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Current assumptions for quantitative microbial risk assessment (QMRA) of Norovirus contamination of drinking water catchments due to recreational activities: an update

Dan Deere[a] and Una Ryan[b,*]

[a] Water Futures and Water Research Australia, Sydney, Australia
[b] Harry Butler Institute, Murdoch University, Perth, Australia
*Corresponding author. E-mail: una.ryan@murdoch.edu.au

ABSTRACT

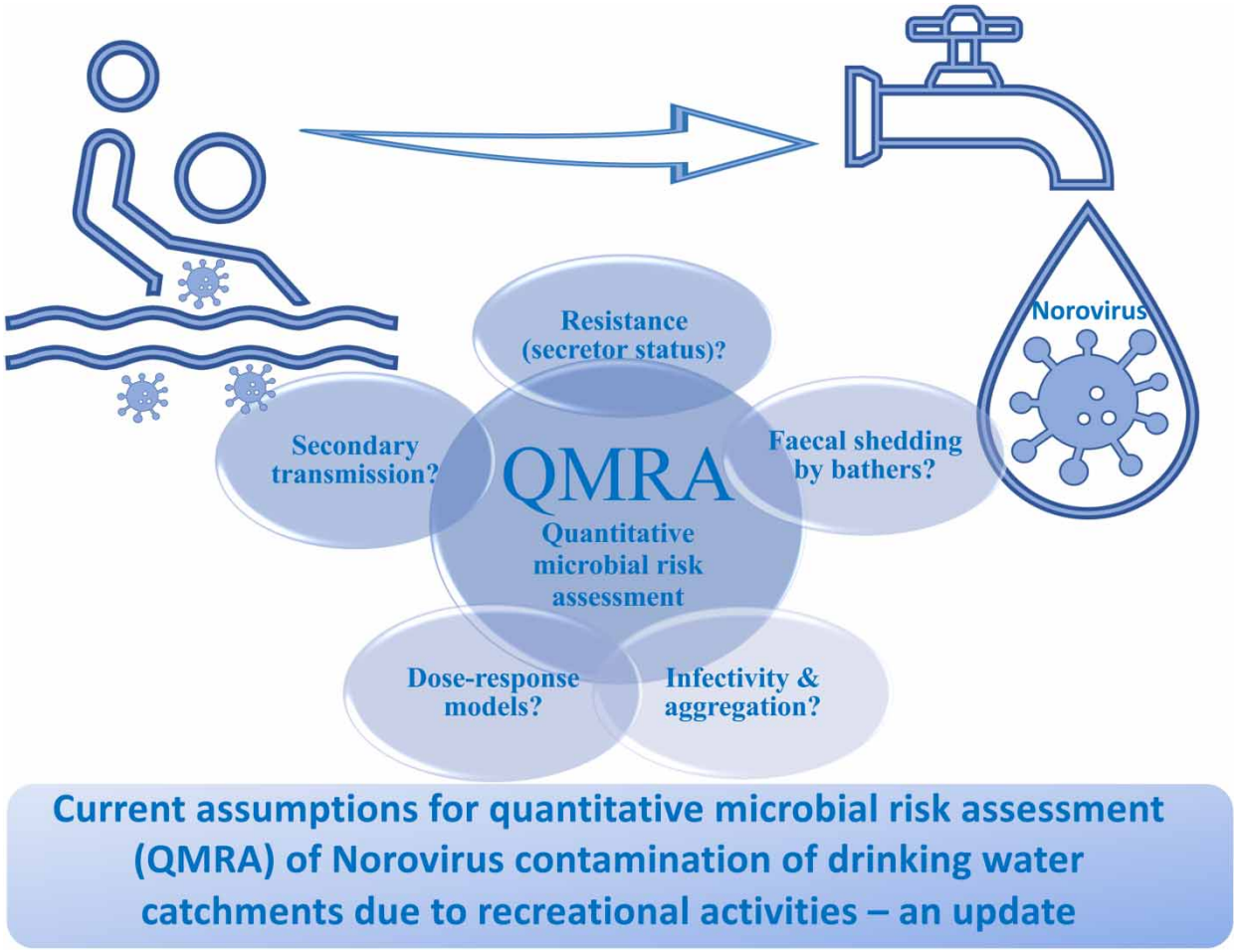
Contamination of drinking water from Norovirus (NoV) and other waterborne viruses is a major public health concern globally. Increasingly, quantitative microbial risk assessment (QMRA) is being used to assess the various risks from waterborne pathogens and evaluate control strategies. As urban populations grow and expand, there is increasing demand for recreational activities in drinking water catchments. QMRA relies on context-specific data to map out the pathways by which viruses can enter water and be transferred to drinking water consumers and identify risk factors and appropriate controls. This review examines the current evidence base and assumptions for QMRA analysis of NoV and other waterborne viral pathogens and recommends numerical values based on the most recent evidence to better understand the health risks associated with recreators in Australian drinking water sources; these are broadly applicable to all drinking water sources where recreational access is allowed. Key issues include the lack of an agreed upon data and dose-response models for human infectious NoV genotypes, faecal shedding by bathers, the extent of NoV infectivity and aggregation, resistance (secretor status) to NoV and the extent of secondary transmission.

Key words: drinking water contamination, Norovirus, QMRA, recreational water use, waterborne viruses

HIGHLIGHTS

- A review of quantitative microbial risk assessment (QMRA) is performed for determining public health risk from drinking water sources contaminated with Norovirus (NoV) by recreational activities.
- A review of NoV epidemiological data is performed for the purpose of exposure assessment, dose-response and risk assessment.
- Key recommendations and guidelines for numerical values are developed for the purpose of QMRA analysis.

GRAPHICAL ABSTRACT



INTRODUCTION

Waterborne viral pathogens are a major threat to human health (Chen *et al.* 2021). Catchment management and protection is a central part of multi-barrier safeguarding of drinking water quality (WHO 2017). Population growth and expansion of urban areas, however, has resulted in increasing recreational demands for water-based recreation globally. This presents significant health risks, particularly when these activities are conducted in drinking water sources. In many countries including Australia, water-based recreation activities including swimming are allowed in some drinking water catchments but not in others (Miller *et al.* 2008).

Quantitative microbial risk assessment (QMRA) is a widely used tool that can model risk from exposures to waterborne pathogens including viruses and assist in quantifying the level of risk (Haas *et al.* 2014; Brouwer *et al.* 2018; Federigi *et al.* 2019; Verani *et al.* 2019; Owens *et al.* 2020). It is particularly useful in that it can quantify the probability of infection, illness, and morbidity by estimating the exposure to pathogens (Kundu *et al.* 2013). The data generated, however, is only as good as the accuracy of input data (which is usually based on data from existing literature and/or site-specific data collection) and the consequent assumptions made. This is particularly problematic for estimating public health risk from the contamination of water used for drinking purposes by waterborne viruses due to swimmers in those waters. For example, the shedding of viral pathogens is highly variable, resulting in large differences in viral pathogen exposure between different individuals at different time points (Wyn-Jones *et al.* 2011; Milbrath *et al.* 2013).

Identifying and defining the sources and extent of uncertainty in QMRA health risk estimates is central to the evaluation of vulnerabilities, informed decision-making and prioritising where more research is needed. As QMRA health risk estimates are

reliant on assumptions, its usefulness can be strengthened by provision of the most current data to underpin and refine current assumptions and numerical values used for QMRA. This review seeks to identify the most important viral waterborne pathogens that can contribute to drinking water source contamination from recreational activities and to provide revised recommendations and numerical values to facilitate more in-depth risk assessments across drinking water sources in which recreational activities are allowed. Site-specific information including transport and fate of viral pathogens in reservoirs is not covered in this review.

RECREATIONAL WATER-ASSOCIATED OUTBREAKS OF VIRAL DISEASE

Viruses are a major cause of outbreaks among recreational water users who can be exposed via contamination of the water from accidental release of faecal matter, saliva, mucus and vomitus from both symptomatic and asymptomatic carriers (WHO 2006). The most commonly reported causes of recreational water-associated outbreaks are Norovirus (NoV), Human Adenovirus (HAdV), Enterovirus (EV) (including coxsackieviruses and echoviruses) and Hepatitis A Virus (HAV) (Sinclair *et al.* 2009; Bonadonna & La Rosa 2019).

Human NoVs are small, non-enveloped, single-stranded RNA viruses and are the chief cause of acute viral gastroenteritis worldwide (Ludwig-Begall *et al.* 2021). In addition to watery diarrhoea, NoV symptoms include projectile vomiting and infections can cause prolonged morbidity and mortality (Ludwig-Begall *et al.* 2021). It is estimated that globally NoV costs >US$ 65 billion in health and societal costs per year (Bartsch *et al.* 2016). Viral particles are shed in faeces in very high numbers (up to 10^{11} NoV particles stool/g) and the extremely low median infectious dose (ID_{50}) of 18 viral particles (Teunis *et al.* 2008), meaning that up to 5 billion ID_{50} doses may be shed by an infected individual per gram of faeces (Hall 2012; Robilotti *et al.* 2015; Ludwig-Begall *et al.* 2021). Vomiting is also a major mode of NoV transmission via contamination of water and surfaces and aerosol generation. Data analysed from several NoV human feeding trials (HFTs) showed that vomiting was more prevalent than diarrhoea as a symptom (i.e. only ~45% of individuals with vomiting also had diarrhoea) (Kirby *et al.* 2016). NoVs are stable and persistent in the environment (Seitz *et al.* 2011; Lopman *et al.* 2012) due to the lack of readily available cell lines to culture human NoV, and murine NoV (MNV) is used as a surrogate for experimental studies (Rachmadi *et al.* 2020).

NoVs are genetically classified into 10 genogroups (GI–GX), but GI and GII are responsible for most human infections (Chhabra *et al.* 2019; Capece & Gignac 2021; Ludwig-Begall *et al.* 2021). GI and GII are further subdivided into 9 (GI.1–9) and 25 (GII.1–27) genotypes, respectively (Nordgren & Svensson 2019). Of these, GII.4 is the predominant genotype globally in recent decades including Australia and is responsible for ~50–70% of all NoV outbreaks, although GII.2, GII.3 and GII.6 are also important causes of childhood NoV infections (Tu *et al.* 2007; Bruggink *et al.* 2018; Lun *et al.* 2018a, 2018b; van Beek *et al.* 2018; Mans 2019; Cannon *et al.* 2021; Farahmand *et al.* 2021).

Adenoviruses are double-stranded DNA viruses and cause a variety of clinical illnesses, and all are excreted in faeces (Rames *et al.* 2016; Lee *et al.* 2020). HAdVs are classified into seven species (HAdV-A to HAdV-G) (Lion 2019; Usman & Suarez 2021), with HAdV-B (serotypes 3 and 7) and HAdV-E (serotype 4) associated with swimming pool outbreaks (Sinclair *et al.* 2009; Li *et al.* 2018; Bonadonna & La Rosa 2019) and HAdV-G (type 52), and particularly HAdV-F (types 40 and 41), associated with an underestimated cause of gastroenteritis globally (Ghebremedhin 2014; Lee *et al.* 2020).

The genus EV that includes coxsackieviruses, echoviruses and poliovirus are small, non-enveloped single-stranded RNA viruses, which are shed in faeces and are among the most common infectious agents worldwide, causing conjunctival, respiratory or gastrointestinal illness; they can also cause poliomyelitis, meningitis and paralysis (Sinclair *et al.* 2009; Sinclair & Omar 2021).

The HAV is a single-stranded RNA virus, transmitted via the oral–faecal route, and the most common infectious cause of acute hepatitis worldwide in rare cases. Infections can result in death due to fulminant hepatitis (Nainan *et al.* 2006; Sinclair *et al.* 2009; Abutaleb & Kottilil 2020; Iorio & John 2021). There is only one serotype, and within this, four genotypes have been identified in humans (Nainan *et al.* 2006; Abutaleb & Kottilil 2020).

A review by Sinclair *et al.* (2009) identified 55 recreational water outbreaks occurring worldwide between the years 1951 and 2006 that were caused by viruses. Almost half of all outbreaks ($n = 25$) were attributed to NoV, 13 to HAdV (types 3, 4 and 7); 13 to EV (including echovirus ($n = 10$) and coxsackievirus ($n = 3$)) and 4 to HAV. Cases reported per outbreak varied from 5 to over 5,000, and 49% of the outbreaks were reported in swimming pools, with the remainder recorded in natural water bodies such as lakes, ponds, rivers or hot springs (Sinclair *et al.* 2009). In natural waters, it is possible that sewage or other inputs were responsible compared to swimming pools where contamination is entirely due to pathogen shedding

from other recreators. HAdV was more commonly associated with swimming pools (85% of HAdV outbreaks), whereas NoV was more commonly associated with natural waterways, such as lakes and rivers (72% of reported NoV outbreaks) (Sinclair *et al.* 2009).

A more recent global review, which focussed on swimming pool outbreaks only between 1951 and 2013, identified 29 public swimming pool outbreaks caused by viruses (Bonadonna & La Rosa 2019). Over half of the outbreaks ($n = 15$) were attributed to HAdV (including HAdv types 3, 4 and 7); six to EV (including echovirus 3 ($n = 5$) and enterovirus-like ($n = 1$)); five to NoV and three to HAV. Cases reported per outbreak varied from 7 to 373 and only one outbreak occurred where adequate biocide was present (Bonadonna & La Rosa 2019). In one of the more recent studies, a swimming pool outbreak of pharyngoconjunctival fever caused by HAdV-4 involving 55 individuals in Beijing, China, also identified 100% identical sequences in two water samples from the implicated pool (Li *et al.* 2018).

QMRA OF VIRAL WATERBORNE PATHOGENS

QMRA is typically based on the following steps: (1) hazard identification, (2) exposure assessment (3) dose-response and (4) risk characterisation.

Hazard identification – which are the most important viruses to focus on?

Any QMRA considering recreation and its impacts on drinking water must include NoV, HAdV and EV, as waterborne outbreaks caused by NoV, HAdV and EV outbreaks are commonplace (Sinclair *et al.* 2009; Bonadonna & La Rosa 2019). In addition, these viruses are stable, prevalent, persistent in the environment and relatively resistant to environmental and disinfection processes, with HAdV having a high resistance to UV disinfection (Mena & Gerba 2009; Cromeans *et al.* 2010; Gall *et al.* 2015; Robilotti *et al.* 2015; Rames *et al.* 2016; Teunis *et al.* 2016; Ding *et al.* 2017; Rachmadi *et al.* 2020). HAV is also important since it continues to cause outbreaks and can cause severe symptoms, including death. However, HAV is significantly less prevalent as a cause of swimming-associated waterborne outbreaks (Sinclair *et al.* 2009; Bonadonna & La Rosa 2019), and risks to HAV can be managed with controls for NoV. Rotaviruses are also major causes of acute gastroenteritis and can cause waterborne outbreaks; however, the introduction and widespread use of vaccines has meant that the threat of waterborne rotavirus infections has decreased (Schollin Ask 2021). Indeed, in rotavirus-vaccinated populations, NoV is now the most common cause of diarrhoea in children (cf. Nordgren & Svensson 2019). Similarly, the widespread use of poliovirus vaccines has been very successful in interrupting the transmission of poliovirus (Connor *et al.* 2021).

To make a QMRA manageable, it is recommended that the risk assessment use NoV as the model virus to predict the risks to drinking water consumers from water polluted by waterborne viruses due to recreational activities in drinking water sources for the following reasons: (1) NoV is the leading cause of viral gastroenteritis globally including Australia (Hall 2012; Tu *et al.* 2007; Bruggink *et al.* 2018, 2021; Lun *et al.* 2018a, 2018b), (2) it is well established as a waterborne pathogen and is shed in very high numbers (Moreira & Bondelind 2017), (3) NoV transmission can occur via contamination of water by both faeces *and* via vomiting (Kirby *et al.* 2016; Ludwig-Begall *et al.* 2021). Historically, faecal shedding is the only input that has been factored into QMRA studies considering drinking water impacted by recreation. This underestimation is particularly relevant for recreation that does not involve body swimming or paddling resulting in direct faecal introduction but where vomiting may still be relevant, and (4) NoV outbreaks are more commonly associated with swimming in natural waterways than with swimming in pools (Sinclair *et al.* 2009).

Exposure assessment

Seasonality and demographics of infection

NoV infects all age groups and has been traditionally described as being highly seasonal as it was originally clinically termed 'winter vomiting disease' (Adler & Zickl 1969). In the northern hemisphere, it is typically a disease that peaks in winter (Ahmed *et al.* 2013; Ludwig-Begall *et al.* 2021). However, in Australia and New Zealand, peaks have more often been reported in spring, from around October, and through into summer and autumn (Lim *et al.* 2016; Bruggink *et al.* 2017; Lun *et al.* 2018a, 2018b). These seasonal peaks are not well aligned temporally and seasonally with peaks in recreational water activity; however, it is important to note that NoV outbreaks due to recreational activity in drinking water sources are much less likely to be reported than swimming pool outbreaks as they likely represent a diverse population group, compared to swimming squads where the individuals know each other, increasing the chances of outbreak and cluster detection (Sinclair *et al.* 2009).

Prevalence of infection

Globally, the prevalence of NoV in patients with gastroenteritis was estimated at ~17% (range 14–20%) (Ahmed *et al.* 2014). However, the actual prevalence of NoV is undoubtedly much higher as NoV is chronically under-reported (Ondrikova *et al.* 2021). One study in the UK, which screened a cohort of 7,033 individuals via PCR for a range of enteric pathogens and then compared with nationally reported cases, concluded that for every reported NoV case, there were 288 unreported community cases (Tam *et al.* 2012). However, another study suggested that the under-reporting factor for NoV was much lower at 1.76 (Bernard *et al.* 2014). Asymptomatic carriage of NoV is common and occurs in all age groups and ranges from <1 to >89% depending on the detection method used and reporting mechanisms (Qi *et al.* 2018; Phattanawiboon *et al.* 2020). A conservative estimate of asymptomatic NoV infections is ~30% (Phillips *et al.* 2011; Teunis *et al.* 2015; Misumi & Nishiura 2021).

In Australia, NoV is the most common cause of gastroenteritis, with one study estimating that NoV was responsible for 2,180,145 cases of acute gastroenteritis in 2010, 12,757 hospitalisations, 17 deaths and 1,109 disability-adjusted life years (DALYs), which was based on collating evidence from a range of sources (Gibney *et al.* 2014). This equates to an annual incidence of 9,760 per 100,000 cases or 9.8% per person (Gibney *et al.* 2014).

To date, numerous NoV HFTs have been conducted using the Norwalk strain (GI.1 genotype), the Snow Mountain virus (SMV) strain (GII.2 genotype) and the globally widespread GII.4 genotype (Cin-1 strain) (Johnson *et al.* 1990; Graham *et al.* 1994; Hutson *et al.* 2002; Lindesmith *et al.* 2005; Atmar *et al.* 2008, 2014; Teunis *et al.* 2008; Seitz *et al.* 2011; Frenck *et al.* 2012). Several challenge studies with GII.4 have been conducted in gnotobiotic pigs including the GII.4 2006b strain (Bui *et al.* 2013) and the GII.4/Cin-1/2003/US strain (Cin-2) (Ramesh *et al.* 2020).

NoV shedding (determined by quantitative RT-PCR) in the HFTs described by Atmar *et al.* (2008, 2014) (GI.1 genotype) was detected between 1 and 56 days after inoculation (mean duration of shedding = 28 days), with shedding peaks persisting for several days but dropping significantly within 1 week (Atmar *et al.* 2008). For GII.4, the most common genotype worldwide, the HFT conducted by Frenck *et al.* (2012) reported viral shedding for a mean of only 5.2 days (range 2–30 days), which peaked by day 3 after challenge.

Recently, Petterson *et al.* (2021) calculated a point prevalence of 0.8% for NoV in Alberta, Canada based on the following formula:

$$\frac{R.U.D}{7 \cdot N \cdot (1 - A)}$$

applying this to Australia, where R is the reported number of cases per week (e.g. in Australia, the value is ~41,926 based on estimates by Gibney *et al.* (2014)), U is the under-reporting factor (e.g. 1.76 as suggested by Bernard *et al.* (2014)), D is the mean duration of excretion (days) (5 days using the data from the GII.4 trial by Frenck *et al.* (2012)), N is the population size (e.g. the population of Australia is 25.6 M) and A is the asymptomatic infection rate (~0.3). This gives a conservative point prevalence of NoV of ~0.3% for Australia. Note in this instance, the under-reporting factor of 288 as reported by Tam *et al.* (2012) was not used as it resulted in an unrealistically high point prevalence when applied to the prevalence data by Gibney *et al.* (2014). However, when applying this formula to data from countries and situations where high levels of NoV under-reporting are evident or suspected, using the under-reporting factor of 288 would be appropriate.

Release of faecal matter and vomitus

The calculation of NoV inputs to water sources must include variables such as accidental faecal releases (AFRs), vomiting directly into water and release of faecal matter via shedding from small quantities of material remaining from previous defecations. Relatively little data are available on the extent of faecal shedding during bathing or washing activities, but previous data based on analysis of greywater (washing machine and bathroom samples) indicate that an average of 1 g of faecal shedding during recreational water activity is reasonable with children shedding more faeces than adults (Rose *et al.* 1991; O'Toole *et al.* 2012).

Despite its importance, evidence-based data on AFR volume and frequency are lacking. The mass of an AFR is assumed to be 200 g since this has been used as the clinical definition of an excessive bowel movement symptomatic of gastroenteritis in NoV HFTs (Atmar *et al.* 2008, 2014) and an AFR frequency of 50% for symptomatic individuals for diarrhoea and a vomiting frequency of 50% has been assumed for those with symptomatic NoV is suggested. Further clinical research is required to test those assumptions.

Pathogen shedding

The pattern of symptoms and pathogen shedding during NoV infection (determined by viral qRT-PCR detection since the virus is not easily cultivable) was described in detail in the HFTs described by Atmar *et al.* (2008, 2014) (based on GI.1) and for vomitus by Kirby *et al.* (2016) (based on GI.1 and GI.2). Shedding of the virus was experienced in persons who had symptoms of diarrhoea (defined as >200 g watery faeces within 24 h), vomiting (≥1 episode), both or neither. Where symptoms were observed, they were of short duration (median approximately 1 day, range 1–2 days). Viral shedding in faecal matter was detected from 18 h following inoculation and continued for a median of 28 days and a range of 1–56 days (Atmar *et al.* 2008, 2014). The time series of the viral shedding in faeces showed a sharp rise towards a median peak concentration of viral genome copies/g of faeces (expressed in $\log_{10}$ units) of 11 and 10 for those with and without clinical gastroenteritis, respectively, followed by an approximately logarithmic decline over linear time, so that by 2 weeks, it had reduced to approximately 8 (Atmar *et al.* 2008, 2014). In contrast, in the HFT study by Frenck *et al.* (2012) using the GII.4 genotype (Cin-1 strain), viral shedding was detected for a mean of only 5.2 days (range 2–30 days), which peaked by day 3 after challenge.

In the study by Atmar *et al.* (2014), a median of 4.6 (range <3.3–7.1) viral genome copies/ml of vomitus (expressed in $\log_{10}$ units) was described. In a later study by Kirby *et al.* (2016) based on several HFTs (GI.1 and GI.2), a median of 8.2 viral genome copies/ml of vomitus (expressed in $\log_{10}$ units) was reported. The inoculums used for HFTs by Atmar *et al.* (2008, 2014) varied between approximately 192 and 1.9 million genome copies/dose. All exposed subjects became infected at the dose of 1,920, but only 8% became infected at a dose of 192 (Atmar *et al.* 2008). Seitz *et al.* (2011) exposed persons to NoV (GI.1) at doses of 8.8 $\log_{10}$ viruses in water (6.5×10^8 genome copies) and all became infected even after the virus was stored for up to 61 days in groundwater at room temperature in darkness. In the study by Frenck *et al.* (2012), the inoculum dose was 2×10^7 genome copies, with 70% becoming infected.

The HFTs were all healthy adult volunteers; however, studies in children, immunocompromised individuals and the elderly have reported higher and more extended viral shedding (up to 8 years) (Nilsson *et al.* 2003; Gallimore *et al.* 2004; Murata *et al.* 2007; Yi *et al.* 2016; He *et al.* 2017; Woodward *et al.* 2017; Davis *et al.* 2020), and these individuals would likely be at increased risk of infection. Strain-specific adaptive human immunity as a result of repeated infections should also be taken into account as multiple infections can result in immunity to symptoms or milder infections and less shedding. More studies are required, but protective immunity may last between 12 months and 4 years (Hassan & Baldridge 2019). It is also important to note that symptomatic infections result in larger volumes of faecal material being shed. For instance, up to 3.6 L of material was reportedly shed in 1 day in a HFT (1.8 L diarrhoea and 1.7 kg in vomitus) (Atmar *et al.* 2008). Therefore, for estimating the peak NoV shedding in faeces, a mass of at least 200 g/day and a peak concentration of at least 11 $\log_{10}$ genome copies/g are a reasonable evidence-based estimate that, although potentially exceeded in extreme cases, aligns with the consensus value given in WHO (2006). This yields a daily peak shedding rate of 13 $\log_{10}$ genome copies/day. Likewise, for estimating the peak NoV shedding in vomitus, a mass of at least 200 g/day and a peak concentration of at least 7 $\log_{10}$ genome copies/g are a reasonable evidence-based estimate. This yields a daily peak shedding rate of 9 $\log_{10}$ genome copies/day.

Support for these assumptions comes from comparison to sewage. For example, a recent review of viruses in wastewater by Corpuz *et al.* (2020) reported NoV concentrations per L from 9 to 10 $\log_{10}$. Concentrations of HAdV and EV were similar at concentrations per L of up to 10 and 9 $\log_{10}$, respectively (Corpuz *et al.* 2020). The orders of magnitude difference in reported NoV concentrations between some studies are likely due to differences in concentration and detection methods used.

Volume of water consumed

A global study by Mons *et al.* (2007) estimated that the mean daily consumption of cold tap water ranged between 0.1 and 1.5 L and QMRA studies on risks to drinking water consumers from microorganisms generally assume that 1 L of unboiled water is consumed daily (NHMRC 2011; WHO 2016). More recently, an Australian study estimated the median total water intake from beverages (including but not specifically tap water) ranged from 1.5 to 2.7 L, with the highest intake during periods of warmer ambient temperature (Mallett *et al.* 2021). Importantly, the study found that water consumption was higher in summer months, which coincides with periods of peak recreational activity. For the Australian context, where risks from recreational activity are likely to be most elevated during warmer regions and periods, 2 L of cold tap is recommended for QMRA studies. In countries with cooler climates, a lower volume of 1–1.5 L may be more appropriate.

DOSE-RESPONSE ASSESSMENT

In humans, the median infectious dose (ID_{50}) of Norwalk virus (GI.1) has been reported to be between 18 and 2,800 viral genome copies (Teunis *et al.* 2008; Atmar *et al.* 2014). In gnotobiotic pigs, the ID_{50} of GII.4 (Cin.2) has been calculated at 2,400–3,400 viral genome copies (Ramesh *et al.* 2020). A wide variety of NoV dose-response models have been used in QMRA and these have been critically reviewed and summarised, with no single 'consensus' model (Messner *et al.* 2014; Schmidt 2015; Van Abel *et al.* 2017; Teunis *et al.* 2020). Current model predictions exhibit wide variations (2.9 orders of magnitude) in the probability of infection values determined, particularly for low doses, due to some of the issues discussed below (Van Abel *et al.* 2017).

Any discussion of dose-response models must take into account the type of concentration and qRT-PCR methods used, the extent of genetic diversity of NoV (Parra *et al.* 2017; Nelson *et al.* 2018), as well as the immune status and genetic susceptibility of the host (Nordgren & Svensson 2019). qRT-PCR results are impacted by the efficiency of the concentration and RNA extraction methods used and the presence of environmental PCR inhibitors, resulting in variable quantitation rates (Farkas *et al.* 2017). Therefore, extraction and quantification controls should be included to measure the performance of these assays. Droplet digital qPCR methods (which can quantify NoV without the need for a standard curve) are more sensitive than standard RT-qPCR and less susceptible to PCR inhibitors and are, therefore, recommended to standardise NoV enumeration (Jahne *et al.* 2020; Han *et al.* 2022; Song *et al.* 2022). A proportion of the human population is largely not susceptible to NoV infection, which is thought to be due to the lack of expression of human histo-blood group antigens (HBGAs), particularly the FUT2 (Secretor), FUT3 (Lewis), and ABO genes (Nordgren & Svensson 2019; Sharma *et al.* 2020). Expression of these HBGAs is controlled by FUT2 and they are located on the surfaces of the intestinal epithelial cells, where they are thought to act as attachment receptors for NoV (Nordgren & Svensson 2019). Therefore, non-secretors (Se−) (i.e. individuals with a non-functional FUT2 who do not have these antigens) are largely resistant to infection with NoV (Frenck *et al.* 2012; Nordgren & Svensson 2019). Evidence to date suggests that ~20–25% of Caucasian, Central Asian, and several African populations are non-secretors (Se−) (Nordgren & Svensson 2019).

Both the GI and GII NoV genogroups recognise the HBGAs and HFTs using the G1.1 genotype as the inoculum showed that non-secretors were protected against both symptomatic and asymptomatic infections (Teunis *et al.* 2008; Atmar *et al.* 2018). In contrast, the SMV HFT (GII.2 genotype) showed no association between secretor status (and other HBGAs) with susceptibility (Lindesmith *et al.* 2005). Analysis of the most clinically relevant GII.4 genotype HFT, in which 23 secretors and 17 non-secretors of HBGAs were challenged, revealed that 70% of secretors became infected compared to only 6% of non-secretors (1 individual) (Frenck *et al.* 2012). A subsequent meta-analysis revealed that secretors had 4.2 times the odds of infection with NoV compared to non-secretors and secretors were 9.9 times more frequently infected with GII.4 NoVs (Kambhampati *et al.* 2016).

A major limitation with assessing risks at low doses based on HFT data from exposures at relatively higher doses is that viruses have a tendency to aggregrate or clump in solution, which can have significant influences on predicted risks (Messner *et al.* 2014; Schmidt 2015; Van Abel *et al.* 2017). In addition, scanning electron microscopy has shown that a proportion of NoVs are shed in stool not only as free viral particles but also as viral clusters inside membrane-bound vesicles, which remain intact during faecal–oral transmission (Santiana *et al.* 2018). If NoVs in the stock solutions used for HFTs are aggregated, as has been demonstrated (Teunis *et al.* 2008), then this would result in fewer infections at lower doses, and consequently, a higher ID_{50} also compromises beta-Poisson dose-response models, which assume that the viruses in the inoculum are disaggregated (Messner *et al.* 2014; Schmidt 2015; Ramesh *et al.* 2020; Teunis *et al.* 2020). The original dose-response model by Teunis *et al.* (2008) modelled infection risks as a function of NoV genome copies, with virus aggregation or disaggregation defining lower-bound or upper-bound infection risk limits, respectively. Messner *et al.* (2014) developed a fractional Poisson model to account for NoV aggregation (and non-secretor immunity), which is computationally simpler than the beta-Poisson model. Van Abel *et al.* (2017) suggested that multiple models need to be used to better capture levels of uncertainty. Nilsen & Wyller (2016) also developed some models for dose-response of aggregated pathogens and concluded that additional dose-response data for unaggregated NoV particles are still required to improve levels of uncertainty (Nilsen & Wyller 2016).

The most recent dose-response analysis by Teunis *et al.* (2020) using a beta-Poisson model also took into account the factors of NoV aggregation, host secretor status and NoV genogroup and also included additional outbreak data from oyster consumption, where the number of individuals exposed, the attack rate, the host secretor status (Se+/Se−), the number of oysters consumed, the concentration of NoVs in the oysters and the genogroup (G1 and GII) were known (Thebault *et al.*

2013). It also included data from a vaccine trial where Se+ individuals were infected with the GII.4 genotype (Bernstein *et al.* 2015). In the analysis by Teunis *et al.* (2020), extensive variation within the GI and GII genogroups in terms of infectivity and pathogenicity was highlighted, and a mean infection risk of 0.28 and 0.076 for GI and GII genogroups, respectively (for Se+ individuals exposed to 1 viral genome copy of NoV), was calculated, whereas for Se− individuals, the mean infection risk was 0.00007 (G1) and 0.015 (GII) (Teunis *et al.* 2020). The WHO (2016) consensus QMRA document and most recent draft of the Australian Guidelines for Water Recycling (AGWR) (AGWR 2006) have both identified relatively conservative models. Future dose-response experiments using disaggregated NoV particles and more studies on the full extent of resistance to infection among non-secretors are required to improve levels of certainty. In the interim, however, it is recommended that the dose-response model recommended in the AGWR, which is aligned to the WHO (2016) dose-response model or the Teunis *et al.* (2020) model, be used and that aggregation and host secretor status must be included. Ideally, the dose-response relationship should be modelled in a number of ways to account for the existing uncertainty in dose-response models.

RISK CHARACTERISATION

The World Health Organization (WHO 2011) proposed the DALY as a metric of health burden from different diseases or health conditions. It is calculated as the sum of the years of life lost (YLL) due to premature death in the population and the years lost due to disability (YLD) for incident (newly arising) cases of the health condition. The WHO has established a drinking water threshold of 1 DALY/million people/year or 1 μDALY/person/year, which is also the metric for tolerable risk in Australia (O'Toole *et al.* 2015). This provides more defined information about the amount of water treatment required depending on the degree of pathogen contamination in the drinking water source. In Australia, based on data from Gibney *et al.* (2014), 1 μDaly allows for 2% of diarrhoeal disease caused by NoV to be associated with consumption of drinking water (O'Toole *et al.* 2015). In order to more accurately calculate health risk, the potential for waterborne disease outbreaks that arise during the periods of elevated recreational water use (and not just average risk) needs to be factored into baseline risks, as the current 1 μDALY tolerable risk is not based on risks from recreation.

Based on the evidence highlighted in this review, Table 1 lists proposed assumptions to assist QMRA to assess risks to drinking water consumers from NoV associated with recreation within drinking water sources to provide a knowledge base to support QMRA for viral contamination. A separate review has provided similar assumptions for the assessment of risk from protozoan pathogens (Ryan & Deere 2022).

Importantly, QMRA best practices should be used to predict the entire range of risks, including hydrodynamic modelling of the fate of NoV in the water column as well as the performance of water treatment processes. A detailed assessment is beyond the scope of this review but is relevant to any QMRA for a drinking water supply.

The drivers behind this publication were to provide a set of best-supported estimates for conducting QMRA using a mathematical approach defined variously as deterministic, point estimate, Tier 1, or screening level (WHO 2016). Such assessments are more readily understood by stakeholders and decision-makers engaged in considering the implications of recreational water activity in drinking water sources. Uncertainty and sensitivity analysis can be undertaken by exploring the effect of changes in the input assumptions on the outputs. However, the literature cited in this publication can also be drawn upon to support more sophisticated stochastic, probabilistic, Tier 2, and in-depth risk assessments (WHO 2016).

CONCLUSIONS

A major limitation of QMRA analysis for NoV is the lack of an agreed upon dose-response model and best practice is to use multiple dose-response models to better understand the levels of uncertainty and provide a range of predicted outcomes for the probability of infection. The three confounding factors in dose-response models are (1) the extent of NoV viral aggregation, (2) the secretor status of the exposed population and (3) the NoV genogroup and genotype.

Many of the HFTs conducted to date have been performed using NoV genotypes (GI.1, GII.2) that are not major causes of infections in humans. GII.4 is still the dominant genotype globally including Australia, followed by GII.2, GII.3 and GII.6 (Cannon *et al.* 2021); therefore, more reliance should be placed on HFTs and dose-response models using these four genotypes (and particularly GII.4) including the HFT using GII.4 by Frenck *et al.* (2012). However, at present, there are insufficient data on the infectivity of the GII.4 genotype and more HFTs need to be conducted on a range of GII.4 variants including recently emerging variants (and other relevant genotypes including GII.2, GII.3 and GII.6) (Nordgren & Svensson 2019; Cannon *et al.* 2021).

Table 1 | Recommended starting point for screening-level QMRA for determining the public health risk due to contamination of drinking water catchments with waterborne viruses due to body-contact recreation in source water (modified from Ryan & Deere 2022)

Parameter	NoV as the example virus	Units	Basis
1. Epidemiological assumptions			
Point prevalence of infection with NoV for recreators visiting a site during popular recreational periods	0.3	% of persons present at the site	Drawing upon the Australian incidence estimates of Gibney *et al.* (2014) and the NoV shedding duration estimates of Frenck *et al.* (2012) for GII.4 and the point prevalence calculation by Petterson *et al.* (2021)
2a. Bather contamination assumptions			
Quantity of faecal shedding by persons entering water	1	g per person entering the water	Based upon greywater studies from O'Toole *et al.* (2012) and Rose *et al.* (1991)
Accidental faecal release frequency among symptomatic recreators entering water	50	% of persons with symptomatic infection	Epidemiological observations of persons with symptoms as described by Atmar *et al.* (2008, 2014)
Accidental faecal release mass	200	g per AFR	Atmar *et al.* (2008, 2014)
Vomitus frequency among symptomatic recreators entering water	50	% of persons with symptomatic infection	Atmar *et al.* (2008, 2014) and Kirby *et al.* (2016)
Vomitus mass	200	g per event	Atmar *et al.* (2008, 2014) and Kirby *et al.* (2016)
2b. Visitor contamination assumptions			
Faecal deposit mass	200	g per faecal deposit	Atmar *et al.* (2008, 2014)
Faecal deposit frequency	50	% of persons with symptomatic infection	Atmar *et al.* (2008, 2014)
Vomitus mass	200	g per event	Atmar *et al.* (2008, 2014) and Kirby *et al.* (2016)
Vomitus frequency	50	% of persons with symptomatic infection	Atmar *et al.* (2008, 2014) and Kirby *et al.* (2016)
3. Microbiological assumptions			
Concentration of NoV in faecal matter	11	Log_{10} NoV/g^{-1}	Epidemiological observations of persons with symptoms as described by Atmar *et al.* (2008, 2014) and benchmarked against reviews of NoV concentrations found in sewage by Corpuz *et al.* (2020)
Concentration of NoV in vomitus	9	Log_{10} NoV/g^{-1}	Based on observations by Atmar *et al.* (2008) and Kirby *et al.* (2016)
4. Exposure assessment assumptions			
Volume of treated water consumed per day during recreational water season	2	L	Mons *et al.* (2007), NHMRC (2011), WHO (2016) and Mallett *et al.* (2021), noting that during periods of the year and in climates where recreation is higher, and cold water consumption is also higher.
5. Dose-response assumptions			
Probability of infection with NoV	0.28 for GI norovirus and 0.076 for GII virus	Ratio	Data from Teunis *et al.* (2020)
Proportion of infections leading to illness	0.7	Ratio	WHO (2016) and NHMRC (2011)

(*Continued.*)

Table 1 | Continued

Parameter	NoV as the example virus	Units	Basis
Secretor + status	~80%	% of persons susceptible to NoV	Nordgren & Svensson (2019)
DALYs per case	0.5×10^{-3}	DALYs	Gibney *et al.* (2014) and NHMRC (2011)
Target tolerable risk	1	μDALY/year	WHO (2016) and NHMRC (2011)

Recently, Santiana *et al.* (2018) reported the intriguing finding that both NoV and rotavirus are also shed and transmitted as viral clusters inside extracellular vesicles, which are capable of passing through the gastrointestinal tract and delivering viral particles directly to the intestinal cells. This highlights our lack of understanding of the life cycle of NoV and adds more complexity to the modelling of aggregation in dose-response models. For rotavirus, vesicle-bound clusters constituted 10–45% of the total rotavirus excreted in stool (Santiana *et al.* 2018). It is not yet known what proportion of NoV is shed as clusters and further research in this area in a priority. Such vesicle-bound clusters might persist longer in the environment, and be more resistant to disinfection in water treatment, than free viral particles. Genogroup is also relevant to aggregation analysis as studies have shown differences in aggregation behaviour between GI.1 and GII.4 genotypes presumably due to differences in amino acid composition (da Silva *et al.* 2011). Until a better understanding of aggregation is achieved, a conservative QMRA should be used to model both disaggregated and aggregated dose-response models to capture the extent of uncertainty.

It is essential that secretor status is considered in QMRA. The majority of HFTs only included Se+ individuals and Se− individuals are often ignored in QMRA analysis. The global prevalence of secretor status is not known but based on estimates that the Se− population comprises ~20–25% of Caucasian, Central Asian, and several African populations (Nordgren & Svensson 2019), and this should be factored into QMRA until more detailed data are available. This is important, because assuming that all individuals are Se+ could result in a 20–25% overestimation of risk in QMRA analysis. Further studies are essential to better understand the prevalence of secretors in Australia and other countries and also to more clearly determine the extent of protection against NoV infection afforded by Se− status. While evidence suggests that non-secretors are protected from infection by GII.4 NoVs (Thorven *et al.* 2005; Tan *et al.* 2008), this protection is not absolute (Carlsson *et al.* 2009; Frenck *et al.* 2012; Jin *et al.* 2013; Costantini *et al.* 2016). Similarly, outbreak studies on the GII.3 genotype, which is a common cause of outbreaks, have revealed conflicting results with several studies showing no association between secretor status and susceptibility (Tan *et al.* 2008; Jin *et al.* 2013; Liu *et al.* 2014). In addition, some NoVs do not bind HBGAs, suggesting that additional binding/co-factors may be involved and additional complexity in the virus–receptor relationship (Huang *et al.* 2005; Murakami *et al.* 2013; Almand *et al.* 2017; Nordgren & Svensson 2019; Chassaing *et al.* 2020). A more thorough understanding of all cellular receptors involved in the release of the NoV genome into human intestinal cells is therefore central to understanding the range of infectivity of NoV genogroups and genotypes.

Until very recently, it has not been possible to determine the fraction of infectious to total NoV viral particles in inoculums used in HFTs due to the lack of a cell culture system for human NoV. However, now that a wide range of NoV genotypes can be replicated in stem cell-derived human intestinal enteroids (Ettayebi *et al.* 2016, 2021), better estimates of NoV infectivity for HFTs should be conducted by comparing the relationship between detection of genome copies and cell culture infectious units.

Other knowledge gaps include the lack of reliable data on faecal shedding by bathers, particularly frequency and mass of AFRs. Similarly, the extent of secondary person-to-person spread of NoV following primary infections arising in recreational waters (Baron *et al.* 1982; Sinclair *et al.* 2009) may need to be considered in the QMRA, because not including secondary spread leads to an underestimation of the true risk to drinking water consumers since only the primary infections are simulated.

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DATA AVAILABILITY STATEMENT

All relevant data are included in the paper or its Supplementary Information.

CONFLICT OF INTEREST

The authors declare there is no conflict.

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