; Maunula and Von Bonsdorff, 2005; Park *et al.*, 2010; Reuter *et al.*, 2008; Siebenga *et al.*, 2007a; Tu *et al.*, 2007). This cluster is identified around the world (Siebenga *et al.*, 2009) and has been circulating for at least 35 years (Bok *et al.*, 2009). The GII.4 strains have been shown to have a higher mutation rate than other clusters (Bull *et al.*, 2010), possibly associated with specific amino acid changes in the viral polymerase (Bruggink and Marshall, 2008, 2009). Six major strain variants of GII.4 NoV were identified between 1990 and 2006 (Lindesmith *et al.*, 2008;

**TABLE 1.1** Examples of norovirus outbreak reports published since 2005

| Outbreak type | Outbreak source | Data available | NoV genotype | Reference |
|---|---|---|---|---|
| Person to person | Contact among patients, relatives, and staff in a nursing home/hospital | Epidemiology and NoV from cases | NR[a] | Grima *et al*. (2009), Grmek Kosnik *et al*. (2007), Leuenberger *et al*. (2007), Simon *et al*. (2006), Sommer *et al*. (2009) |
| | Contact among patients, relatives, and staff in multiple nursing homes | Epidemiology and NoV from cases | GII | Calderon-Margalit *et al*. (2005) |
| | Contact among students at a university residence | Epidemiology and NoV from cases | NR | Honish *et al*. (2008) |
| | Contact among guests at a hotel | Epidemiology and NoV from cases | NR | Michel *et al*. (2007) |
| | Contact between passengers on a ship | Epidemiology and NoV from cases | NR, GII.1, GII.4, GII.5 | Chimonas *et al*. (2008), Sasaki *et al*. (2006) |
| | Contact between passengers on a flight | Epidemiology and NoV from cases | NR | Holmes and Simmons (2009), Kirking *et al*. (2010) |
| | Contact among evacuees in a shelter | Epidemiology and NoV from cases | NR, GII.17 | Nomura *et al*. (2008), Yee *et al*. (2007) |
| | Contact between infants/children at a nursery | Epidemiology and NoV from cases | GI.4, GII.3, GII.6 | Uchino *et al*. (2006), Tsugawa *et al*. (2006) |
| | Exposure to vomit | Epidemiology and NoV from cases | NR, GII.4 | Holmes and Simmons (2009), Kuo *et al*. (2009b), Schmid *et al*. (2005b) |
| Fomites | Environmental surfaces in a long-term care facility | NoV sequenced from swabs and cases | GII.4 | Wu *et al*. (2005) |

| | | | | |
|---|---|---|---|---|
| | Surfaces in shared houseboats | NoV detected from swabs and cases | NR | Jones *et al*. (2007) |
| | Computer surfaces in a school | NoV sequenced from swabs and cases | GII | CDC (2008) |
| | Juice dispensing taps at a hotel | NoV sequenced from cases with no other contact | GII.4 | Visser *et al*. (2010) |
| Food handlers | Rolls prepared by symptomatic baker | NoV sequenced from worker and cases | GII | de Wit *et al*. (2007) |
| | Sandwiches and salads prepared by symptomatic handler | NoV sequenced from worker and cases | GI.3 | Sala *et al*. (2005) |
| | Pastry prepared by symptomatic handler | NoV sequenced from worker and cases | GII.4 | Oogane *et al*. (2008) |
| | Wedding cakes decorated by symptomatic handler | NoV sequenced from worker and cases | NR | Friedman *et al*. (2005) |
| | Salads prepared by symptomatic handler | NoV sequenced from worker and cases | GII.7 | Schmid *et al*. (2007) |
| | Burgers assembled by handler who later became symptomatic | NoV sequenced from worker and cases | GI.3 | Zomer *et al*. (2010) |
| | Salads prepared by handler who later became symptomatic | NoV sequenced from worker and cases | GII.6 | Vivancos *et al*. (2009) |
| | Food served at a seminar, handler had been previously symptomatic | NoV sequenced from recovering worker and cases | GI.3 | Nordgren *et al*. (2010) |
| | Sandwiches prepared by asymptomatic handler | NoV amplified from child of worker and cases | GII | Kuo *et al*. (2009a) |

(*continued*)

**TABLE 1.1** (*continued*)

| Outbreak type | Outbreak source | Data available | NoV genotype | Reference |
|---|---|---|---|---|
| | Sandwiches prepared by asymptomatic handler | NoV detected from worker and cases | NR | Godoy *et al*. (2005) |
| Food and water | Hotel/resort/camp water source | NoV sequenced from water and clinical specimens | Multiple, GIIb | Hewitt *et al*. (2007), Kim *et al*. (2005), Migliorati *et al*. (2008), ter Waarbeek *et al*. (2010) |
| | Municipal water supply | NoV detected or sequenced in water and clinical specimens | NR, multiple, GI.5 | Gallay *et al*. (2006), Scarcella *et al*. (2009), Werber *et al*. (2009) |
| | Flood water | Epidemiology | NR | Schmid *et al*. (2005a) |
| | Recreational water | NoV detected in water and clinical specimens | NR | Podewils *et al*. (2007), Sartorius *et al*. (2007) |
| | Shellfish | NoV sequenced in food and clinical specimens | Multiple | David *et al*. (2007), Gallimore *et al*. (2005a), Huppatz *et al*. (2008), Iizuka *et al*. (2010), Le Guyader *et al*. (2006b, 2010), Ng *et al*. (2005), Sala *et al*. (2009), Symes *et al*. (2007), Webby *et al*. (2007), Westrell *et al*. (2010) |
| | Frozen raspberries | Epidemiology, NoV sequenced in food and clinical specimens | NR, GI.4 | Hjertqvist *et al*. (2006), Korsager *et al*. (2005), Maunula *et al*. (2009) |
| | Lettuce | Epidemiology, NoV sequenced in food and clinical specimens | Multiple | Ethelberg *et al*. (2010), Gallimore *et al*. (2005b), Wadl *et al*. (2010) |

[a] NR = not reported.

Siebenga *et al.*, 2007b; Zheng *et al.*, 2010). In each year, a novel strain was seen to circulate, the number of NoV outbreaks increased to atypical levels in many countries simultaneously ( Johansen *et al.*, 2008; Lopman *et al.*, 2004; Siebenga *et al.*, 2010). The testing of archived patient sera supports a hypothesis where herd immunity is acquired at the community level to an existing GII.4 strain, reducing the number and size of outbreaks in years without novel variants (Cannon *et al.*, 2009). The detection of a new variant strain in the summer has been proposed as a predictor for winter epidemic seasons of NoV infection (Verhoef *et al.*, 2008).

GII.4 NoVs are the most common genotype in outbreak statistics. However, most data is obtained from institutions, and it is primarily in closed or semiclosed settings that GII.4 NoVs have the largest impact (Blanton *et al.*, 2006; Bruggink *et al.*, 2010; Kittigul *et al.*, 2010; Lopman *et al.*, 2003; Pang *et al.*, 2010). Studies that examine NoV genetic diversity in sewage and in environmental samples typically identify a much larger proportion of GI and other GII viruses. For example, 11 different NoV types were detected in only 49 Dutch sewage samples (van den Berg *et al.*, 2005). Testing in France and Italy also determined that sewage samples contained a mixture of GI and GII viruses in raw and treated sewage (da Silva *et al.*, 2007; La Rosa *et al.*, 2010). Environmental water samples have also been shown to contain both GI and GII NoVs (Kamel *et al.*, 2010; La Rosa *et al.*, 2007).

When outbreak surveillance focuses on food and waterborne transmission routes, the GII.4 NoV no longer predominate as a source of illness (Bon *et al.*, 2005; Koek *et al.*, 2006; Lysen *et al.*, 2009; Pang *et al.*, 2010). GI NoVs are the most common strains identified in cases of waterborne transmission (Lysen *et al.*, 2009), while a mixture of GI and GII genotypes has been associated with shellfish-related outbreaks (Bon *et al.*, 2005; Kageyama *et al.*, 2004). This distinction has been presented as a mechanism to predict the origin of an outbreak based on the genetic typing of the infecting NoV strain, with a non-GII.4 etiology indicative of potential food or waterborne transmission (Verhoef *et al.*, 2009; Verhoef *et al.*, 2010). The GII.4 NoVs circulate widely in the community and exhibit very little sequence variation within an epidemic season (Dingle, 2004), making it difficult to establish an unambiguous epidemiological link between a positive food product and the patient. Food testing could therefore be focused on non-GII.4 outbreaks where the link between clinical and environmental samples is more likely to be clearly established.

## III. NOROVIRUS OUTBREAKS SPREAD PERSON TO PERSON

NoV can spread directly from person to person due to their low infectious dose. Human volunteer studies have estimated that a single infectious NoV particle could cause illness in a susceptible individual (Teunis *et al.*, 2008).

There is a wide range of reported NoV attack rates during outbreaks (Harris *et al.*, 2010), but this is probably complicated by differing genetic susceptibilities among those exposed. Different blood groups or Lewis antigen profiles may confer susceptibility to different NoV genetic types (Cheetham *et al.*, 2007; Hutson *et al.*, 2005; Lindesmith *et al.*, 2003). Although most studies agree that secretor positive individuals (with a functional FUT2 allele) are susceptible to NoV infection, there are reports of NoV illness in secretor negative persons (Carlsson *et al.*, 2009; Marionneau *et al.*, 2005).

Many large surveillance studies have shown that the majority of NoV outbreaks are caused by GII.4 NoV spread directly from person to person in hospitals and long-term care facilities (Doyle *et al.*, 2009; Godoy *et al.*, 2009; Kelly *et al.*, 2008). It has been suggested that the predominance of GII.4 infections can be explained by higher attack rates and more symptomatic disease during GII.4 outbreaks than during infections with other genetic types (Friesema *et al.*, 2009b).

There is a large reservoir of NoV in the community, as evidenced by surveys of community acquired and sporadic cases of gastroenteritis (Buesa *et al.*, 2002; Haustein *et al.*, 2009; Karsten *et al.*, 2009; Lindell *et al.*, 2005). Syndromic surveillance of vomiting reports also indicates that the presence of NoV infections is constantly fluctuating in different areas (Cooper *et al.*, 2008). This widespread reservoir means that NoVs are continually introduced into hospital settings where they can spread rapidly despite efforts to interrupt transmission (Cunliffe *et al.*, 2010; Koopmans, 2009; Sommer *et al.*, 2009). Preventing the introduction of this widespread pathogen is nearly impossible (Koopmans, 2009; Yee *et al.*, 2007).

NoV outbreaks that are spread directly from person to person do not usually implicate a single-point source introduction, and the course of the outbreak can be complicated (Grmek Kosnik *et al.*, 2007). Multiple links between outbreaks in different sectors or in different institutions may be suggested, but only some of these will be supported by epidemiological evidence (Calderon-Margalit *et al.*, 2005; Lopman, 2006; Schmid *et al.*, 2005b). Multiple strains circulating in a single outbreak and the transfer of infected persons between facilities can complicate epidemiology and prolong the outbreak (Uchino *et al.*, 2006; Yamagami and Hara, 2007). There is the additional complication that hospital patients and long-term care facility residents have other, pre-existing health concerns that can contribute to an increased severity or prolonged course of NoV disease (Siebenga *et al.*, 2008; Simon *et al.*, 2006; Tsang *et al.*, 2008; Westhoff *et al.*, 2009).

Other closed or semiclosed settings where large person-to-person NoV outbreaks have been documented are associated with travel, on cruise ships and on airplanes. Cruise ships represent an interesting situation

where a few infected passengers embarking can spread a low level of infection among staffs and passengers with whom they have direct contact (Cramer *et al.*, 2006; Koopmans *et al.*, 2006; Neri *et al.*, 2008). The presence of infection control measures does not seem to prevent NoV transmission in this setting (Takkinen, 2006), and risk is more significantly associated with case behavior than with environmental health measures (Chimonas *et al.*, 2008; Isakbaeva *et al.*, 2005). Multiple viruses or strains can cocirculate in these conditions and complicate efforts to trace the source of infection (Sasaki *et al.*, 2006). Transmission on airplanes is more easily traced to an index event of vomiting or diarrhea within the confined space of the aircraft (Holmes and Simmons, 2009; Kirking *et al.*, 2010). Attack rates of 5% or less among airplane passengers are not likely to be linked to the flight and would probably be considered to be sporadic cases in the absence of a dramatic reason for linking the cases (Kornylo *et al.*, 2009).

NoV outbreaks in hotels or schools have also been initiated by virus spread directly from person to person. The cause can be a significant vomiting event to which a large group is simultaneously exposed (Kuo *et al.*, 2009b; Michel *et al.*, 2007), or it can be unknown but clearly diffuse in origin (Honish *et al.*, 2008). Outbreaks with no clear beginning or end and no association with food or water are frequently identified as transmitted from person to person, although fomite contamination is also often suspected as a possible contributor to the spread of infection (Honish *et al.*, 2008).

NoV outbreaks in hospital settings can be expensive, with one case report identifying costs totaling over $650,000 for a single outbreak (Johnston *et al.*, 2007). A 2007 review found that NoV outbreaks in hospitals had a 44% rate of requiring unit closures, much higher than the rates for other nosocomial pathogens (Hansen *et al.*, 2007).

Recommendations for preventing and limiting the spread of person-to-person outbreaks of NoV generally follow commonsense guidelines for limiting the transmission of other infectious diseases (Friesema *et al.*, 2009a; Greig and Lee, 2009; Harris *et al.*, 2010). However, NoV has a very low infectious dose (Teunis *et al.*, 2008) and resists environmental disinfection (Girard *et al.*, 2010; Terpstra *et al.*, 2007), so the efficacy of any individual control measure can be less than for bacterial or enveloped viral targets. In fact, systematic literature reviews have failed to find a statistical difference in the duration of NoV outbreaks whether pathogen-specific control measures were or were not followed (Friesema *et al.*, 2009a; Greig and Lee, 2009; Harris *et al.*, 2010). These reviews are all complicated by the fact that they cannot account for the impact of basic infection control measures already present before an outbreak (Harris *et al.*, 2010). Mathematical modeling indicates that one important parameter for stopping NoV outbreaks in semiclosed settings is the short-term

immunity acquired by the exposed population during the course of the outbreak (Vanderpas *et al.*, 2009).

Nonetheless, infection control measures are universally recommended to limit the person-to-person spread of NoV (Harris *et al.*, 2010). One study identified reduced illness among staff members as a result of infection control (Vivancos *et al.*, 2010b), and a review has identified that some measures can reduce the number of illnesses, if not the duration of the outbreak (Friesema *et al.*, 2009a). It is important to note that as a direct result of the person-to-person transmission route, the enhanced disinfection of surfaces is not sufficient to control these outbreaks (CDC, 2009a,b; Vivancos *et al.*, 2010a). This distinguishes them from outbreaks transmitted via point source fomite contamination, which are discussed in Section IV. For outbreaks spread directly between individuals, limiting interaction between infected and uninfected persons is critical. Cohorting of patients within medical facilities, exclusion of staff for up to 72 h following an attack of gastroenteritis, and cancellation of social events have all been recommended (CDC, 2009a; Rao *et al.*, 2009; Vivancos *et al.*, 2010b). The use of personal protective equipment when working with patients or patient samples has been identified as a factor affecting outbreak spread (CDC, 2009b; Ebihara *et al.*, 2008). In addition, hand hygiene has been particularly well studied as a method of interrupting transmission of NoV during outbreaks (Gilbride *et al.*, 2009; Heijne *et al.*, 2009; Moe *et al.*, 2001; Surgeoner *et al.*, 2009), although the efficacy of alcohol-based hand rubs against NoV is controversial (Bloomfield *et al.*, 2007; Cheng *et al.*, 2009; Liu *et al.*, 2010; Macinga *et al.*, 2008; Steinmann *et al.*, 2010). Some studies indicate that washing with soap and water is required to eliminate NoV transmission (Bidawid *et al.*, 2004; Lages *et al.*, 2008; Liu *et al.*, 2010; Martin *et al.*, 2008), while others suggest that ethanol-based rubs are sufficient as an infection control tool (Cheng *et al.*, 2009). All authors agree that the use of hand rubs is indicated where soap and water are not available (CDC, 2009a; Steinmann *et al.*, 2010).

## IV. NOROVIRUS OUTBREAKS SPREAD BY FOMITE CONTAMINATION

NoV are readily transferred from hands to fomites and vice versa (Bidawid *et al.*, 2004; D'Souza *et al.*, 2006). The pronounced environmental stability of NoV particles also contributes to the spread of outbreaks from point sources of surface contamination. All stability studies have made use of surrogate organisms to model NoV response to conditions, since the human virus is not easily grown in cell culture (Duizer *et al.*, 2004b; Straub *et al.*, 2007). The murine norovirus (MNV) and the feline calicivirus (FCV) have both been used, with the mouse virus providing more

relevant data under conditions of low pH (Cannon *et al.*, 2006). Efforts have been made to develop methods to quantify human NoV persistence and disinfection by detection of genetic material (Lamhoujeb *et al.*, 2008; Mormann *et al.*, 2010; Ngazoa *et al.*, 2008; Nuanualsuwan and Cliver, 2002; Topping *et al.*, 2009), but the correlation of genetic material to infectious titer remains controversial (Baert *et al.*, 2008c; Hewitt *et al.*, 2009; Rodriguez *et al.*, 2009). Persistence of infectious FCV has been demonstrated for up to 7 days dried on stainless steel, formica, or ceramic surfaces (D'Souza *et al.*, 2006; Mattison *et al.*, 2007). Other more complex inanimate surfaces, such as telephone buttons and computer keyboards, support the survival of infectious FCV for 0.5–3 days (Clay *et al.*, 2006).

The particular resistance of NoV to disinfection is an additional factor in the spread of NoV infections from contaminated fomites. Table 1.2 presents a summary of studies on disinfection of the FCV and MNV surrogates. Data from disinfection studies must be interpreted with care, as many demonstrate efficacy in suspension tests (Beekes *et al.*, 2010; Belliot *et al.*, 2008; Duizer *et al.*, 2004a; Poschetto *et al.*, 2007), but the carrier test using surface-dried virus is more appropriate for surface cleaners (Terpstra *et al.*, 2007). Contact time also plays an important role, with some disinfectants exhibiting efficacy after 10 min that cannot be demonstrated after 1 min (Jimenez and Chiang, 2006; Whitehead and McCue, 2010). In general, 1000 ppm of available chlorine effectively inactivates the FCV and MNV surrogates (D'Souza *et al.*, 2009; Girard *et al.*, 2010; Whitehead and McCue, 2010). Hypochlorous acid, trisodium phosphate, sodium bicarbonate, and glutaraldehyde are also effective on surfaces, at sufficient concentrations and contact times (D'Souza *et al.*, 2009; Magulski *et al.*, 2009; Malik and Goyal, 2006; Malik *et al.*, 2006a; Park *et al.*, 2007). Alcohols and quaternary ammonium compounds are less effective against the *Caliciviruses* (D'Souza *et al.*, 2009; Gulati *et al.*, 2001; Magulski *et al.*, 2009; Malik *et al.*, 2006b; Solomon *et al.*, 2009; Whitehead and McCue, 2010), although combinatorial formulations can be effective (Malik *et al.*, 2006a; Whitehead and McCue, 2010). These should be evaluated on a case-by-case basis, using a protocol based on their proposed use (i.e., surface carrier test for surface disinfectants, fingerpad test for hand rubs) (Macinga *et al.*, 2008; Whitehead and McCue, 2010). More complex surfaces, such as woven fabrics, carpets, or porous materials, can be more difficult to disinfect (Malik *et al.*, 2006a). UV disinfection overcomes some of the issues with soft fabrics, but the light must reach all crevices to be effective (Lee *et al.*, 2008). The use of gas disinfection in sealed rooms is an interesting alternative to reach all areas, but this requires long incubation times and the ability to seal an area (Hudson *et al.*, 2007).

There is not always a clear distinction between outbreaks transmitted via inanimate surfaces as compared to those that are linked to direct

**TABLE 1.2** Resistance of FCV and MNV surrogate viruses to physical inactivation

| Virus | Treatment | Matrix | Contact time | Log reduction | Reference |
|---|---|---|---|---|---|
| MNV | Heat 56 °C | Buffer | 3.4 min | 1 | Cannon *et al.* (2006) |
| | 63 °C | Buffer | 0.4–1 min | 1 | Cannon *et al.* (2006), Hewitt *et al.* (2009) |
| | 72 °C | Buffer | 0.2 min | 1 | Cannon *et al.* (2006), Duizer *et al.* (2004a) |
| | Heat 65 °C | Raspberry puree | 0.5 min | 2 | Baert *et al.* (2008a) |
| | 75 °C | Raspberry puree | 0.25 min | 3 | Baert *et al.* (2008a) |
| | Freezing | Vegetables | 6 months | <1 | Baert *et al.* (2008b) |
| | High pressure 300 MPa | Buffer | 2 s | 1 | D'Souza *et al.* (2009) |
| | 450 MPa | Buffer | 5 min | 7 | Kingsley *et al.* (2007) |
| | 400 MPa | Oyster meat | 5 min | 4 | Kingsley *et al.* (2007) |
| | Bleach 1000 ppm | Surface | 1–5 min | 5–6 | D'Souza *et al.* (2009), Girard *et al.* (2010) |
| | Chlorine 0.2–0.5 mg/L | Water | 0.02–1 min | 4 | Cromeans *et al.* (2010), Kitajima *et al.* (2010), Lim *et al.* (2010a) |
| | Chlorine dioxide 0.3 mg/L | Water | 1 min | 4 | Lim *et al.* (2010a) |
| | HOCl 50–190 ppm | Surface | 10 min | >3.5 | Park *et al.* (2007) |
| | Ethanol 70% | Surface | 1 min | 0 | D'Souza *et al.* (2009) |
| | 60% | Surface | 5 min | 6 | Magulski *et al.* (2009) |
| | Isopropanol 60% | Surface | 5 min | 3 | Magulski *et al.* (2009) |
| | Trisodium phosphate 5% | Surface | 1 min | >6 | D'Souza *et al.* (2009) |
| | Glutaraldehyde 2% | Surface | 1–5 min | 4 | D'Souza *et al.* (2009), Magulski *et al.* (2009) |
| | Quaternary ammonium 800 ppm | Surface | 5 min | 0.5 | Girard *et al.* (2010) |

| | | | | | |
|---|---|---|---|---|---|
| | Peracetic acid 1000 ppm | Surface | 5 min | 4 | Magulski *et al*. (2009) |
| | Ozone 1 mg/L | Buffer | 2 min | 2 | Lim *et al*. (2010b) |
| | UV light 25 mJ/cm$^2$ | Surface | n/a | 3–4 | Lee *et al*. (2008) |
| FCV | Heat 56 °C | Buffer | 6.7 min | 1 | Cannon *et al*. (2006) |
| | 63 °C | Buffer | 0.4 min | 1 | Cannon *et al*. (2006) |
| | 72 °C | Buffer | 0.1–0.2 min | 1 | Buckow *et al*. (2008), Cannon *et al*. (2006) |
| | Heat 75 °C | Leafy herbs | 2.5 min | >4 | Butot *et al*. (2009) |
| | 95 °C | Leafy herbs | 2.5 min | >4 | Butot *et al*. (2009) |
| | Freezing | Herbs | 2 days | <1 | Butot *et al*. (2008) |
| | | Acidic berries | 2 days | 1–3 | Butot *et al*. (2008) |
| | High pressure 200–300 MPa | Buffer | 3–5 min | >5 | Chen *et al*. (2005), Grove *et al*. (2008), Kingsley *et al*. (2002) |
| | 500 MPa | Sausages | 5 min | 3 | Sharma *et al*. (2008) |
| | Bleach 100–400 ppm | Surface | 1 min | 0.3–2 | Gulati *et al*. (2001), Whitehead and McCue (2010) |
| | 1000 ppm | Surface | 1 min | >4 | D'Souza and Su (2010), Whitehead and McCue (2010) |
| | Chlorine 0.3–1 mg/L | Water | 5 min | 5 | Thurston-Enriquez *et al*. (2003a), Urakami *et al*. (2007) |
| | Chlorine dioxide 1–20 mg/L | Water | 1 min | 4 | Thurston-Enriquez *et al*. (2005a), Zoni *et al*. (2007) |
| | HCl 0.4% | Surface | 1 min | >5 | Whitehead and McCue (2010) |
| | Ethanol 60% | Surface | 1 min | 1–2 | Malik *et al*. (2006b), Whitehead and McCue (2010) |
| | 70% | Surface | 1 min | 0–2 | D'Souza *et al*. (2009), Malik *et al*. (2006b) |
| | Isopropanol 60% | Surface | 1 min | <0.5–2 | Malik *et al*. (2006b), Whitehead and McCue (2010) |
| | 70% | Surface | 1 min | 1.5 | Malik *et al*. (2006b) |

(*continued*)

**TABLE 1.2** (*continued*)

| Virus | Treatment | Matrix | Contact time | Log reduction | Reference |
|---|---|---|---|---|---|
| | 70% | Fabric/carpet | 1 min | 0.5–2 | Malik *et al*. (2006a) |
| | Trisodium phosphate 5% | Surface | 1 min | >6 | D'Souza *et al*. (2009) |
| | Quaternary ammonium 3000 ppm | Surface | 1 min | 1 | Whitehead and McCue (2010) |
| | 1800 ppm | Surface | 10 min | 2 | Gulati *et al*. (2001), Solomon *et al*. (2009) |
| | Phenol 550 ppm | Surface | 1 min | 2 | Whitehead and McCue (2010) |
| | Glutaraldehyde 2% | Surface | 1 min | >6 | D'Souza *et al*. (2009) |
| | 1.3% | Fabric/ Carpet | 1 min | 1–4 | Malik *et al*. (2006a) |
| | Sodium bicarbonate 10% | Surfaces | 1 min | 4 | Malik and Goyal (2006) |
| | Ozone 20 ppm gas | Room surfaces | 30 min | 2–4 | Hudson *et al*. (2007) |
| | 0.01–0.03 mg/L | Buffer | 1 min | 4 | Thurston-Enriquez *et al*. (2005b) |
| | UV light 16–36 mJ/cm$^2$ | Buffer | n/a | 3–4 | De Roda Husman *et al*. (2004), Thurston-Enriquez *et al*. (2003b), Tree *et al*. (2005) |
| | 120 mJ/cm$^2$ | Vegetables | n/a | 4 | Fino and Kniel (2008) |
| | 120 mJ/cm$^2$ | Strawberries | n/a | 2 | Fino and Kniel (2008) |

transmission from person to person. The role of fomites in NoV transmission in closed settings can never be completely separated from other risk factors (Wu *et al*., 2005). However, contaminated surfaces are associated with outbreaks in closed facilities (Gallimore *et al*., 2006; Gallimore *et al*., 2008), and inappropriate routine disinfection practices may be a predictor for NoV outbreaks (Carling *et al*., 2009; Dancer, 2009; Weber *et al*., 2010).

Outbreaks that have been linked to a point source fomite contamination are characterized by infected populations that have few or no other epidemiological links. For example, an outbreak linked to a certain seating area in a concert hall the day after a vomiting episode (Evans *et al*., 2002) or consecutive occupants of a houseboat ( Jones *et al*., 2007). Two coach tours visiting the same hotel at different times are also linked mainly by common surfaces at the hotel (Visser *et al*., 2010). Although school outbreaks are frequently associated with person-to-person transmission, one investigation indicated shared computers as a possible fomite source of infection (CDC, 2008). The implementation of environmental swabs as a part of routine outbreak investigation would serve to highlight this potential transmission (Boxman *et al*., 2009b).

In theory, the interruption of NoV transmission after fomite contamination is straightforward: the affected objects must be disinfected. In practice, disinfection can become a complex problem. The school described above had implemented a rigorous cleaning protocol with an appropriate bleach solution but failed to consider the computer mice and keyboards for disinfection (CDC, 2008). Vomiting events are particularly difficult to clean, as the contaminated area can be large, and infectious aerosols are postulated to persist in the environment (Evans *et al*., 2002; Marks *et al*., 2003).

## V. NOROVIRUS OUTBREAKS SPREAD BY FOOD HANDLERS

Foods can become contaminated with pathogens at any point during production, processing, and preparation (Greig *et al*., 2007). For NoV outbreaks, there is a strong association with food handlers and poor personal hygiene practices (Baert *et al*., 2009b; Dominguez *et al*., 2010; Hedberg *et al*., 2006, 2008; Thakur *et al*., 2010). This, together with the higher incidence of secondary spread during outbreaks (Martinez *et al*., 2008), has been cited to suggest that NoV does not share the characteristics of a traditional foodborne pathogen (Dreyfuss, 2009).

Some characteristics of NoVs are important when considering food handlers as a transmission route. These viruses are stable in the environment and have been shown to be transmitted between surfaces, hands, and foods (Bidawid *et al*., 2004; Boxman *et al*., 2009a; D'Souza *et al*., 2006; Mokhtari and Jaykus, 2009). Outbreaks in a variety of settings, such as

hospitals, schools, catered events, and restaurants, have all been associated with infected food handlers as the source of contamination (Anderson *et al*., 2001; Costas *et al*., 2007; Friedman *et al*., 2005; Nordgren *et al*., 2010; Oogane *et al*., 2008; Sala *et al*., 2005; Schmid *et al*., 2007; Shinkawa *et al*., 2008; Vivancos *et al*., 2009; Xerry *et al*., 2009). Additional outbreaks have been associated with food handlers based on an indication that multiple food products were involved in a single outbreak (Dominguez *et al*., 2008; Ohwaki *et al*., 2009). In addition, NoV infections result in a higher number of vomiting incidents than other foodborne pathogens (Kaplan *et al*., 1982; Wyatt *et al*., 1974). Vomiting events can be difficult to manage in a food service environment, and outbreaks where food service workers have vomited may be particularly large (de Wit *et al*., 2007) with high attack rates (Zomer *et al*., 2010). Finally, food handlers may harbor asymptomatic NoV infections (Okabayashi *et al*., 2008; Ozawa *et al*., 2007). Outbreaks have been associated with foods handled by workers with no symptoms, although they may have had evidence of recent exposure to NoV (Godoy *et al*., 2005; Kuo *et al*., 2009a; Medici *et al*., 2009).

Control of transmission from infected food handlers relies on an understanding and compliance with food safety procedures (Clayton and Griffith, 2004). Restaurant inspections and recommendations are only effective up to a point (Dominguez *et al*., 2010). Food safety training programs and on-site management committed to food safety can have an impact in reducing NoV outbreaks (Hedberg *et al*., 2006). This could limit noncompliance with policies, a possible cause of outbreaks transmitted during food preparation (Anderson *et al*., 2001; Clayton and Griffith, 2004; Godoy *et al*., 2005; Schmid *et al*., 2007). Additional measures to prevent NoV transmission are more difficult to implement. The exclusion of asymptomatic workers known to have been exposed to NoV or after recovery from gastrointestinal illness is not always realistic when they would lose their pay (Moe, 2009). There are still reports of food handlers working while symptomatic for fear of job loss (Schmid *et al*., 2007), although exclusion of ill workers is clearly indicated as a control measure to prevent NoV outbreaks (Moe, 2009).

## VI. NOROVIRUS OUTBREAKS ATTRIBUTED TO WATER AND FOOD

The stability and persistence of NoV is also a contributing factor to food and waterborne outbreaks. Compared to surfaces, water has a protective effect for calicivirus survival, with 5.5 days required for a 1-log reduction of FCV in water and 11 days required for a 1-log reduction of MNV in water (Bae and Schwab, 2008). Food products provide varying degrees of protection or antiviral activity, depending on their properties. FCV has

been shown to survive for 7 days on ham, 3–5 days on lettuce, 1–5 days on cantaloupe, 3–4 days on bell peppers, and 1 day on strawberries (Mattison *et al.*, 2007; Stine *et al.*, 2005), although it is rapidly inactivated in the acidic environment of marinated mussels (Hewitt and Greening, 2004).

Temperature control is a key parameter for control of bacterial pathogens in food but less relevant for eliminating NoV (Baert *et al.*, 2009a). See Table 1.2 for a summary of the resistance parameters of surrogate viruses. Both MNV and FCV are relatively resistant to heating, requiring temperatures over 60 °C to achieve a 5-log reduction in less than 5 or 10 min in liquid (Baert *et al.*, 2008c; Buckow *et al.*, 2008; Cannon *et al.*, 2006; Doultree *et al.*, 1999; Duizer *et al.*, 2004a; Hewitt *et al.*, 2009). Pasteurization of food purees or steam blanching of herbs does not always eliminate all infectious virus, and time/temperature combinations for these treatments must be chosen with care (Baert *et al.*, 2008a; Butot *et al.*, 2009). Freezing is not suitable for control of NoV contamination, rather long-term frozen storage preserves the infectious virus. Studies have shown that there is less than a 1-log reduction of MNV after 6 months of storage on frozen onions or spinach (Baert *et al.*, 2008b). Similar findings were obtained for FCV on blueberries and frozen herbs after 2 days (Butot *et al.*, 2008). FCV was inactivated after frozen storage on raspberries (1 log) and strawberries (3 logs) (Butot *et al.*, 2008), but these data are confounded by the known sensitivity of FCV to low pH conditions (Cannon *et al.*, 2006; Duizer *et al.*, 2004a).

Physical inactivation can also be achieved by nonthermal processing such as high pressure treatment or ultraviolet (UV) and gamma irradiation (Baert *et al.*, 2009a; Hirneisen *et al.*, 2010). High hydrostatic pressure from 200–300 MPa can quickly reduce infectious FCV by over 5 logs in liquid media, although temperature and pH must be monitored for optimum results (Buckow *et al.*, 2008; Chen *et al.*, 2005; Grove *et al.*, 2008; Kingsley and Chen, 2008; Kingsley *et al.*, 2002). MNV is slightly more resistant, and higher pressure is required to achieve comparable log reductions (D'Souza *et al.*, 2009; Kingsley *et al.*, 2007). Food may provide some protection from high pressure treatment, but inactivation can still be achieved by a 5-min treatment (Kingsley *et al.*, 2007; Sharma *et al.*, 2008). UV light is effective against FCV in buffer and water (De Roda Husman *et al.*, 2004; Thurston-Enriquez *et al.*, 2003b; Tree *et al.*, 2005). UV irradiation is less useful for decontaminating foods. Food surfaces may provide some protection from UV light, as higher doses are required for inactivation of FCV, and the light must equally reach all sides of a food product (Fino and Kniel, 2008).

Chemical treatment of drinking water and food wash waters can also be used to reduce the presence of infectious NoV. Washing can remove 1–3 logs of FCV or MNV from fruits and vegetables (Baert *et al.*, 2008b; Butot *et al.*, 2008), although the viruses then persist in the wash water

(Baert *et al.*, 2009c; Gil *et al.*, 2009). Although disinfection of wash water does not significantly increase the removal of viruses from produce, it can prevent cross-contamination of the next product washed (Baert *et al.*, 2009c; Gil *et al.*, 2009). Effective decontamination of water typically requires more disinfectant than for equivalent bacterial reductions. The concentration of chlorine is important for inactivation in short time periods. MNV is typically inactivated by 0.5 mg/L chlorine in 5 min, but it takes 120 min for inactivation with 0.1 mg/L (Kitajima *et al.*, 2010; Lim *et al.*, 2010a), although shorter inactivation times have been observed in some systems (Cromeans *et al.*, 2010). FCV is sensitive to chlorine within the same concentration range (Thurston-Enriquez *et al.*, 2003a; Urakami *et al.*, 2007). RT-PCR quantification of NoV RNA has demonstrated a reduction in response to treatment with 1 mg/L chlorine, but the relationship between RNA and infectious particles cannot be determined and lower concentrations may be sufficient to reduce infectivity (Shin and Sobsey, 2008). Rapid FCV inactivation with chlorine dioxide requires concentrations from 1 to 20 mg/L, where temperature and pH have a significant effect on the efficacy of $ClO_2$ (Thurston-Enriquez *et al.*, 2005a; Zoni *et al.*, 2007). MNV inactivation has been demonstrated at 0.3 mg/L $ClO_2$ (Lim *et al.*, 2010a). Ozone effectively inactivates 4 logs of FCV at less than 0.03 mg/L for 1 min, but 0.1 mg/L is required to achieve comparable inactivation of MNV (Lim *et al.*, 2010b; Thurston-Enriquez *et al.*, 2005b).

There are many peer-review publications reporting NoV outbreaks due to food and water. In spite of a recognized publication bias toward these outbreaks, there is a consensus that the scientific literature underestimates the contribution of NoV to food and waterborne disease (Hall *et al.*, 2005; Hoffmann *et al.*, 2007; O'Brien *et al.*, 2006). Source contamination of food and water is clearly implicated in NoV outbreaks around the world.

Waterborne outbreaks have been identified in both drinking and recreational waters, although the route of entry is clearly via consumption of the contaminated water. As detection methods improve, more water-related outbreaks have been associated with NoV contamination (Bosch *et al.*, 2008; Ford, 2006; Maunula *et al.*, 2005). Recreational water outbreaks have been associated with lakes (Sartorius *et al.*, 2007) and swimming pools (Podewils *et al.*, 2007), with most of the swimming pool outbreaks attributed to inadequate water treatment (Sinclair *et al.*, 2009). Flood water has also been contaminated with NoV and infections resulted from direct exposure to the water (Schmid *et al.*, 2005a). Drinking water has been shown to become contaminated with NoV through a variety of means. Individual wells can become contaminated and contribute to local outbreaks (Nygard *et al.*, 2003; Parshionikar *et al.*, 2003; ter Waarbeek *et al.*, 2010). These local outbreaks have the potential to seed secondary cases of infection in the community (Beller *et al.*, 1997). Similarly, local hotel or

resort water distribution systems have been identified as the source of NoV outbreaks (Hewitt *et al.*, 2007; Kim *et al.*, 2005; Migliorati *et al.*, 2008). These are easily traced epidemiologically because the affected populations are infected at the same time and have no other common food intake or personal contacts. Outbreaks in community water supplies and groundwater have only been recognized when they reach massive proportions (Gallay *et al.*, 2006; Scarcella *et al.*, 2009; Werber *et al.*, 2009). It is possible that lower levels of contamination could go undetected in the background of community acquired NoV cases throughout the year.

Shellfish are the most commonly implicated food category in NoV outbreaks. These filter feeders accumulate virus if grown in contaminated waters (McLeod *et al.*, 2009; Wang *et al.*, 2008), and they are not effectively decontaminated during depuration (Savini *et al.*, 2009; Ueki *et al.*, 2007). It has been suggested that NoVs interact specifically with carbohydrate structures in the bivalve digestive diverticula (Le Guyader *et al.*, 2006a; Tian *et al.*, 2007, 2008). NoVs have been detected in shellfish grown around the world (Boxman *et al.*, 2006; Cheng *et al.*, 2005; Croci *et al.*, 2007; Elamri *et al.*, 2006; Formiga-Cruz *et al.*, 2002; Hansman *et al.*, 2008; Nishida *et al.*, 2007; Polo *et al.*, 2010; Suffredini *et al.*, 2008), and low levels of contamination are routinely identified in retail shellfish surveys (Costantini *et al.*, 2006; DePaola *et al.*, 2010; Terio *et al.*, 2010). There is no way to determine if the NoV RNA detected is infectious, but the presence of RNA has been associated with reports of illness (Lowther *et al.*, 2010). In addition, there are numerous reports of outbreaks where viruses identified in contaminated shellfish share the same sequence as those isolated from outbreak patients (David *et al.*, 2007; Doyle *et al.*, 2004; Iizuka *et al.*, 2010; Le Guyader *et al.*, 2010; Nenonen *et al.*, 2008; Ng *et al.*, 2005; Sala *et al.*, 2009; Webby *et al.*, 2007). In many other cases, epidemiological evidence points to oyster consumption as the cause of the outbreak, although virus cannot be detected in oyster samples (Gallimore *et al.*, 2005a; Huppatz *et al.*, 2008; Symes *et al.*, 2007; Westrell *et al.*, 2010). The epidemiology can be strengthened by the association of multiple viruses or genotypes with the same outbreak, a common indicator for sewage contamination in shellfish-associated outbreaks (Gallimore *et al.*, 2005a; Kageyama *et al.*, 2004; Le Guyader *et al.*, 2006b; Symes *et al.*, 2007).

Control measures for shellfish-associated outbreaks rely on high quality growing waters. Although bacterial indicators may return to baseline levels after a contamination event, opening a shellfish harvest area too soon can lead to an NoV outbreak (Huppatz *et al.*, 2008). Frozen shellfish from contaminated waters should be clearly labeled to ensure that they are not served raw (Ng *et al.*, 2005; Webby *et al.*, 2007). If waters are known to be contaminated, additional virus-specific relaying or depuration conditions can be implemented to manage the associated risk of NoV gastroenteritis (Dore *et al.*, 2010). Consumer education is useful to reduce

consumption of illegally harvested shellfish (Le Guyader *et al*., 2010) and to increase awareness of the hazards associated with eating raw shellfish (Sala *et al*., 2009).

Fresh fruits and vegetables may also be contaminated with NoV during production or processing prior to distribution. Contaminated irrigation water or wash water can transfer NoV to fresh products (Bassett and McClure, 2008; Cheong *et al*., 2009; Mara and Sleigh, 2010), and surrogate viruses have been shown to attach and persist on fruit and vegetable surfaces (Mattison *et al*., 2007; Urbanucci *et al*., 2009; Wei *et al*., 2010). NoV has been implicated as the cause of outbreaks of gastroenteritis from salads (Allwood *et al*., 2004; Bailey *et al*., 2005; Ethelberg *et al*., 2010; Gallimore *et al*., 2005b; Mesquita and Nascimento, 2009; Wadl *et al*., 2010), cantaloupe (Bowen *et al*., 2006), and frozen raspberries (Hjertqvist *et al*., 2006; Korsager *et al*., 2005; Maunula *et al*., 2009). NoV genomes have been detected in up to 6% of prepackaged salads, and the prevalence of GI NoV indicates a potential association with contaminated water at some point during production (Mattison *et al*., 2010).

Cooking is an effective control measure for NoV contamination but is not applicable to the fresh fruit and produce category. Washing in clean water can reduce levels of NoV contamination from 1 to 3 logs (Baert *et al*., 2008b; Mara and Sleigh, 2010). The most effective intervention is to prevent contamination from occurring. Appropriate treatment of irrigation and wash water can inactivate NoV (Baert *et al*., 2009c). Surveillance networks may detect point source foodborne outbreaks, and this information can be used to prevent or limit the spread of disease (Koopmans *et al*., 2003).

## VII. CONCLUSIONS

NoV outbreaks are spread by a variety of transmission routes, leading to confusion when seeking the ''true'' source of the hazard. The difference between person-to-person and foodborne NoV transmission during outbreaks is not always clear and should not need to be defined. Many outbreaks that begin with contaminated food can later spread person to person and vice versa. Instead of focusing on a label for the source of NoV outbreaks, it is more important to increase overall awareness and understanding of this emerging pathogen. NoV outbreaks are spread in many different ways, including ingestion of contaminated food products. This information can be used to develop strategies for integrating public health and food safety surveillance networks that will provide alerts and interrupt transmission for all categories of NoV outbreaks.

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