**Norovirus**

Norovirus (NoV) is the main cause of viral gastroenteritis in humans worldwide. It is highly contagious due to its very low infectious dose, stability in the environment and resistance to many common disinfectants.

**Description of the organism**

NoV belongs to the *Caliciviridae* family of viruses. NoV is a non-enveloped virus and has a small (27­ – 40nm) icosahedral shaped capsid that contains a 7.7kb single stranded RNA genome (Richards et al. 2012; Green 2013).

A standard NoV classification scheme was established by Zheng et al. (2006) which divides NoV sequentially into genogroups, genoclusters and strains. The genogroups and genoclusters are designated numerically, with the genogroup indicated first in roman numerals followed by the genocluster number (Zheng et al. 2006; Donaldson et al. 2008). NoV is classified into five genogroups: GI – GV. Human NoVs belong to genogroups GI, GII and GIV; the former two cause the majority of human infections. The genogroup and genocluster information are combined to generate the genotype, for example GII genocluster 4 is designated as the GII.4 genotype. In humans the GII.4 genotype is most commonly found, causing the majority of outbreaks and approximately 80% of infections (Donaldson et al. 2008; Sharps et al. 2012). Human NoV strains are typically named after the location of the outbreak where they were first isolated, for example Norwalk virus, Hawaii virus and the NoV GII.4 Sydney 2012 strain (Green 2013; van Beek et al. 2013).

NoV has also been isolated from animals, with GIII NoVs detected in cattle and GV NoV detected in mice. GII NoVs have been found in pigs and GIV NoV detected in a dog and lion cub. However, the animal genotypes are different to those found in humans (Martella et al. 2008; Bank-Wolf et al. 2010).

### **Growth and survival characteristics**

NoV requires host specific living cells in order to replicate. As viruses cannot grow in food, the level of NoV contamination cannot increase due to viral replication during processing or storage of food (Zainazor et al. 2010; Green 2013). The environmental spread of NoV is influenced by factors such as pH, temperature and how readily it attaches to the surfaces of fomites (Girard et al. 2010).

NoV is stable in the environment. D’Souza et al. (2006) demonstrated that when NoV was artificially transferred onto formica, stainless steel or ceramic surfaces, the virus could be detected on those surfaces for seven days (study duration). NoV has been shown to persist in groundwater for at least three years and remains infectious in groundwater for at least 61 days (Seitz et al. 2011).

Freezing has little effect on NoV survival. Richards et al. (2012) used NoV positive stool samples to show that freezing at -80°C for 120 days or performing up to 14 freeze/thaw cycles (-80°C/+22°C) did not affect capsid integrity, viral RNA titres or viral infectivity. A study by Butot et al. (2008) demonstrated that the NoV titre in artificially inoculated blueberries was reduced by less than 1 log10 after 2 days and 2.3 log10 after 90 days storage at -20°C.

The effect of heat treatment on NoV is variable and highly dependent on the initial level of contamination, time and temperature of heating, virus strain, and type of food matrix (Codex 2012). Studies performed using artificially inoculated foods showed that consumer practices, such as baking (inoculated) pizza at 200°C for 12 minutes, led to a significant reduction in NoV titres. However, pasteurising spiced tomato sauce at 72°C for 1 minute or heating mussels to 80°C for 15 min did not result in a significant reduction in NoV titre (Mormann et al. 2010; Croci et al. 2012). Heating to an internal temperature of at least 90°C for 90 seconds is considered adequate to destroy viral infectivity in most foods (Codex 2012).

NoV is able to survive acidic conditions. A study by Mormann et al. (2010) showed that there was no significant reduction in NoV titre in tomato ketchup stored at pH 4.5 for 58 days at 6°C. Also, Dolin et al. (1972) demonstrated that NoV stored at pH 2.7 for 3 hours retained the ability to cause illness.

NoV is generally resistant to detergents and ethanol-based reagents used to clean environmental surfaces and fomites, so additional chemical disinfection is required. Disinfectants effective against NoV include hypochlorite, hydrogen peroxide and phenolic-based cleaners (Green 2013). Studies have shown that full inactivation of NoV on stainless steel requires 10 minutes contact time with sodium hypochlorite-based disinfectant, with only a 2-log reduction occurring after 5 minutes of exposure (Girard et al. 2010).

### **Symptoms of disease**

Infection with NoV generally leads to symptoms of gastroenteritis, although asymptomatic infection can also occur. Explosive or projectile vomiting is usually the first sign of illness and is often used to characterise the illness. Other symptoms of NoV infection include diarrhoea, abdominal cramps, nausea, headache, low grade fever, chills, muscle aches and lethargy. The incubation period before onset of disease is usually 24 – 48 hours but may be as short as 12 hours. The illness generally lasts for 12 – 60 hours (Karst 2010; FDA 2012; Sharps et al. 2012). NoV may be shed in the faeces of infected individuals before the onset of any clinical symptom (from 18 hours after infection). Viral shedding continues for a median period of four weeks and can continue for at least eight weeks (Atmar et al. 2008).

In immunocompromised individuals the duration of disease can be prolonged and it can develop into a chronic infection with recurrent episodes (Westhoff et al. 2009). Most patients show complete recovery. However, if severe dehydration occurs due to fluid loss the infection can be fatal (Sharps et al. 2012).

A systematic review of the international literature performed by Desai et al (2012) estimated the NoV hospitalisation rate to be 70 per 10,000 cases and the fatality rate 7 per 10,000 cases when NoV outbreaks were analysed.

**Virulence and infectivity**

NoV virions are acid stable and survive passage through the stomach. The primary site of viral replication is thought to be the upper intestinal tract. It has been proposed that nausea and vomiting associated with NoV may result from abnormal gastric motor function, and diarrhoea may result from both epithelial barrier and secretory pathway dysfunction (Meeroff et al. 1980; Green 2013).

The infectivity of NoV is linked to the ability of the viral capsid to bind to receptors on host cells and subsequently to enter the host cell. The NoV capsid is predominantly constructed of a major structural protein, VP1. Part of the VP1 protein protrudes from the capsid surface and has a role in binding to the ABO histo-blood group antigen receptor of host cells (Mattison 2011; Green 2013). The “*host factors that influence disease”* section presents further information on the role of histo-blood group antigens. Mutations in or near the viral receptor binding domain may result in a newly evolved NoV strain that can bind to different host receptors. This could enable the virus to infect a new subset of the population with a different ABO blood type. Mutations may also inhibit the ability of host antibodies to bind to the new NoV variant strain, and so assist the virus to evade the host immune response. This evolution could be associated with the continued prevalence and emergence of new GII.4 strains worldwide. Variant strains of GII.4 NoV emerge every 2 – 10 years and have been responsible for several pandemics (Donaldson et al. 2008; Lindesmith et al. 2008; Sharps et al. 2012; van Beek et al. 2013).

**Mode of transmission**

NoV can be transmitted via the consumption of contaminated food or water, person-to-person contact, aerosolised vomit particles or contaminated surfaces. NoV is highly contagious and outbreaks frequently occur in semi-closed communities such as nursing homes, military settings, schools, hospitals and cruise ships (Karst 2010; Tuladhar et al. 2013). Asymptomatic individuals can be involved in ‘silent’ transmission of the virus as both symptomatic and asymptomatic individuals shed similar quantities of NoV in their faeces (Ozawa et al. 2007).

Zoonotic transmission of NoV cannot be completely discounted; however no animal NoV strains have been detected in human samples (Bank-Wolf et al. 2010).

NoV can be transferred between fomites, hands and food. Sharps et al. (2012) showed that 58% of NoV was transferred from artificially inoculated gloved fingertips to food contact surfaces (stainless steel) under wet conditions. Conversely, Tuladhar et al. (2013) demonstrated that when clean finger pads were pressed onto artificially inoculated stainless steel 4.2% of GI.4 NoV strain and 3.5% of GII.4 NoV strain were transferred from the stainless steel to the finger pads.

The level of NoV transfer is reduced when the virus is left to dry, compared to a freshly inoculated surface. For example, D’Souza et al. (2006) showed that when lettuce samples were placed onto freshly inoculated stainless steel, NoV was transferred to 94% of lettuce samples (n=18). However, when NoV was dried onto the stainless steel for at least 30 minutes prior to application, NoV only transferred to 72% of wet lettuce samples (n=18) and no transfer occurred for dry lettuce samples (n=18).

Infected food handlers have been associated with NoV outbreaks. For example, Boxman et al. (2009) described an outbreak where GI.6 NoV was detected on the hands of a food handler working in a restaurant associated with the outbreak. GI.6 NoV is a rare strain and matched the virus isolated from stools of people who became ill and environmental swabs of the restaurant’s kitchen and bathroom surfaces.

There have been multiple NoV outbreaks associated with asymptomatic food handlers who shed NoV in their stools yet had no gastrointestinal symptoms (Barrabeig et al. 2010; Nicolay et al. 2011). Food handlers with asymptomatic NoV infection not associated with transmitting disease during an outbreak have been reported at low prevalence: 1.0% in food catering facilities in South Korea (n=6,441) (Jeong et al. 2012), 3.4% in elementary schools in Korea (n=776) (Yu et al. 2011) and 11.9% at a catering facility in Japan (n=159) (Okabayashi et al. 2008).

Therefore, appropriate hand hygiene is very important in order to control transmission and prevent NoV infection. A study by Liu (2010) demonstrated that liquid soap treatment or rinsing with water yielded the greatest reduction in the level of NoV contamination on hands. The alcohol based hand sanitiser was relatively ineffective against the non-enveloped NoV (ethanol based hand sanitisers are more effective against enveloped viruses such as influenza and herpes simplex viruses). As such, the CDC (2011) recommends thorough handwashing with running water and soap as the best method to remove NoV from hands.

### **Incidence of illness and outbreak data**

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NoV is not a notifiable disease in Australia. It has been estimated that 18% of NoV infections in Australia are foodborne, with 276,000 cases of foodborne gastroenteritis associated with NoV annually in Australia. This comprises approximately a third of the cases of foodborne illness caused by known pathogens (Kirk et al. 2014). In New Zealand, NoV caused 23% and 16.5% of foodborne outbreaks reported in 2015 and 2014, respectively (Horn et al. 2015; Lopez et al. 2016).

In Europe in 2015, NoV caused 9% of foodborne outbreaks and 26.6% of cases of illness associated with foodborne outbreaks where a link to the implicated food could be established based on strong evidence. This was similar to 2014 when NoV caused 13% of foodborne outbreaks and 28.9% of cases of illness associated with foodborne outbreaks supported by strong evidence (EFSA 2015; EFSA 2016). In the Netherlands it has been estimated that in 2009 there were 662 gastroenteritis cases per 100,000 population and 0.07 fatalities per 100,000 population attributed to foodborne NoV infection (Verhoef et al. 2013).

In the United States (US) it was estimated that NoV accounts for 58% of cases of foodborne illness caused by 31 major pathogens (Scallan et al. 2011). In 2009 – 2010 NoV was detected in 21% of children under the age of five who sought medical attention for acute gastroenteritis (n=1295), although this included both foodborne and non-foodborne cases (Payne et al. 2013).

NoV infection occurs throughout the year, however, it is most prevalent in the winter season in temperate climates (van Beek et al. 2013). The seasonal occurrence of NoV outbreaks associated with oysters can be attributed to several environmental factors including increased humidity, low temperatures, reduced solar inactivation, low salinity and heavy rains (Wang and Deng 2012). A study by Lowther et al. (2008) demonstrated that in the British Isles during 2004 – 2006 the overall level of NoV was 17-fold higher in oysters harvested in the winter compared to the summer (this increase in NoV level took into account the number of NoV positive samples and the level of NoV contamination).

Outbreaks of NoV have frequently been associated with shellfish, as well as fruit and vegetables and ready-to-eat foods that are typically consumed without additional heat treatment (Zainazor et al. 2010; FDA 2012). Refer to Table 1 for examples of foodborne outbreaks of NoV.

**Table 1:** Selected major foodborne outbreaks associated withNoV (>50 cases and/or ≥1 fatality)

| **Year** | **No. of cases**  | **Food** | **Country** | **Comments** | **Reference** |
| --- | --- | --- | --- | --- | --- |
| 2015 | >450 | Pork liver and lamb chops | Taiwan | Asymptomatic food handlers positive for NoV. Inappropriate hygiene practices by food handlers may have contributed to food contamination. | (Chen et al. 2016) |
| 2015 | 70 | Ham hock | England | Food handler vomited <48 hours before preparing the ham hock | (Smith et al. 2017) |
| 2013 | 525 | Oysters | Australia | Underwater sewerage pipe leak near harvest area. | (Lodo et al. 2014) |
| 2012 | 10,950 | Frozen strawberries | Germany | Multiple NoV genotypes isolated from patients matched NoV genotypes from unopened boxes of imported strawberries. Contamination could have occurred on farm due to sewage contaminated irrigation water.  | (Made et al. 2013) |
| 2011 | 147 | Raw vegetables | France | Restaurant cook had fallen ill 24 hours before outbreak occurred. | (Mayet et al. 2011) |
| 2009 | 177 | Steamed oysters | US | Cooking temperatures were inadequate to inactivate NoV. | (Alfano-Sobsey et al. 2012) |
| 2009 | >240 | Oyster, passionfruit jelly lavender dish | England | Shellfish from the implicated seabeds were positive for NoV. Some staff worked while ill. | (Smith et al. 2012) |
| 2007 | 413 | Tomatoes | Sweden | Food handler vomited after preparing tomatoes, food may have been contaminated during pre-symptomatic phase. | (Zomer et al. 2010) |
| 2006 | 115 | Raw oysters | New Zealand | Labelling on imported frozen oysters recommended cooking prior to consumption but oysters were served raw. NoV detected in unopened bags from same batch, suggesting sewage pollution of growing waters.  | (Simmons et al. 2007) |

### **Occurrence in food**

*Seafood*

Seafood such as oysters can be contaminated with NoV in the marine environment. Oysters are filter feeders and filter large volumes of water through their gills. As such, oysters grown in faecally contaminated waters can accumulate NoV within their tissues (Noda et al. 2008; Wang and Deng 2012). Burkhardt and Calci (2000) used a viral indicator and demonstrated that oysters can accumulate up to 99-fold higher levels of virus than the surrounding estuarine waters. NoV binds strongly to oyster tissue and so remains present in the oyster when consumed. Ueki et al. (2007) performed a study which involved artificially contaminating oysters with NoV and then subjecting these oysters to a depuration process. Depuration involves moving oysters to clean water for several days to allow the oyster to purge pathogens. The average NoV concentration did not significantly decrease over the 10 day depuration. NoV is difficult to eliminate from contaminated oysters due to the specific viral attachment to oyster tissues such as gills and digestive glands. As such, depuration is a relatively ineffective method of removing accumulated NoV from oysters (Wang and Deng 2012; Smith et al. 2012).

NoV has been isolated from shellfish in many international studies. The prevalence of NoV in samples collected from harvesting areas was found to be: <2% in oysters across Australia (n=300) (Torok et al. 2018), 37% of shellfish batches in Portugal (n=49) (Mesquita et al. 2011), 49.4% in mussels from Spain (n=81) (Manso and Romalde 2013) and 76.2% in oysters from the United Kingdom (n=844) (Lowther et al. 2012). The prevalence of NoV in samples collected at retail was 3.9% in oysters sampled in the US (n=388) (DePaola et al. 2010), 14.1% of oysters in Korea (n=156) (Moon et al. 2011) and 73.9% in shellfish collected from southern Italy (n=46) (Pepe et al. 2012). The dominant NoV genotypes isolated were GI or GII, with some samples positive for both GI and GII. The difference in geneotype prevalence may be attributed to factors such as season, location, virus extraction method, molecular test employed, and the sensitivity and specificity of the assay (DePaola et al. 2010; Moon et al. 2011). Also, the water quality of the harvesting area in regard to potential effluent contamination and good hygienic practices throughout the supply chain can influence the prevalence of NoV.

The magnitude of NoV accumulation in oysters varies between strains. The GI.1 strain is efficiently concentrated in oysters and accumulates in the midgut and digestive tissues. GII.3 and GII.4 bind to digestive tissues, gills and mantle. GII.3 is moderately accumulated, while GII.4 is poorly accumulated. This matches with outbreak data, as oyster related outbreaks are often associated with GI and GII.3 NoV strains (that accumulate in oysters) but rarely with GII.4 strains. The variation between strains appears to be linked to the binding affinity of particular NoV strains for carbohydrate receptors within different oyster tissues (Maalouf et al. 2011; le Guyader et al. 2012).

*Fresh produce*

Sewage polluted water can introduce NoV contamination during the growing of fresh produce in the field or during processing, if used. Picking, packing or preparation of fresh produce by hand is another potential NoV contamination source. This is because produce can be contaminated directly by ill or asymptomatic fo­­od handlers practicing inadequate hand hygiene or indirectly after a healthy worker touches a contaminated surface (Baert et al. 2011; Sharps et al. 2012).

In surveys of fresh produce collected during 2009 – 2010 in Belgium, Canada and France, NoV was detected on 33% (n=6), 28% (n=641) and 50% (n=6) of individual leafy green samples collected in each country, respectively. NoV was also detected on 34% (n=29) and 7% (n=150) of individual berry samples collected in Belgium and France, respectively. The fresh produce samples were positive for either or both GI NoV and GII NoV strains (Baert et al. 2011).

**Host factors that influence disease**

People of all ages are susceptible to NoV infection, however infants, the elderly and immunocompromised individuals can have more severe symptoms (Karst 2010). There is a small risk that NoV infection will be fatal in elderly people (Harris et al. 2008).

Hutson et al. (2002) identified a relationship between an individual’s ABO histo-blood group antigen and the risk of infection with NoV GI strain (Norwalk virus). Individuals with type O blood had increased susceptibility to infection, while individuals expressing the type B antigen were more resistant to infection. However, this association between ABO histo-blood group antigen and NoV infection appears to be specific to GI NoV strains only. Halperin et al. (2008) studied 176 patients from 2 separate outbreaks caused by GII NoV strains and found there was no association between ABO histo-blood group antigen and the risk of clinical disease.

Expression of most ABO histo-blood group antigens is dependent on the presence of a functional α(1,2)fucosyltransferase (*FUT2*) gene. Individuals with an inactivating *FUT2* gene mutation are called non-secretors (Se-); wild-type individuals are called secretors (Se+). The Se- phenotype occurs in about 20% of the European and North American populations (Marionneau et al. 2002; Lindesmith et al. 2003; Rockx et al. 2005). Se- individuals are resistant to infection with NoV GI strain (Norwalk virus) as they do not express the appropriate ABO histo-blood group antigens necessary for docking and possibly viral entry (Lindesmith et al. 2003; Lindesmith et al. 2008). However, other NoV strains can infect Se- individuals (Lindesmith et al. 2008; Debbink et al. 2012). GII.4 strains have been shown to infect about 6% of Se- individuals compared to 70–77% of Se+ individuals across both outbreak and human challenge settings (Carlsson et al. 2009; Frenck et al. 2012).

Both short-term and long-term immunity to NoV has been demonstrated; however the mechanism mediating the immune response remains unclear (Donaldson et al. 2008). In an early human challenge study Dolin et al. (1972) demonstrated that when volunteers who had previously been susceptible to NoV (Norwalk virus) infection were rechallenged 6 – 14 weeks later none of the volunteers became ill (n=6). This suggested the development of short-term immunity (for at least 6 – 14 weeks) against homologous virus infection. In another early study Parrino et al. (1977) showed that when volunteers who had previously become ill were rechallenged with the same NoV strain (Norwalk virus) 27 – 42 months later they became ill again. However, when challenged a third time, an additional 4 – 8 weeks later, most volunteers did not become ill. Johnson et al. (1990) performed multiple challenge studies in adult volunteers. Progressively greater resistance to clinical illness occurred with repeated exposure to NoV (Norwalk virus) with 60% of individuals becoming ill after the first exposure (n=42), 18% after the second exposure 6 months later (n=22) and none after the third exposure an additional 6 months later (n=19).

There is currently no licensed vaccine available for NoV infection. Several candidate vaccines are under development, with some progressing to the clinical trial stage.

### **Dose response**

Teunis et al (2008) developed a dose response model for NoV GI strain (Norwalk virus) from human challenge data. The average probability of infection on ingestion of a single viral particle was approximately 0.5. Infected individuals had a dose dependent probability of becoming ill that ranged from 0.1 for a dose of 103 viral genomes to a probability of 0.7 for a dose of 108 viral genomes. As NoV GI strain (Norwalk virus) does not infect Se- individuals, this dose response model only utilised data from Se+ individuals that are susceptible to infection.

The attack rate (proportion of people who become ill) may be influenced by factors such as the amount of infectious virus particles ingested, host susceptibility and virus pathogenicity. A study by Noda et al. (2008) showed that the attack rate in oyster-related outbreaks was higher than in food handler-associated outbreaks. This may be attributed to food handler outbreaks being associated with a single NoV strain. In comparison, various NoV strains (such as GI and GII.3) have been shown to accumulate in oysters in the sea environment and this joint bioaccumulation could result in multiple NoV strains being associated with a single oyster outbreak. Also, the attack rate in outbreaks associated with GII.4 strains was lower than for GII.3 strains. This suggests that GII.4 may cause asymptomatic infection more frequently than other NoV genotypes (Noda et al. 2008; Maalouf et al. 2011).

**Recommended reading and useful links**

FDA (2012) Bad bug book: Foodborne pathogenic microorganisms and natural toxins handbook, 2nd ed, US Food and Drug Administration, Silver Spring, p. 149–153.

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