

# Norovirus: a challenging pathogen

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**Abstract.** Noroviruses account for over 90% of all viral gastroenteritis cases and ~50% of all outbreaks worldwide. Each year in Australia, there are an estimated 1.8 million cases. Cases may be sporadic or part of outbreaks, occurring in either the community or healthcare setting. Outbreaks are associated with significant morbidity and some mortality. They incur substantial costs and can be difficult to control in healthcare institutions or other closed settings.

Multiple factors (related to virus biological properties, human immune responses or inadequate management modalities) make it a challenging pathogen to control. They include: multiple transmission routes, low infectious dose, environmental survival, spread and persistence, diagnostic difficulty, hand hygiene controversies, imperfect immunity and immune evasion, asymptomatic and prolonged shedding, lack of vaccine and lack of antiviral treatment. The purpose of this article is to promote a better understanding of these factors in order that health professionals may be better equipped to manage the problems posed by noroviruses.

Until large-scale effective vaccination and specific treatments become available, the safeguarding of food and water supplies and the rigorous and timely application of outbreak management and infection control measures will remain the key to norovirus disease prevention and control.

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## Introduction

Noroviruses account for over 90% of all viral gastroenteritis cases and ~50% of all outbreaks worldwide.<sup>1</sup> Infections occur at all ages and cause up to 200 000 deaths annually in children under 5 years of age in developing countries.<sup>2</sup> Each year in Australia, there are an estimated 1.8 million cases, making it the commonest cause of gastroenteritis.<sup>3</sup> Cases may be sporadic or part of outbreaks which occur in closed settings, such as hospitals, hotels, cruise ships, day-care centres and residential aged-care institutions. Outbreaks have significant health and cost implications and are difficult to control. This article highlights the reasons why norovirus is so challenging to manage.

## Background

The syndrome of sudden-onset, self-limiting vomiting and diarrhoea, peaking in the colder season, was first described in 1929 by Zahorsky, and named 'Hyperemesis hemis' or 'winter-vomiting disease'.<sup>4</sup> In 1972, the causative agent, Norwalk virus, was identified and characterised.<sup>5,6</sup> Subsequently, similar viruses were described.<sup>7</sup> Norwalk virus became the prototypic agent of the genus *Norovirus* (previously called 'Norwalk-like viruses'), one of five genera within the family *Caliciviridae*.<sup>1</sup>

Noroviruses are non-enveloped, contain an RNA genome and cannot be cultured effectively *in vitro*.<sup>8</sup> They can be

classified into five genogroups (GI through GV), which are sub-divided into at least 34 genotypes. Human disease is primarily caused by GI and GII noroviruses, with most worldwide outbreaks since 2001 caused by GII.4 (i.e. genogroup II, genotype 4) strains.<sup>9,10</sup> Significant strain diversity exists, even within a single genogroup and genotype. For example, GII.4 has evolved linearly over time, giving rise to multiple strain clusters.<sup>11</sup> During the past decade, new GII.4 strains have emerged every 2 to 3 years, replacing previously predominant GII.4 strains. Emergence of these new norovirus strains has often, but not always, led to increased outbreak activity.<sup>9</sup> In March 2012, a new GII.4 norovirus strain was identified in Australia. Named GII.4 Sydney, this emergent strain has since caused acute gastroenteritis outbreaks in multiple countries,<sup>12</sup> apparently replacing the previously predominant strain, GII.4 New Orleans, in the USA and UK.<sup>9,13</sup> Compared with other genotypes, GII.4 outbreaks are associated with more hospitalisations and deaths.<sup>14</sup>

## Clinical features

Norovirus gastroenteritis has an incubation period of 12 to 48 h. Illness begins with acute onset of nausea, vomiting, abdominal cramps and myalgias.<sup>1,8,15</sup> Fever occurs in less than 50% of cases. Non-bloody diarrhoea is the commonest symptom, occurring in over 90% of cases.<sup>16</sup> Resolution of symptoms generally occurs in 2 to 3 days, but symptoms can last for longer (e.g. 4 to 6 days or beyond) in hospitalised

### Implications

- Norovirus outbreaks cause significant morbidity, some mortality, incur substantial costs and are difficult to control
- Multiple factors (related to virus biological properties, human immune responses or inadequate management modalities) make it a challenging pathogen
- Safeguarding food and water supplies and applying outbreak management and infection control measures remain the key to prevention and control

patients, the elderly and children.<sup>16–18</sup> Asymptomatic infection is also possible.<sup>19</sup> Symptomatic disease ranges from mild to severe. Complications include dehydration, necrotising enterocolitis (mainly in neonates)<sup>20,21</sup> and death (mainly in older persons).<sup>22–24</sup> Post-infectious irritable bowel syndrome may occur.<sup>25</sup>

In the immunocompromised, prolonged symptomatic illness and prolonged shedding after symptom resolution may both occur. In outbreaks among haematology and oncology patients, median virus shedding was 2 to 3 weeks longer than median symptom duration, with some patients symptomatic or shedding for months and even over 1 year,<sup>26–28</sup> thereby indicating the emergence of the entity called ‘chronic norovirus gastroenteritis’.<sup>29</sup>

### Impact and cost

Norovirus gastroenteritis outbreaks are very costly and consume health resources. A GII.4 outbreak from January to May 2004 at Johns Hopkins Hospital (Baltimore, Maryland, USA) involved 265 healthcare workers (HCW) and 90 patients.<sup>30</sup> It resulted in closure to new admissions (at various times) of an intensive care unit, coronary care unit (CCU) and psychiatry ward. The CCU had to be emptied for cleaning and 138 echocardiograms were delayed. Psychiatry group therapy was suspended. Complete visitor prohibition to the areas was necessary. Nursing staff were cohorted and not permitted to attend shared meals or catered conferences. The cost of the outbreak was estimated at US\$657 644 for lost revenue due to closure of units to new admissions, cleaning, equipment replacement and payment of over 2500 h of sick leave and overtime.

In an economic model focussing solely on lost bed-days (i.e. not including any additional costs), it was estimated that an outbreak in a 15-bed ward starting with a single symptomatic case would result, by the fifth day after admission of the index case, in five infected (four symptomatic) patients and would cost US\$38 914 ± US\$14 439, if the norovirus-attributable length of stay of each case was 4 to 6 days and no control measures were instituted.<sup>31</sup>

In Edinburgh, NHS (National Health Service) Lothian, from September 2007 to June 2009, there were 192 unit

#### Box 1. Factors making norovirus a challenging pathogen to control

- Multiple transmission routes
- Low infectious dose
- Environmental survival, spread and persistence
- Diagnostic difficulty
- Hand hygiene controversies
- Imperfect immunity and immune evasion
- Asymptomatic and prolonged shedding
- Lack of vaccine
- Lack of antiviral treatment

#### Box 2. Transmission of norovirus<sup>15</sup>

- Waterborne
  - Drinking (potable) water
  - Recreational (lake or swimming pool) water
- Foodborne
  - Shellfish (oysters, clams), salads, cake frosting and meats
  - Undercooked, contaminated foods or improper hand hygiene by an infected food-handler
- Person-to-person
  - Vomitus and faeces

outbreaks. Lost bed-days and staff absence due to gastroenteritis cost NHS Lothian £1.2 million for the two norovirus seasons.<sup>32</sup> A study in Avon, England, identified 227 unit outbreaks from April 2002 to March 2003, with 63% being norovirus-related. Bed-days lost plus staff absence was calculated to cost £635 000 per 1000 beds. By extrapolation, gastroenteritis outbreaks likely cost the entire English NHS £115 million that year.<sup>33</sup>

### What makes norovirus a challenging pathogen?

Several factors make norovirus a challenging pathogen to control. Refer to Box 1.

#### Multiple routes of transmission

Humans are the only known reservoir for human norovirus. Transmission occurs by three general routes: foodborne, waterborne, and person-to-person.<sup>15</sup> Refer to Box 2.

Community outbreaks are often associated with contaminated food or water. In healthcare settings, outbreaks tend to be associated with person-to-person transmission, although contaminated food and water (e.g. hospital kitchen) may sometimes be implicated.<sup>34</sup> Person-to-person transmission occurs through: (1) direct contact with faeces or vomitus from infected cases, (2) contact with contaminated fomites or the environment or (3) aerosolisation and droplets (usually from the infected person vomiting). The final common pathway is ultimately ingestion of virus particles (virions) arriving in the mouth or upper aerodigestive tract.<sup>15</sup>

While contact resulting in faecal–oral transmission has generally been accepted, outbreaks from aerosols generated by vomiting have also been documented.<sup>35</sup> For example, in a

restaurant norovirus outbreak where the foods served at the meal could not be demonstrated to be the cause, 52 of 126 guests present in the same dining room at the time became ill after a woman had vomited on the polished wooden floor. There were two ceiling fans in the room. Subsequent analysis of attack rates by dining table showed an inverse relationship with the distance from the position where the index case had vomited. Since affected individuals had not had contact, presumably the virions in vomitus had been aerosolised and spread throughout the room.<sup>36</sup> Aerosols can also contaminate fomites, leading to outbreaks.<sup>37</sup>

### *Low infectious dose*

Norovirus is highly infectious, having an estimated ID<sub>50</sub> (i.e. dose required to cause infection in 50% of exposed subjects) as low as 18 virions. The average probability of infection for a single virion has been calculated at 0.5. The probability of developing symptomatic disease has been shown to be dose-dependent, being 0.1 at a dose of  $1 \times 10^3$  virions and 0.7 at a dose of  $1 \times 10^8$  virions.<sup>38</sup> Given that the median peak shedding from an infected person has been shown to be  $9.5 \times 10^{10}$  virions per gram of faeces,<sup>39</sup> a single gram of faeces therefore contains enough doses to potentially cause  $2.5 \times 10^9$  infections!

### *Environmental survival*

Norovirus in contaminated food can survive below freezing temperatures ( $-18^\circ\text{C}$ ) and is stable to heating at  $60^\circ$  for 30 min. Norovirus titres remain unchanged under pasteurisation conditions ( $72$  to  $74^\circ\text{C}$  for 1 min).<sup>40,41</sup> Persistence in groundwater for over 3 years has been demonstrated.<sup>42</sup> The virus withstands between 3.5 to 10 ppm chlorine,<sup>43,44</sup> which has implications for potential outbreaks, since Australian drinking water guidelines require no more than 5 ppm chlorine<sup>45</sup> and many Australian swimming pools have 1.5 to 5 ppm chlorine.<sup>46,47</sup> Norovirus can persist on food preparation surfaces (e.g. stainless steel, formica, ceramics) up to 7 days and can be transferred to food items,<sup>48</sup> especially if food residue is present.

### *Environmental spread and persistence*

The environment clearly plays a role in the transmission of norovirus. In experimental studies, fingertips coming into contact once with faecally contaminated toilet tissue could transfer norovirus sequentially for up to seven clean surfaces.<sup>49</sup> Subsequently, clean hands touching the contaminated surfaces were able to transfer norovirus to other objects, such as door handles, taps and telephones. Faecally-contaminated surfaces still showed traces of norovirus both after single-step wiping with a cloth soaked in detergent, as well as after single-step wiping with a cloth soaked in detergent following application of hypochlorite (5000 ppm available chlorine) for 1 min on the surface. Norovirus was only undetectable after a two-step process involving using a cloth soaked in detergent to wipe away all organic matter first before application of hypochlorite for at least 1 min and then

wiping again. Where a surface was not norovirus-free after wiping, virus was shown to be transferred to cleaners' hands as well as a second surface wiped with the same cloth. Wiping the same surface twice with a cloth rinsed in detergent and wrung out in between the two wiping attempts also failed to remove all traces of virus. Inadequate environmental cleaning and disinfection procedures not only allow norovirus to persist but can facilitate its spread.

The environmental persistence of norovirus has been implicated in outbreaks. In one incident, two carpet fitters were infected after working on a carpet in a hospital ward where an outbreak had ended 13 days earlier.<sup>50</sup> In a GI.6 outbreak among flight attendants, aircraft contamination was implicated. A passenger had vomited onto the carpet. This had been cleaned by a flight attendant and disposed of in the restroom at the rear of the aircraft. Over the next 6 days, 27 flight attendants across eight different flight sectors developed gastroenteritis symptoms. Each flight sector aircrew had no significant contact with other sectors' aircrew or any sick persons. The attack rates were inversely proportional to the time elapsed since the initial vomiting event, suggesting that the aircraft was the vehicle of infection transmission.<sup>51</sup> Another outbreak involved over 300 cases of gastroenteritis among 1229 school children who had attended a lunchtime school concert. The index case was a concert attendee from the evening before, who had vomited in the auditorium and adjacent male toilet. The attack rate was higher among those seated on the same level as the place this person had vomited the night before.<sup>52</sup> Disinfection procedure following the initial vomiting incident had been poor and no hypochlorite had been used. Transmission likely occurred through contact with the contaminated environment. In a prolonged outbreak on a cruise ship which lasted 3 months and involved 587 symptomatic cases spanning six separate cruises, closing the ship after the end of the second cruise for 1 week of thorough cleaning reduced, but failed to completely prevent, ongoing cases in subsequent cruises.<sup>53</sup> This not only pointed to environmental contamination as the key factor in perpetuating the outbreak, but also demonstrated the difficulties with achieving adequate decontamination of large, complex, closed environments.

### *Diagnostic difficulty*

One of the major challenges in controlling norovirus outbreaks is the difficulty in identifying norovirus as the cause early in a gastroenteritis outbreak. Traditionally, the epidemiologic diagnosis has been made using Kaplan's criteria,<sup>54</sup> as outlined in Box 3, but Kaplan's criteria are limited by the delay in excluding bacterial pathogens and the need for sufficient numbers of cases to make it meaningful (i.e. after the outbreak is already established). Furthermore, the criteria are highly specific (99%) but not very sensitive (68%).<sup>55</sup>

For early accurate diagnosis of outbreaks, and also diagnosis of individual cases, laboratory testing is required. Australia's Public Health Laboratory Network has published a laboratory case definition involving tests using either antigen

**Box 3. Kaplan's criteria for diagnosing an outbreak of gastroenteritis caused by norovirus<sup>54</sup>**

All of the following should be present:

- (1) vomiting in more than half of affected persons
- (2) average incubation period of 24 to 48 h
- (3) average illness duration of 12 to 60 h
- (4) absence of bacterial pathogen in stool culture

detection, nucleic acid amplification (NAA) or electron microscopy (EM).<sup>56</sup>

Faeces are the most suitable specimens to collect. Although norovirus can be detected in vomitus, this should only be collected after consultation with nominated laboratories. The yield of virus is better from faeces than vomitus. Also, some laboratories do not have assays validated for testing vomitus. Detection of norovirus in food samples is technically difficult, expensive and is not routinely performed in laboratories. Given the complexity of testing food, it is inappropriate to test foods contaminated by food handlers that have caused localised point source outbreaks.<sup>57</sup>

Stool examination by light microscopy is unable to provide a diagnosis. Since the virus has not been cultivated in cell lines, cell culture is not used in diagnosis.<sup>1</sup> Serology is not used for clinical diagnosis. It takes time and may not be useful because antibody presence does not always correlate with protection from infection.<sup>58</sup>

Antigen detection tests (using antibodies) performed on stool are relatively simpler, more rapid and cheaper than NAA. Since some antibodies are genotype-specific (or even strain-specific), broadly cross-reactive antibody pools are needed to ensure that infections from a diverse range of strains are not missed. Several available tests detect GII viruses better than GI viruses.<sup>59,60</sup> Depending on the assay used, specificity ranges from 47 to 100% and sensitivity from 36 to 80%,<sup>15</sup> compared with reverse-transcription polymerase chain reaction (RT-PCR). Given their moderate to high specificity but limited sensitivity, antigen tests are more useful in identifying norovirus as the cause of an outbreak (where multiple stool samples are tested) rather than diagnosing a sporadic case.<sup>1,15,56</sup> For optimal detection of norovirus using these tests, faecal samples should be collected from at least six individual patients in outbreak settings.<sup>61</sup> This may be difficult if the outbreak size is small. Due to poor sensitivity, it is recommended that stool samples with negative antigen test results should undergo RT-PCR testing,<sup>59</sup> which will increase diagnostic costs and delay.

The NAA tests currently in use are either conventional or real time RT-PCR, used to detect the presence of the norovirus RNA genome. Although this is widely considered to be the optimal method<sup>56</sup> and commercial assays exist, there is limited availability in many laboratories. RT-PCR is more sensitive than direct antigen detection and electron microscopy<sup>62</sup> but false negative results are possible due to norovirus genetic diversity (i.e. the PCR primer cocktail may not enable detection of all variants), low virus concentration in faeces,

improper specimen storage, inefficient RNA extraction and faecal reverse transcriptase inhibitors.<sup>2</sup> In interpreting positive results, there are clinical specificity issues. Detection of norovirus RNA does not always imply disease causality. Stool viral loads are lower in asymptomatic than symptomatic GII strain infection. Therefore, patients with diarrhoea and detectable GII norovirus but low viral loads may actually have another cause for their symptoms (e.g. bacterial pathogen or rotavirus) but incidental norovirus co-infection.<sup>63</sup> Most laboratories do not offer diagnostic viral load testing. Furthermore, detection of norovirus by RT-PCR does not always imply infectivity, since RT-PCR does not discriminate between infectious and inactivated virus particles. Since norovirus capsid attachment to cell surface receptors is a necessary first step to causing infection, virus particles incapable of binding are not infectious. Specialised binding RT-PCR studies show that a proportion of norovirus detectable by RT-PCR is actually representative of non-binding, and thus non-infectious, particles.<sup>64</sup> For PCR-based outbreak investigation, Australian guidelines recommend that three or more specimens are necessary for adequate sensitivity.<sup>57</sup>

EM, the original method of diagnosis, is unavailable in most laboratories. Estimated sensitivity is poor (17%),<sup>62</sup> but immune EM using post-infectious sera has better sensitivity (58%).<sup>65</sup> Some consider EM to be more specific than RT-PCR or antigen detection tests.<sup>62,65</sup>

Despite diagnostic advances, a recent study found that norovirus infections in healthcare institutions were frequently missed despite routine laboratory testing (up to almost 50% of cases) and that underdiagnosis was associated with costly abdominal imaging and nosocomial clustering.<sup>66</sup>

### *Hand hygiene controversies*

Controversies surrounding the optimal method for performing hand hygiene contribute to the challenge in controlling norovirus transmission.

In general, to evaluate the ability of a hand sanitiser product to reduce infectivity of a virus, the accepted method is to perform virus culture in the presence and absence of exposure to the product. However, human norovirus (HuNoV) cannot be cultured, so alternative evaluation methods must be used. The first group of methods involves studying HuNoV using quantitative RT-PCR in the presence and absence of exposure to hand sanitiser. However, as mentioned earlier, the detection of RNA does not necessarily correlate with infectivity. Sanitisers may damage the viral capsid, removing the ability of the virus to bind receptors and cause infection without necessarily destroying the RNA. Thus, 'false positive' results may be obtained after effective use of a hand sanitiser. The second group of methods involves extrapolating results from culture of a surrogate cultivable virus (with similar properties to HuNoV) in the presence and absence of exposure to hand sanitiser. However, there is debate as to whether Feline Calicivirus (FCV) or Murine Norovirus (MNV) best reflects the properties and behaviour of



HuNoV. Furthermore, correlation between results obtained from studying FCV and MNV is variable and correlation of both to RT-PCR studies is poor. Thus, there appears to be no optimal method to determine which hand sanitiser is most active against HuNoV.<sup>67–69</sup>

One key issue is the use of alcohol-based hand rub (ABHR) versus soap and water. Laboratory studies appear to indicate that ABHR is less active against non-enveloped viruses than soap and the physical rinse with water. One study of HuNoV utilising RT-PCR measurement showed an average log<sub>10</sub> reduction in quantity of only 0.34 for ABHR, as compared with 1.10 for liquid soap and 1.38 for water rinse.<sup>70</sup> In a survey involving self-reported hand hygiene practices in American long-term care facilities, 61 facilities reported 73 outbreaks, 29 of which had norovirus confirmed. Facilities reporting that staff were equally or more likely to use ABHR than soap and water for routine hand hygiene had higher odds of a confirmed norovirus outbreak than facilities with staff less likely to use ABHR. The authors concluded that preferential use of ABHR over soap and water for routine hand hygiene might be associated with increased risk of norovirus outbreaks.<sup>71</sup> However, this conclusion was criticised by others, who pointed out that association did not imply causation in this cross-sectional study. Furthermore, the multivariate analysis had failed to take into account hand hygiene compliance. The critics suggested that an alternate hypothesis for the association should have been considered i.e. better infection control practices (of which ABHR use was an indicator) led to better outbreak detection and confirmation. This was supported by the original study's finding on univariate analysis that having a part-time or full-time infection control practitioner in the facility was associated with a greater likelihood of a confirmed norovirus outbreak.<sup>72</sup> More recently, a culture-based evaluation demonstrated, *in vitro* and *in vivo*, the superior activity of various ABHR over a variety of antiseptic soaps when used against FCV and MNV.<sup>73</sup>

At present, the jury is still out. World Health Organization experts 'recommend the use of alcohol-based handrubs during outbreaks of noroviral gastroenteritis.'<sup>74</sup> On the other hand, the Centers for Disease Control and Prevention (CDC), USA, state that '...hand washing with soap and running water ...reduce norovirus contamination. ... whereas hand sanitisers might serve as an effective adjunct... but should not be considered a substitute...'<sup>15</sup> Australian guidelines recommend that 'hand hygiene should be performed using soap and water when *Clostridium difficile* or non-enveloped viruses such as norovirus are known or suspected to be present and gloves have not been worn'.<sup>75</sup> In considering which hand hygiene product to advocate in healthcare settings, consideration should also be given to the impact of diminished hand hygiene compliance (if advocating against ABHR) on other pathogens (e.g. MRSA).

#### *Imperfect immunity and immune evasion*

The immune response following norovirus infection in humans is incompletely understood. Short-lived immunity to

the same strain lasts 6 weeks to 6 months then wanes.<sup>1,76</sup> Infected persons can be reinfected with the same virus 2 to 3 years after their initial infection.<sup>77</sup> Furthermore, there may be only partial or even no immunity to different strains. Within genogroups, there is some cross-protection following infection, more for GI than GII strains. Between genogroups, however, cross-protection is minimal or absent.<sup>76,78</sup> Thus, any given individual may be susceptible to multiple infection episodes over the lifetime.

Viral mutation results in diversity which contributes to norovirus persistence in human populations by two mechanisms – different receptor usage and different antigenic structure.<sup>78</sup> First, adaptation, driven by herd immunity, results in viruses capable of binding different and sometimes novel receptors, allowing an expansion of host range or penetrance into a previously naive population. Important norovirus receptors are the histoblood group antigens (HBGA), which are not only expressed on red blood cells but also gut epithelium. Individuals of blood type O appear to be more susceptible to infection than individuals of other blood types.<sup>79</sup> Viral mutation may enable a strain to bind more effectively to gut receptors in, say, patients with blood type A, and thus perpetuate virus transmission in subpopulations with a predominance of this blood type. Second, genetic variation of antigens allows escape from the predominant herd immunity, resulting in a virus competent to infect the same population that has previously been infected.<sup>76,78</sup>

#### *Asymptomatic and prolonged virus shedding*

In cases of symptomatic norovirus infection, studies of infected volunteers have demonstrated that peak viral shedding in the faeces occurs ~3 days post-symptom onset, corresponding with the last symptomatic day or first asymptomatic day.<sup>39</sup> However, asymptomatic shedding at lower levels may occur before symptomatic infection (3 to 14 h before symptom onset) and also after symptomatic infection (up to 3 to 4 weeks in most cases, but longer in some) even in immunocompetent healthy patients.<sup>16,39</sup> More studies are needed to confirm whether these persistently shed virus particles are infectious.<sup>80</sup> In addition, asymptomatic shedding occurs during the course of asymptomatic infection. Prevalence studies in asymptomatic populations have detected norovirus in stool in various proportions: United Kingdom, 12.0%;<sup>81</sup> Netherlands, 5.2%;<sup>82</sup> Germany, 3.4%;<sup>83</sup> Brazil (children aged <3 years), 13.3%.<sup>84</sup> One study demonstrated a wintertime seasonality for asymptomatic infection, with highest prevalence in children aged less than 5 years.<sup>81</sup> Cases of asymptomatic infection generally have lower viral loads than symptomatic infection.<sup>63</sup> More work is needed to understand whether asymptomatic infections are important for norovirus transmission leading to sporadic illness and outbreaks.<sup>81</sup>

In particular, the role of asymptomatic shedding in causing nosocomial infection is unclear. One study suggested that asymptomatic excretion of noroviruses can occur in HCWs and patients without causing nosocomial infections.<sup>85</sup> A

recent study of five outbreaks showed that symptomatic patients and HCWs were more often involved in norovirus transmission events than asymptomatic shedders.<sup>86</sup> In an outbreak on a haematology and haemopoietic stem cell transplant unit, there were no nosocomial transmissions of norovirus once cases had recovered and been symptom-free for 48 h, although shedding was ongoing.<sup>87</sup>

Foodborne norovirus outbreaks, on the other hand, have occurred as a result of asymptomatic shedding from food handlers with asymptomatic infection<sup>88</sup> and also symptomatic infection in the pre-symptomatic<sup>89</sup> and post-symptomatic<sup>90</sup> stages of illness.

#### *Lack of available vaccine*

No clinical vaccine is available to prevent norovirus illness or infection. Although an experimental virus-like particle (VLP) vaccine has demonstrated that vaccination provides some degree of protection against infection and illness,<sup>91</sup> many issues with vaccine development still need to be addressed before it can be shown that norovirus can be prevented on a large scale by vaccination.<sup>92</sup>

#### *Lack of specific anti-viral treatment*

There is no specific treatment for norovirus gastroenteritis.<sup>7,29,80,93</sup> Research on treatments is hampered by the fact that noroviruses cannot be cultured. Nitazoxanide has shown promise in shortening disease duration in a very small study of immunocompetent patients<sup>94</sup> and a case report of an immune-suppressed patient,<sup>95</sup> but more study is required. Although anecdotal evidence suggests that oral immunoglobulin therapy may be effective in immunocompromised patients,<sup>29,96,97</sup> a small retrospective study has not confirmed this.<sup>98</sup>

### **How do we meet the challenge posed by norovirus?**

#### *Treatment*

Fluid and electrolyte replacement, anti-emetics and analgesics (if required) form the mainstay of treatment of symptomatic cases. The role of anti-peristaltic agents is unclear.<sup>7</sup>

#### *Prevention and control measures*

In the absence of an available vaccine and specific anti-viral treatment, prevention involves ensuring food and water contamination does not occur. Surveillance systems play an important role. Outbreak management and infection control measures are vital to the control of norovirus. Several comprehensive guidelines are available<sup>15,57,75,99</sup> and some key points are listed in Box 4.

Do infection control measures really work? A recent review of 54 nosocomial outbreaks listed a broad range of recommended measures perceived to be helpful in outbreak control.<sup>100</sup> Despite these recommendations, a systematic review of 72 norovirus outbreaks in enclosed and semi-enclosed settings in industrialised countries detected no significant differences in the outbreak duration or attack rate when comparing those where infection control measures were

#### **Box 4. Norovirus outbreak management and infection control measures<sup>15,57,75,99</sup>**

- Confirm occurrence of outbreak and establish case definitions
- Identify source and main mode of transmission (point source or person-to-person)
- Investigate
  - collect clinical and epidemiologic information
  - collect stool samples from cases
- Control and eliminate contaminated food or water source
- Enforce strict hand hygiene
- Isolate symptomatic cases occurring in healthcare facilities or closed settings (until at least 48 h after last diarrhoeal stool)
  - hospital inpatients should be managed with Contact and Droplet precautions
  - appropriate personal protective equipment should be used by healthcare workers (gown, gloves, mask and goggles)
- Exclude healthcare workers, childcare workers, food-handlers from work (until at least 48 h after last diarrhoeal stool)
- Protect food preparation areas
- Implement visitor restrictions to affected areas
- Close facility or ward to new admissions
- Provide enhanced environmental cleaning and disinfection (e.g. using bleach-based solution)
- Ensure appropriate linen and laundry management
- Notify jurisdictional public health authority

and were not implemented.<sup>101</sup> However, the authors noted that, in their review of outbreak reports, they had assumed that infection control measures had not been instituted if they were not discussed. This might have led to misclassification of outbreaks. They also noted that data collection was suboptimal in many reports, making it difficult to make definite conclusions on the utility of infection control interventions. Only one report had robust data to support the conclusion that the outbreak duration was shorter (by 7 days) when infection control measures (i.e. closure of unit to new admissions within 3 days of index case) were instituted early.<sup>33</sup> They acknowledged, however, the results of a Cochrane database review of 14 randomised controlled trials (not restricted to norovirus) which showed that hand washing decreased diarrhoeal episodes by 30%.<sup>102</sup> The authors of the systematic review concluded that 'sound infection control procedures are key to controlling norovirus outbreaks but unfortunately, the present body of the published literature does not provide an evidence-base for the value of specific measures.'<sup>101</sup> This is reflected in guidelines from the Healthcare Infection Control Practices Advisory Committee of the CDC, USA, which make strong recommendations for managing norovirus outbreaks in healthcare settings while acknowledging the paucity of high-quality supporting evidence.<sup>99</sup>

### **Conclusion**

Norovirus is a leading cause of gastroenteritis, both in community and healthcare settings, often causing outbreaks. These are associated with significant morbidity, some mortality and incur substantial costs. Multiple factors (related

to virus biological properties, human immune responses or inadequate management modalities) make it a challenging pathogen to control. Until large-scale effective vaccination and specific treatments become available, the safeguarding of food and water supplies and the rigorous and timely application of outbreak management and infection control measures will remain the key to norovirus disease prevention and control.

### Conflicts of interest

The author has no conflicts of interest to declare.

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