

Recreational and drinking waters as a source of norovirus gastroenteritis outbreaks: a review and update

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Key words: drinking water, molecular detection, norovirus, outbreak, recreational water

ABSTRACT

The distribution of noroviruses is worldwide. In industrialized countries, noroviruses are the most common viral cause of gastroenteritis outbreaks and play an important role in sporadic gastroenteritis as well. Transmission may occur through the ingestion of contaminated foods or water, through person-to-person contact, or by way of direct contact with contaminated surfaces.

Of particular importance is their ability to cause waterborne outbreaks linked either to the direct consumption of water or to its recreational uses. This article reviews the clinical manifestations and epidemiology of norovirus infection, and describes over 40 waterborne norovirus outbreaks, their respective probable sources of contamination and – where water samples were tested – the genetic types identified.

INTRODUCTION

Noroviruses are considered as emerging pathogens due to: their widespread distribution in diverse environments, ability to cause clinically relevant infections in all age groups, numerous modes of transmission, genetic diversity and the fact that they induce only short-term immunity in humans. These viruses can cause waterborne outbreaks linked either to the direct consumption of water or to its recreational use. Since infected individuals can excrete millions of viral particles (in stools and/or vomit), these viruses can be found in great numbers not only in raw sewage but also in treated waters, recreational waters and water destined for human consumption. In most countries, the absence of adequate surveillance programs results in a lack of systematic virologic research on clinical and environmental samples. Data on the distribution of the virus is thus scarce, and the occurrence and scope of waterborne outbreaks are often underestimated.

This paper describes over 40 waterborne norovirus outbreaks and their respective probable sources of contamination. The frequency of norovirus outbreaks associated with different types of water underscores the need for a careful evaluation of the presence of such viruses in these waters. In recent years, advances in molecular biology

and the resulting development of molecular diagnostic systems, gave fresh impetus to the study of the virological and epidemiological characteristics of noroviruses. The molecular approach to norovirus diagnosis – allowing the identification of sources of infection and the subsequent development of efficacious prevention strategies – is destined to become an integral part of epidemiological surveillance of waterborne and foodborne diseases.

CLASSIFICATION OF NOROVIRUSES

Noroviruses belong to the family Caliciviridae, named after the typical cup-like depressions on their surface (from Latin calix = cup, goblet). The family comprises four genera: *Lagovirus*, *Vesivirus*, *Sapovirus* and *Norovirus*. The first two are viruses of animals; the remaining are etiological agents of human gastroenteritis (Figure 1). Norovirus was first described following a 1969 gastroenteritis (winter vomiting disease) outbreak in a school of Norwalk, Ohio (Alder and Zickl 1969; Kapikian et al. 1972). This group currently represents the most common viral cause of gastroenteritis worldwide – for outbreaks as well as for sporadic cases (Atmar and Estes 2006; Blanton et al. 2006; Fankhauser et al. 2002; Koopmans and Duizer 2004).

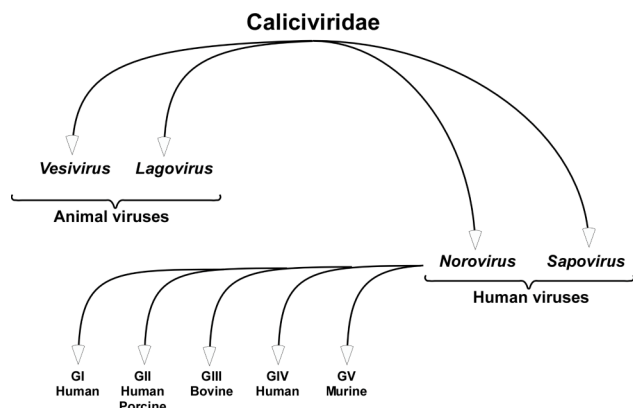


Figure 1. Norovirus classification.

Noroviruses are classified into five different genogroups (named GI to GV), subdivided into 29 genetic clusters which, in turn, are further subdivided into various types (Zheng et al. 2006). Genotypes GI, GII and GIV infect humans, causing gastroenteritis, whereas GIII and GV typically infect animals. Recently, human norovirus strains (GII-4 like) have been found to be present in livestock (Mattison et al. 2007), indicating possible zoonotic transmission. Genogroup I includes, among others, the Norwalk (prototype of the GI-1), the Southampton (GI-2), the Desert Shield (GI-3) and the Valetta (GI-4) strains. Genogroup II includes the Hawaii (GII-1), the Snow Mountain and Melksham (GII-2) as well as the Toronto and Mexico (GII-3) and the Bristol and Grimsby (GII-4) strains. In addition to human strains, this genogroup also includes porcine strains (GII-11) (Wang et al. 2006). The Jena strain, isolated for the first time in the feces of a calf, is the prototype of Genogroup III (Liu et al. 1999). Genogroup IV has the Alphantron virus as its prototype (Koopmans et al. 2000). Genogroup V includes murine norovirus 1 (MNV-1) (Blanton et al. 2006); three new strains of murine norovirus have been identified recently, which differ from MNV-1 in their molecular and pathogenic characteristics (Hsu et al. 2007).

MOLECULAR STRUCTURE OF NOROVIRUS

Noroviruses are small (average size 27-35nm), nonenveloped viruses. Their genome consists of a single strand of positive-sense RNA, about 7.5kb in length, with a polyadenylated tail at the 3' end and a protein (VPg) attached to the 5' end (Atmar and Estes 2001) organized into three open reading frames (ORFs, Figure 2). The first frame (ORF1) codes for a polyprotein precursor to the functional proteins NTPase, VPg, Protease and Polymerase. The second open reading frame (ORF2) encodes VP1, the capsid's main structural protein. This open reading frame can be further subdivided into two domains: the N-terminal/S which forms the icosahedral shell, highly conserved in Caliciviridae family, and the C-terminal/P

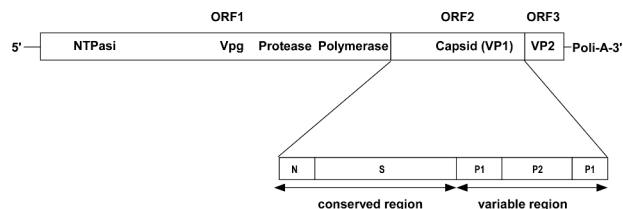


Figure 2. Organisation of the norovirus genome.

which forms the more variable protruding part of the capsid. The third open reading frame (ORF3) codes for a small basic protein (VP2) which seems to regulate the expression and stability of VP1 (Bertolotti-Ciarlet et al. 2003).

SYMPTOMS OF NOROVIRUS INFECTION AND NATURAL HISTORY OF RELATED DISEASES

The symptoms of norovirus related diseases are those typical of gastroenteritis, that is, vomiting, watery diarrhea and abdominal cramps (Hutson et al. 2004; Widdowson et al. 2005). Vomiting is a characteristic symptom in the majority of norovirus infections (64% of adults and 81% of children). Other symptoms such as general malaise, low grade fever, nausea and fatigue are also present in over 90% of cases (Gotz et al. 2001). The incubation period of the disease is generally between 12 and 48 hours, while infection lasts between 12 and 60 hours. Infection may also be asymptomatic, and thus contribute to the spread of the virus in the community (Radford et al. 2004). As a rule, the disease does not have serious consequences, and most patients recover within 1-2 days without complications. Debilitated patients and persons with weaker immune systems such as children, elderly or chronic patients may be affected by more serious forms of the disease. Specifically, dehydration may represent a serious complication for children, the elderly and persons with a precarious metabolic balance or cardio circulatory instability.

MAIN CHARACTERISTICS FACILITATING THE SPREAD OF NOROVIRUS

Low infectious dose

Noroviruses have a very low infectious dose [10-100 viral particles (Kapikian et al. 1996)]. The portal of entry for infection is the oropharynx. The virions are acid-stable, enabling them to pass the gastric barrier and replicate in the intestine. One gram of feces may contain up to 10,000,000 viral particles, and a single episode of vomiting may contaminate the environment with 30,000,000 viral particles. These characteristics render noroviruses highly contagious. In more or less closed communities, such as hospitals, restaurants, schools, and hotels, fast-moving widespread of outbreaks may occur.

Prolonged, sometimes asymptomatic excretion

In individuals who present clinical symptoms, viral excretion may appear not only during the symptomatic period but also before the manifestation of symptoms and after clinical recovery (Gaulin et al. 1999; Graham et al. 1994; Parashar et al. 1998). Virus shedding generally persists for up to three days after the resolution of symptoms. Yet, various studies have shown that in approximately 30% of patients, viral shedding may persist for as long as three weeks from the time of infection. Adequate hygiene protocols for the postsymptomatic period are thus necessary to limit the spread of the virus. Immunocompromised patients may shed virus for as long as a few months (Gallimore et al. 2007; Kaufman et al. 2003). In addition, a small proportion of asymptomatic individuals shed virus through feces (de Wit et al. 2001).

Environmental stability

Noroviruses are highly resistant to adverse environmental conditions. They can survive chlorination (in concentrations up to 10ppm) and temperatures ranging from below 0°C to 60°C and higher (Schaub and Oshiro 2000). A recent study regarding the persistence of human noroviruses in waters showed that norovirus genome may persist 1-3 months in different types of water (mineral, tap water and river) (Ngazoa et al. 2008).

Strain diversity and absence of long-term immunity

Noroviruses present considerable genetic and antigenic diversity. To date, five different genogroups have been identified, subdivided into 29 genetic clusters, each comprising several types (Zheng et al. 2006). This variability is linked to a number of factors, including genetic mutations. Indeed, compared to DNA viruses, RNA viruses generate a relatively high number of mutations, as their replicase is unable to correct replication errors. Further, due to possible genetic interactions among virions infecting the same cell, genetic recombination may occur (Bull et al. 2006; Phan et al. 2007; Waters et al. 2007). New variants are thus continually generated, which can supplant existing predominant strains (Van den Berg et al. 2005) when better fit to infect susceptible hosts or survive in the presence of adverse environmental conditions. Due to the great genetic and antigenic variability of noroviruses, mechanisms of immunization are not sufficiently understood. Immunity acquired through infection is usually temporary and applies specifically to the genotype of the virus causing the infection: a previously infected individual remains susceptible to infection by different variants of the virus. Owing to the existence of multiple genotypes, infection with one type does not confer immunity to other types.

Multiple modes of transmission

As noted above, the virus is highly infectious, and has many possible routes of transmission (Figure 3).

- *Consumption of contaminated food or water.* Since norovirus infection is transmitted via the fecal-oral route, outbreaks may be associated with the consumption of various

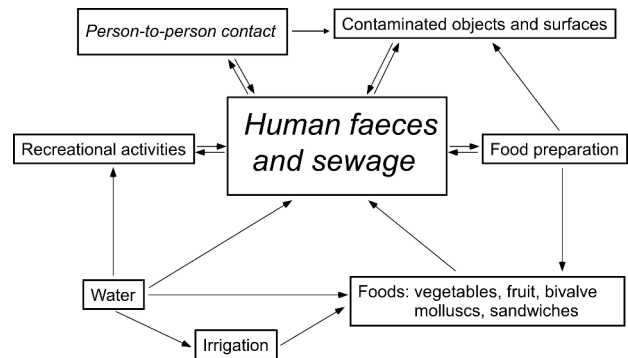


Figure 3. Possible routes of norovirus transmission.

contaminated foods, such as, cold foods (sandwiches, salads), fruits (especially berries), meat, fish (raw or undercooked) and baked goods. Edible bivalves and especially oysters are particularly significant in this context. These molluscs, being filter-feeders, tend to accumulate in their bodies viral particles present in contaminated seawater, thus transmitting them to humans (Rutjes et al. 2006; Shieh et al. 2003). Tap water, mineral water, well water, river water, ice, lake water and recreational waters (sea, swimming pool) – can all constitute possible sources of infection (Beuret et al. 2002; Hafliger et al. 2000; Hoebe et al. 2004; Kukkula et al. 1997; Maunula et al. 2005; Schvoerer et al. 1999). In addition, polluted water can contaminate some foods at the source, such as in the case of seafood, fresh vegetables or berries.

- *Person-to-person contact or contact with contaminated surfaces.* The virus can be carried to the mouth on contaminated hands through contact with objects previously contaminated by vomit or feces (Brugha et al. 1999; Kjeldsberg et al. 1989; Koopmans et al. 2000; Mead et al. 1999; Schaub and Oshiro 2000). This mode of transmission plays an important role in the spread of outbreaks, particularly in communal environments. It is indeed not unusual for the outbreak to be found in relatively confined, crowded settings such as nursing homes, schools, restaurants, hotels, etc. Especially notorious is so-called traveler's diarrhea (Okhuysen 2007) caused by norovirus, typically occurring on board of cruise ships, where crowding results in outbreaks affecting almost all passengers and crew (Dahl 2006). In 2006, a total of 35 gastroenteritis outbreaks have been registered in 13 cruise ships on European waters. In 9 of 13 ships, the etiological agent implicated was norovirus, having caused a total of 1088 cases, 60% of them were passengers (Koopmans et al. 2006).
- *Airborne transmission.* Since norovirus is excreted not only in feces but also in vomit, airborne transmission through virus-containing particles is also important. This is especially evident in cases of particularly rapid spread in places where people congregate (Marks et al. 2000, 2003; Sawyer et al. 1988).

DIAGNOSIS

Laboratory diagnosis of norovirus is rendered difficult both by the growing genetic heterogeneity of the strains and by the absence of culture methods for these viruses. The inability to propagate them in cell cultures has always been an obstacle to the study of these viruses (Duizer et al. 2004), and despite recent significant progress in this field (Straub et al. 2007) the methods remain complex and the results difficult to reproduce. For years, the identification of viral particles in vomit and/or stool samples by electron microscopy has been among the methods of choice for the diagnosis of norovirus related infections. Yet, electron microscopy often lacks sufficient sensitivity – the limit of resolution of this technique is approximately 10^6 norovirus particles per gram of stools (Atmar and Estes 2001; Kapikian et al. 1996). Sensitivity can be increased 10-100 fold through the use of immune electron microscopy (Rabenau et al. 2003). In addition, enzyme immunoassays are available for the identification of certain *Calicivirus* strains. These assays, however, are unable to identify the majority of strains implicated in episodes of norovirus gastroenteritis (Jiang et al. 1995).

The identification of the genetic structure of norovirus and the complete genomic sequencing of the Norwalk prototype in the 1990s (Xi et al. 1990), allowed the development of rapid molecular diagnostic systems – specifically tests based on the amplification of fragments of viral genome by Reverse Transcription PCR (RT-PCR) (De Leon et al. 1992). This stimulated both virological and epidemiological norovirus researches. Several assays have since been designed and optimized to identify a wide spectrum of norovirus genotypes, especially in genes which code for non-structural proteins (Fankhauser et al. 1998; Green et al. 1993). Currently, RT-PCR is commonly used for both diagnostic and research purposes, in clinical and environmental samples, as well as in food matrices (Dreier et al. 2006; La Rosa et al. 2007; Le Guyader et al. 2006; Medici et al. 2005; Wolf et al. 2007). In addition, the sequencing of amplified PCR products provides more precise information regarding genotypes of the virus, thus facilitating the identification of new variants in epidemiological studies.

CONTROL AND PREVENTION

There are no specific prophylactic methods for the control of norovirus gastroenteritis. Therapy is symptomatic, based on the oral administration of liquids and electrolytes. No vaccines exist, although some immunogenic strains are currently being experimented (LoBue et al. 2006). The spread of the virus may be limited through the adoption of appropriate hygienic measures (frequent, proper handwashing; special attention in the handling of food and water). This is especially relevant to workers involved in the preparation and distribution of food. Cooking foods and boiling water inactivate the virus.

EPIDEMIOLOGY

Noroviruses have a worldwide distribution. In industrialized countries these viruses are the major cause of gastroenteritis outbreaks, and play an important role in sporadic gastroenteritis as well (Atmar and Estes 2006; Blanton et al. 2006; Fankhauser et al. 2002; Koopmans and Duizer 2004). These viral agents have been estimated to be the main cause of nonbacterial gastroenteritis worldwide, for all age groups (Fankhauser et al. 2002). According to the American Center for Disease Control and Prevention, norovirus accounts for 23 million cases of acute gastroenteritis a year (Mead et al. 1999). In Europe, too, noroviruses are deemed the most important infectious agents of nonbacterial gastroenteritis. European surveillance systems attribute about 50% of gastroenteritis reported in England and Wales to norovirus (Dedman et al. 1998; Lopman et al. 2003). Data from Finland (Lew et al. 1994), Sweden (Hedlund et al. 2000), the Netherlands (Koopmans et al. 2000) and Germany (Schreier et al. 2000) are similar. Recent Eurosurveillance data show a rise in the number of cases of norovirus gastroenteritis in Germany, United Kingdom, Denmark and other European countries (Kroneman et al. 2006). The rise is attributable to improved detection techniques, as well as to an increased awareness to this pathogen, leading to the establishment of new surveillance systems in various countries. Parallel to a rise in the number of gastroenteritis cases reported, a new variant of the virus (GII-4) emerged in nine European countries (Kirkwood 2004; Lopman et al. 2003, 2004). The detection of this variant seems to have preceded a number of outbreaks which were atypical, in that they occurred in spring rather than in autumn or winter (due to its tendency to strike during the colder months of the year, norovirus gastroenteritis is also called “winter vomiting disease”). New variants have recently emerged in various European countries as well as in other parts of the world (Bull et al. 2006; Gallimore et al. 2007; Ho et al. 2007; Kearney et al. 2007; Kroneman et al. 2006; Leuenberger et al. 2007; Nguyen et al. 2007), replacing common existing genotypes. Genogroup II plays more important role causing norovirus gastroenteritis than genogroup I (Bon et al. 1999; Foley et al. 2000; Froggatt et al. 2004; Gallimore et al. 2004; Kirkwood et al. 2005; Martinez et al. 2002; Nakata et al. 2000; Subekti et al. 2002; Traore et al. 2000). Higher fecal viral concentrations in patients infected with norovirus GII, as compared to those infected with GI (Chen et al. 2006), may point to a higher transmissibility of GII strains.

Italy does not have a surveillance system in place for nonbacterial gastroenteritis, making difficult to assess the impact of norovirus on the population. Clinical and epidemiological studies on these pathogens and on episodes of gastroenteritis are rather limited (Caracciolo et al. 2007; La Rosa et al. 2007; Medici et al. 2005; Pelosi et al. 1999; Ramirez et al. 2006). Equally, if not more limited, is the information regarding the distribution of the virus in the environment in general, and its spread through sewage treatment systems, surface waters, and water destined for recreation and human consumption in particular (La Rosa et al. 2007).

WATERBORNE OUTBREAKS

The presence of viral pathogens in water environments is considered as an emerging problem in the evaluation of biological risk. Noroviruses are currently considered as important outbreak-causing waterborne pathogens. Since infected individuals excrete millions of viral particles in feces, these viruses are likely to be found in great numbers not only in raw sewage but also in treated waters, recreational waters and water destined for human consumption. In most countries, systematic virologic research on environmental samples is lacking and the occurrence of waterborne outbreaks is often underestimated.

Reviews on waterborne outbreaks caused by norovirus have already been published (Maunula 2007; Maunula et al. 2005); very recently the number of reports about waterborne norovirus gastroenteritis has multiplied and this paper presents an update of the literature about recreational and drinking waters as sources of norovirus outbreaks.

Forty-four occurrences of waterborne outbreaks due to norovirus (as the only etiological agent or together with other enteric viruses), associated either with the direct consumption of water (and/or ice) or with water-related recreational activities, are described in the literature. These waterborne outbreaks, summarized in Table 1, took place in various parts of the world, between 1977 and 2007. For each outbreak, the table presents the bibliographic reference, the time and place of occurrence, the probable source of contamination, and – where water samples were tested – the genetic types identified.

In some of the outbreaks, the same norovirus genotype was found both in samples taken from patients and in water samples. The investigation carried out by Beller and co-authors (Beller et al. 1997) was the first to establish a clear link between a waterborne norovirus outbreak (caused by a GII-4 strain) and its source, by comparing norovirus genotypes in stool samples taken from patients and in water samples. Similar investigations were subsequently carried out for other outbreaks (Anderson et al. 2003; Hewitt et al. 2007; Kim et al. 2005; Maunula et al. 2004, 2005; Martinelli et al. 2007; Nygard et al. 2003; Parshionikar et al. 2003). For other outbreaks, the link to the water as the probable source of contamination was based exclusively on epidemiological evidence. In some cases, following massive viral contamination from sewage, the water matrix contained – in addition to the genotype causing gastroenteritis – other genogroups and genotypes, attesting to a substantial spread of the pathogen in the environment.

Interestingly, it appears that although most norovirus outbreaks were associated with the direct consumption of contaminated water, many were instead linked to recreational activities in water. The first documented case occurred in June 1977 in a swimming pool used by students and teachers of an elementary school in Ohio (Kappus et al. 1982). Norwalk virus was detected in the water and in more than 100 students presenting symptoms characteristic for norovirus gastroenteritis (vomiting and abdominal cramps). Other waterborne outbreaks linked to recreational activities were later described, linked to swimming in pools (CDC 2004; Maunula et al. 2004) or lakes (Sartorius et al. 2007), canoeing (Gray et al. 1997) or playing in a fountain (Hoebe et al. 2004).

Table 1. Waterborne norovirus outbreaks.

Reference	Year	Country	Probable source of contamination	Results of norovirus testing and genotyping in water samples*
Kappus et al. 1982	1977	USA	swimming in a pool	ND
Taylor et al. 1981	1978	USA	consumption of water	NT
Baron et al. 1982	1979	USA	recreational activity (swimming in a lake)	NT
Cannon et al. 1991	1987	USA	consumption of ice	NT
Kaplan et al. 1982	1980	USA	consumption of water	NT
Lawson et al. 1991	1989	USA	consumption of water	NT
McAnulty et al. 1993	1989	Australia	consumption of water (river)	ND
Khan et al. 1994	1993	Hawaii	consumption of ice	NT
Brugha et al. 1999	1994	UK	consumption of water	NT
Gray et al. 1997	1994	UK	recreational activity (canoeing)	NT
Kukkula et al. 1997	1994	Finland	consumption of water	NT
Beller et al. 1997	1995	USA	consumption of water (well)	GII-4

* ND = positive sample, norovirus genotype not determined; NT = water not tested for norovirus

Table 1. Continuation.

Reference	Year	Country	Probable source of contamination	Results of norovirus testing and genotyping in water samples*
Brieseman et al. 2000	1996	New Zealand	consumption of water	NT
Brown et al. 2001	1998	Bermuda	consumption of water	GII-2
Hafliger et al. 2000	1998	Switzerland	consumption of water	GI-2
Kukkula et al. 1999	1998	Finland	consumption of water	GII-4
Maurer and Sturchler 2000	1998	Switzerland	consumption of water	ND
Maunula et al. 2005 (9 different outbreaks)	1998-2003	Finland	consumption of water	GI-3, G1-6, GII-4, GII-NA, GII-1
Schvoerer et al. 1999	1999	France	consumption of water	GII
Boccia et al. 2002	2000	Italy	consumption of water	NT
Gallay et al. 2006	2000	France	consumption of water	NT
Kuusi et al. 2004	2000	Finland	consumption of water	Negative
Anderson et al. 2003	2001	USA	consumption of water	GII
Maunula et al. 2004	2001	Finland	swimming in a pool	GII-4
Parshionikar et al. 2003	2001	USA	consumption of water and/or ice	GI-3
Nygaard et al. 2003	2002	Sweden	consumption of water	GIIb
Almagro-Nieves et al. 2006	2002	Spain	consumption of water	ND
Carrique-Mas et al. 2003	2002	Sweden	consumption of water	Negative
Hoebe et al. 2004	2002	Netherlands	recreation (playing in a fountain)	GI-3
Nygaard et al. 2004	2002	Norway	consumption of water; use of showers	Negative
CDC 2004	2004	USA	swimming in a pool	NT
Kim et al. 2005	2004	Korea	consumption of water	GI-3, GI-1, GII-3, GII-6
O'Reilly et al. 2007	2004	USA	consumption of water	Negative
Podewils et al. 2007	2004	USA	swimming in a pool	NT
Sartorius et al. 2007	2004	Sweden	swimming in a lake	NT
Tokutake et al. 2006	2004	Japan	consumption of water	GII
Godoy et al. 2006	2005	Spain	consumption of water	NT
Papadopoulos et al. 2006	2005	Greece	consumption of water	NT
Rizzo et al. 2007	2005	Italy	consumption of ice (plus other foods)	NT
Schmid et al. 2005	2005	Austria	consumption of water	NT
CDC 2007	2006	USA	consumption of water	Negative
Hewitt et al. 2007	2006	New Zealand	drinking water supply	GI-5
Martinelli et al. 2007	2006	Italy	consumption of water	GGII.4

* ND = positive sample, norovirus genotype not determined; NT = water not tested for norovirus

The frequency of these norovirus outbreaks underscores the need for a careful assessment of the presence of this pathogen in recreational waters. The development of recreational water quality monitoring techniques is of utmost importance for safeguarding the health of the population. Rising awareness of food-related and environmental risks has stimulated research into the virological testing of potentially contaminated matrices. Yet, environmental matrices present far greater diagnostic difficulties than clinical samples, due both to the low concentration of the virus in such matrices, and to the lack of appropriate culture methods for its routine biological amplification. A number of systems have been developed for the concentration of norovirus from food and water samples, and molecular diagnostic systems have been designed to identify target sequences of the viral genome through amplification techniques (RT/PCR) (Dreier et al. 2006; La Rosa et al. 2007; Le Guyader et al. 2006; Medici et al. 2005; Wolf et al. 2007). Real-time PCR represents the latest innovation in the detection and quantification of DNA and RNA. This technique is highly sensitive, specific and versatile, and yields more accurate results than traditional end-point PCR. Recently, it has been successfully used to determine and quantify norovirus in both clinical and environmental samples (Wolf et al. 2007). The availability of quantitative as well as qualitative (presence/absence) data in different matrices is crucial for a good risk assessment, especially for pathogens that are difficult or impossible to grow in cell culture. The molecular approach is thus destined to become an integral part of the epidemiological surveillance of waterborne and foodborne diseases, with the aim of identifying sources of infection and elaboration of effective preventive strategies.

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