**Control of Norovirus Infection**

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**Abstract**

**PURPOSE OF REVIEW:** The purpose of the review is to provide an update on control measures for norovirus (NoV), which is the most commonly implicated pathogen in acute gastroenteritis and outbreaks, causing major disruption in nurseries, schools, hospitals and care homes.

**RECENT FINDINGS:** Important developments include (a) the discovery that virus particles, previously considered to be the infectious unit, also occur in clusters, which appear to be more virulent than individual virus particles;(b) a working culture system using human stem-cell derived enteroids; (c) promising results from early phase clinical trials of candidate NoV vaccines, which appear to be safe and immunogenic; (d) chronic NoV affects patients with primary and secondary immune deficiencies. Although several treatments have been used none are supported by well-designed clinical trials; (e) infection control procedures are effective if properly implemented.

**SUMMARY:** Norovirus remains an important cause of morbidity and mortality. Although there are exciting developments on the vaccine front, the mainstay of control remains good hand hygiene, adherence to infection control procedures and limiting contamination of food, water and the wider environment. Once vaccines are available there will be important decisions to be made about how best to implement them.

**Key Words**

Norovirus, control, transmission, vaccine, healthcare, acute gastroenteritis, mathematical modelling, fomites, faecal-oral, environment, person-to-person, infection control, hygiene, chronic gastroenteritis, asymptomatic excretion

**Abbreviations**

CoP

FCV

GI

GII

HAVI

HBGA

IPC

MNV

NoV

ORS

RNA

VLP

WASH

**Introduction**

Noroviruses (NoV), which are non-enveloped, single-stranded RNA viruses, are the most commonly diagnosed cause of acute gastroenteritis worldwide [1\*]. They affect people of all ages, causing sudden onset, often explosive, diarrhoea and vomiting whilst immunity is short-lived. Host genetic factors, the histo-blood group antigens (HBGA), are associated with NoV susceptibility [2\*\*]. Children <5 years and adults >75 years are especially vulnerable to severe outcomes [3,4]. Asymptomatic shedding is a particular problem and can occur before symptom onset [5] and after symptoms have resolved [5]. NoV infection can cause chronic diarrhoea in patients with immune deficiencies, cancers and transplants [7, 8\*]. The infectious dose is very low (around 10 virus particles) and symptomatic individuals excrete millions of virus particles. They are transmitted faecal-orally via multiple routes including person to person; environment to person; through contaminated food or water, which makes infection control a challenge. NoV contaminate the surrounding environment where they can survive for prolonged periods on surfaces leading to fomite transmission [9].

It was generally accepted that individual virus particles were the infectious unit responsible for cellular infection and person-to-person transmission [10]. However, new research has shown that during faecal-oral transmission vesicle-cloaked NoV clusters in the faeces of infected hosts are more infectious than free virus particles [11\*\*]. These vesicles deliver high inocula to receiving hosts and they appear to be highly virulent transmission units.

The viruses hyper-mutate at regular intervals [12]. Currently NoV are divided into seven genogroups of which three (genogroups I, II and IV) can infect humans [13]. Since 1996 at least six human norovirus pandemics have occurred. All the pandemic strains have been genetically related and belong to the genogroup II- genotype 4 (GII.4) grouping within the NoV genus [14]. The last major pandemic occurred in 2012 when the so-called Sydney 2012 variant was recognised. Recently, however, a novel NoV lineage containing the GII.P16 polymerase and pandemic GII.4 Sydney 2012 capsid was detected in Asia and in Germany. Subsequent investigations showed that this lineage has also been circulating in the UK and USA since at least October 2014 [15\*]. It remains to be seen whether or not this variant will go on to generate the next global pandemic. Finally, NoV poses particular challenges in closed or semi-closed settings like nurseries, schools, cruise ships, hospitals or care homes where outbreaks are common, especially during the winter months [1\*]. Evaluating interventions against NoV infection has, until recently, been hampered by lack of suitable in vitro cultivation systems. However, in ground-breaking research, the creation of stem-cell derived human enteroids has created opportunities to study human host-pathogen interactions of previously non-cultivatable pathogens, and to evaluate methods to prevent and treat NoV infections [16\*\*].

**Primary prevention of norovirus**

*Hand hygiene*

Good hand hygiene remains one of the most important means of controlling NoV spread. Washing hands with soap and water is better at removing NoV from hands than using alcohol-based hand disinfectants [17]. A recent systematic review of hand sanitisers suggested that hand rubs containing 70–90% ethanol are usually effective against murine norovirus (MNV) within 30 seconds [18]. Evidence of effectiveness of hand sanitisers is often demonstrated using surrogate viruses, e.g. MNV or feline calicivirus (FCV), because they are culturable. Unfortunately culturable surrogates do not necessarily behave like NoV, and NoV appears to be more resistant to typical food and environmental control measures [19\*].

*Disinfection*

NoV can survive on environmental surfaces for prolonged periods (up to 140 days) depending on surface type and environment conditions [20]. As a result subsequent transmission via fomites plays an important role in outbreaks [21]. Environmental sanitation is important to prevent and control NoV spread. However, NoV is resistant to many commonly used disinfectants e.g. phenolic and quaternary ammonium compounds. Current recommendations for cleaning surfaces contaminated with NoV include the use of bleach, which is suitable for hard surfaces but can damage soft surfaces like carpet and soft furnishings. A systematic review of viral inactivation on soft surfaces indicated that chlorine, glutaraldehyde, fogged ozone, and hydrogen peroxide were the most successful in producing a greater than 3-log10 reduction against enteric viruses [20]. Recent studies using fogged chlorine dioxide- and hydrogen peroxide-based disinfectants [22,23] and silver dihydrogen citrate [24] all show activity against NoV.

*Infection control in health and care settings*

Outbreaks of NoV in healthcare settings are extremely costly and disruptive. In a retrospective analysis of routinely collected time-series data for the winters 2010/11 to 2015/16 a median of 88,000-113,000 beds were closed due to acute gastroenteritis each winter [25\*]. Of these, 19.6-20.4% were unoccupied. On average, 80% of NHS providers were affected, and beds were closed for a median of 15-21 days each winter. Hospital costs of closed beds were £5.7-£7.5 million, which increased to £6.9-£10.0 million when including staff absence costs due to illness [25\*].

Comprehensive prevention bundles are often deployed to control the spread of NoV, in health [26] and care settings [27]. The precise composition of bundles varies but hand hygiene, exclusion of ill individuals, and environmental cleaning all feature and there is ample evidence that they are effective if implemented correctly. A recent study of a novel prevention bundle for paediatric healthcare-associated viral infections (HAVI) in the US showed that the iterative creation, implementation, and improvement of targeted prevention practices were associated with a statistically significant reduction in paediatric HAVI, including NoV, from a monthly average of 0.81 to 0.60 infections per 1,000 patient days [28\*]. A similar multidimensional quality improvement initiative implemented in the UK targeting NoV specifically produced impressive results [29]. Annual outbreak numbers at a single NHS Trust fell by 91% between 2009-2010 and 2010-2014. Patients affected by NoV-like symptoms fell by 92%, affected staff by 81% and days of disruption by 88% [29\*]. Ward closure can also be cost-effective, particularly if targeted to high-throughput units [30]. However, there can be considerable variation in guidelines for the control of NoV outbreaks. For example, in a survey of state guidelines for NoV outbreaks in healthcare setting in the US, there were 21 different sets of recommendations with respect to guidance on stool sample collection [31].

Hospital design can also play a part in limiting the spread of NoV. In an analysis NoV outbreaks at North Bristol NHS Trust, following the move to a new-build hospital with 75% single rooms, bed-days lost due to NoV outbreaks were significantly reduced (pre-move an average of 172 bed-days were lost per 100,000 compared with 57 bed-days lost per 100,000 post-move) [32\*].

*Reducing the burden of NoV through the food chain*

Food may either be contaminated at source, e.g. oysters [33], or during preparation by infected food-handlers [34]. During an experiment preparing cucumber sandwiches it was estimated that at least one infective NoV was transferred from contaminated hands to the sandwich if the food handlers’ hands contained 3 log10 or more NoVs before they donned gloves [35]. This re-emphasises the importance of good hand hygiene in controlling onward transmission.

Standardised methods for NoV detection in a variety of food matrices are now available [36\*] making it easier to implicate food vehicles in NoV outbreaks. Oysters grown in coastal areas are vulnerable to contamination by NoV, which are shed in high numbers in human faeces and are highly resistant in the environment. In a recent survey of oysters collected at point-of-sale to the consumer in the UK, NoV RNA was detected in 68.7% of 630 samples with strong winter seasonality [37\*]. However, modern sewage plants fitted with membrane bioreactor sewage treatment equipment can significantly reduce NoV levels in treated sewage and oysters [38\*].

For live oysters placed on the market, depuration is a key method for reducing levels of potential pathogens [39]. In the U.K. the minimum depuration period is 42 hours which is sufficient to reduce the *Escherichia coli* counts (an indicator of faecal contamination) to acceptable levels (less than 230 *E. coli*/100g). Using mathematical modelling, however, it has been suggested that the minimum depuration time for NoV should be substantially longer [39].

Salad leaves and berry fruits (produce) are also recognised food vehicles in outbreaks [40,41]. In the US, between 1998 and 2013, 972 raw produce outbreaks were reported and during the study period the proportion of outbreaks attributed to raw produce increased from 8% during 1998-2001 to 16% during 2010-2013 [42]. Norovirus was the most frequently reported pathogen (54% of outbreaks). NoV is known to be stable on lettuce leaf surfaces for at least 2 weeks [43], but little is known about internalisation and onward distribution. In experiments using lettuce and spinach, NoV was inoculated through the roots of seedlings and the petiole of leaves from mature plants [44\*]. NoV was tracked using confocal microscopy on day 1 and 6 post-root inoculation and on 16h and 72h post petiole-inoculation andinternalised to roots and leaves at similar RNA titres. It was stable inside the roots and leaves for at least six days and disseminated inside the central veins and the leaf lamina raising concerns that internal contamination may occur through irrigation and/or wash water.

*Sanitation*

In a recent systematic review and meta-analysis a high density of NoV in wastewater influent was demonstrated (overall mean = 4.6 log10 genome copies/litre) [45]. Although it has been suggested that traditional chlorine-based sewage treatment might not inactivate NoV efficiently [46], or even promote selection pressure [47], recent research indicates that current waste water treatment employing free chlorine is likely to protect public health against NoV, achieving at least 3-log10 reduction in NoV GI and GII RNA [48]. A trial of a comprehensive water, sanitation and hygiene (WASH) intervention in Mali provided evidence of benefit in the 21 schools chosen to receive the intervention compared with 21 matched comparison schools. There were significant reductions in antibody levels to food/water-transmitted enteric disease and person-to-person transmitted enteric disease in pupils attending the schools benefitting from the intervention [49\*\*]. This study is one of only a few using objective health measures to evaluate reductions in disease and exposure to pathogens.

*Vaccination*

There are exciting developments with respect to norovirus vaccination [50]. For example, in a single site, randomised, double-blind, placebo-controlled phase I clinical trial of an oral norovirus vaccine it was well-tolerated and generated substantial immune responses, including systemic and mucosal antibodies as well as memory IgA/IgG [51\*\*]. Similarly encouraging results have been obtained in a phase IIb randomised, controlled, double-blind clinical trial using intramuscular vaccination with NoV virus-like particle (VLP) antigens [52\*\*]. Norovirus vaccination needs to target high risk populations, including the young and the elderly, and protect against the most common circulating NoV strains. However, to justify the investment and to guide vaccination strategy and policy there need to be better burden and cost estimates [53].

*Clinical and Public Health Surveillance*

Molecular epidemiological methods have proved useful to track outbreaks in healthcare settings [54\*]. For example, in a 19 month study conducted at a paediatric tertiary referral hospital, the utility of molecular epidemiology using full genome sequences was compared with routine Infection Prevention and Control (IPC) investigations [55\*]. By generating norovirus genomes from new episodes of NoV, verified using clinical and epidemiological data, it was possible to demonstrate frequent introductions of multiple NoV strains with extensive onward nosocomial transmission.

Understanding the true burden of NoV disease is hampered by the fact that only a minority of cases are formally recorded in surveillance systems [56]. To overcome this investigators in the U.S. have proposed using an integrated healthcare delivery system as a surveillance platform [57\*]. They identified all cases of acute gastroenteritis that presented to a single healthcare provider using the electronic patient record and invited a sample of them into the study. Over 50% of people who met enrolment criteria agreed to participate, and 76% of them returned a stool sample. This surveillance scheme fulfils an important gap in many population burden of illness studies – namely the collection of stool samples to gain information on the aetiology of acute gastroenteritis.

*Mathematical Modelling*

Forecasting NoV is complicated by four key epidemiological features described above i.e. multiple transmission pathways; asymptomatic but infected individuals who may shed virus thereby infecting others unwittingly; a poor understanding of pathogen-immune interactions; and substantial under-reporting of disease.

Faecal-oral transmission of NoV relies on contact between individuals, which is comparatively small scale [58] so social interactions play a large part in effective disease transmission. However, NoV survival on fomites, variations in immune status and asymptomatic shedding in the host as well as underlying disease progression occur at different spatial and temporal scales. Despite this much modelling research has focussed on particular spatial sub-units within the at risk susceptible population, particularly in small- to medium-sized organisational units like hospitals, schools, care-homes and cruise-ships. In these situations introduction of NoV by an infected individual or fomite can lead to rapid spread in a more-or-less closed or at least well defined susceptible population. Whilst the impact of outbreaks in these institutions can be high locally, these units usually have comparatively small populations at risk and are easier to study because case-ascertainment is usually well defined.

Applications of population level models for NoV transmission are impractical because the deterministic format is not easily employed in such complex disease settings. Comparing models created for different institutional settings is problematic, because disease processes are not easily generalised e.g. the physical environment for fomite-induced transmission will depend on the physical structure of the institution. Given the propensity for outbreaks to occur in different settings at different times disease spread is clearly hierarchical and probably driven by different exposure pathways at different times of year, locations and age of individuals so variation in epidemiological parameters is best modelled either at institutional or individual case level. Whilst it is theoretically possible to account for fomites, asymptomatic shedding and immune competence, deterministic models are clumsy and crude as the system effectively becomes more multivariate in nature. The imperative is to develop stochastic models which simulate more realistically the physical environment, social demography and the hierarchical nature of disease transmission in different institutional settings.

**Secondary prevention of norovirus**

*Management of patients with acute symptoms*

The mainstay of treatment is correcting the dehydration caused by NoV diarrhoea and vomiting using either reduced-osmolality oral-rehydration solutions (ORS) or, if the patient is unable to tolerate ORS, intravenous rehydration [1\*].

**Tertiary prevention of norovirus infection**

*Treatment of chronic norovirus*

Chronic NoV occurs in patients with primary and secondary immune deficiencies in whom it can cause severe, protracted symptoms [59]. Various treatments have been proposed including exclusion diets, enteral and intravenous immunoglobulins, breast milk, immunosuppressants, ribavirin and nitazoxanide but there is, as yet, scant supportive evidence from well-designed randomised controlled trials [7].

**Conclusion**

Norovirus gastroenteritis and outbreaks remain major public health concerns. Candidate vaccines are in clinical trials, although the propensity of NoV to hyper-mutate might, nevertheless, cause challenges for developing a vaccine that induces cross-protective immunity. Once a suitable vaccine has been developed the next task will be to decide who should receive it, for which robust, realistic mathematical models will be needed.

**Key points**

* Virus particles, previously considered to be the infectious unit, also occur in clusters, which appear to be more virulent than individual virus particles
* A working culture system using human stem-cell derived enteroids has been developed
* There are promising results from early phase clinical trials of candidate NoV vaccines, which appear to be safe and immunogenic
* Chronic NoV affects patients with primary and secondary immune deficiencies and, although several treatments have been used, none are supported by well-designed clinical trials
* Infection control procedures are effective if properly implemented.

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**Disclaimer**

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, the Department of Health or Public Health England.

**Conflicts of Interest**

None

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