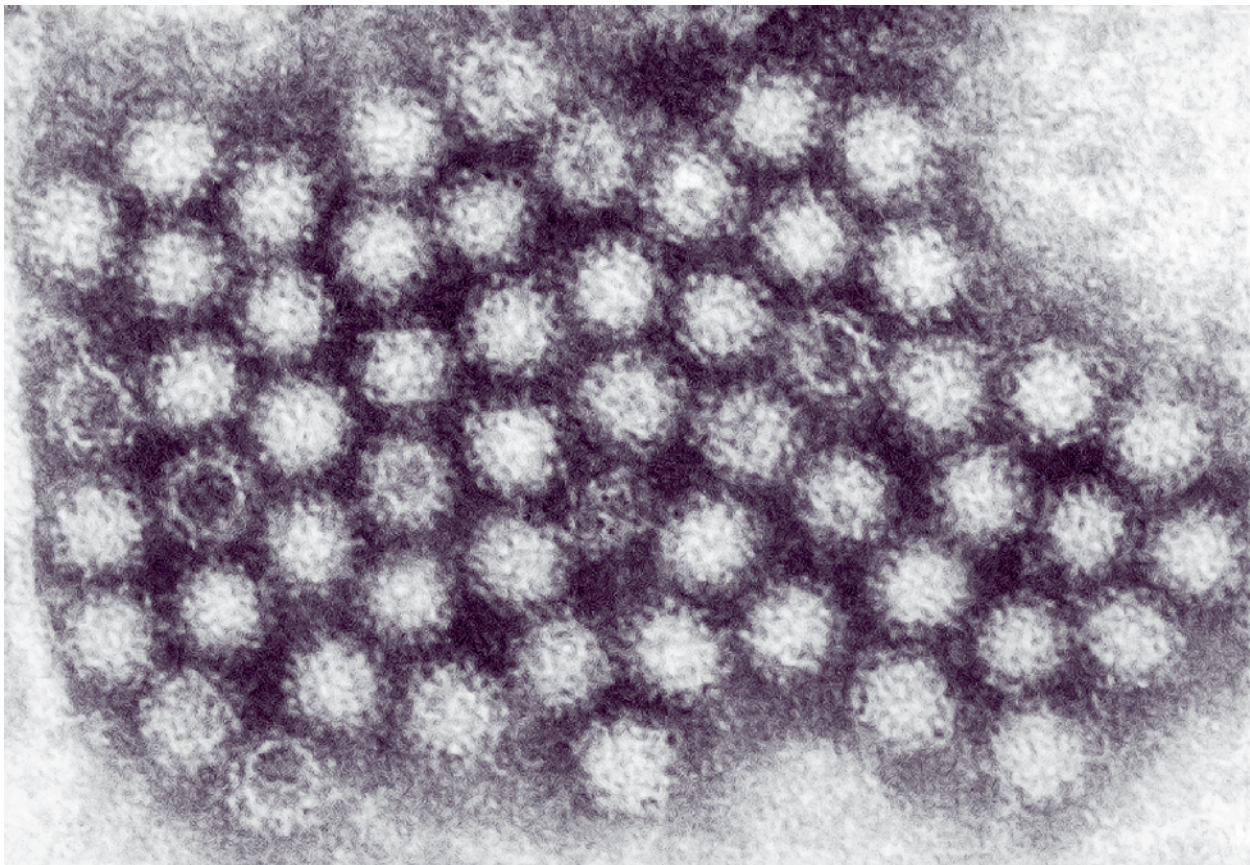


Updated Norovirus Outbreak Management and Disease Prevention Guidelines



Continuing Education Examination available at <http://www.cdc.gov/mmwr/cme/conted.html>



U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

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On the cover: Transmission electron micrograph of norovirus particles (Courtesy: Charles D. Humphrey, PhD, CDC).

The *MMWR* series of publications is published by the Office of Surveillance, Epidemiology, and Laboratory Services, Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services, Atlanta, GA 30333.

Suggested Citation: Centers for Disease Control and Prevention. [Title]. *MMWR* 2011;60(No. RR-#):[inclusive page numbers].

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Updated Norovirus Outbreak Management and Disease Prevention Guidelines

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Summary

Noroviruses are the most common cause of epidemic gastroenteritis, responsible for at least 50% of all gastroenteritis outbreaks worldwide, and a major cause of foodborne illness. In the United States, approximately 21 million illnesses attributable to norovirus are estimated to occur annually. Since 2001, when the most recent norovirus recommendations were published (CDC. “Norwalk-like viruses.” Public health consequences and outbreak management. MMWR 2001;50[No. RR-9]), substantial advances have been made in norovirus epidemiology, immunology, diagnostic methods, and infection control. As molecular diagnostic techniques have improved in performance and become more widely available, detection and reporting of norovirus outbreaks have increased. Although the inability to culture human noroviruses in vitro has hampered progress, assessment of the performance of disinfectants has been facilitated by the discovery of new, cultivable surrogates for human noroviruses. In addition, the periodic emergence of epidemic strains (from genogroup II type 4, GII.4) and outbreaks in specific populations (e.g., the elderly in nursing homes) have been characterized. This report reviews these recent advances and provides guidelines for outbreak management and disease prevention. These recommendations are intended for use by public health professionals investigating outbreaks of acute gastroenteritis, including state and local health authorities, as well as academic and research institutions.

Introduction

The prototype norovirus was first identified as the cause of a gastroenteritis outbreak in Norwalk, Ohio, in 1968 (1). However, the epidemiology of noroviruses remained poorly characterized until relatively recently because of the lack of widespread availability of sensitive diagnostic methods. Electron microscopy was the first tool used for identifying noroviruses but proved to be a time-consuming and insensitive method that was rarely available outside of research settings. Immunologic assays developed during the late 1970s and 1980s improved detection rates (2) but lacked broad reactivity to detect the full spectrum of noroviruses and were not widely available, limiting their utility for routine use

in outbreak investigations. Consequently, the cause of the majority of gastroenteritis outbreaks could not be determined. Because of these limitations of laboratory diagnostics, clinical and epidemiologic criteria were developed to help attribute gastroenteritis outbreaks to norovirus (3). These criteria have subsequently been validated as highly sensitive (99%) and moderately specific (68%) (4). Since the 1990s, the development and subsequent widespread use of molecular diagnostic assays have led to substantial improvements in understanding the role of noroviruses in gastroenteritis outbreaks (5), particularly among those involving foodborne transmission and those occurring in long-term-care facilities (6,7). Nonetheless, progress in the characterization and control of norovirus has been hampered by the lack of a rapid and sensitive assay for use in clinical settings and the inability to cultivate human noroviruses in cell culture.

Since 2001, when CDC published the most recent norovirus recommendations (8), substantial advances have been made in norovirus epidemiology, immunology, diagnostic methods, and infection control. This report reviews these advances and provides guidelines for outbreak management and disease prevention. Specific recommendations include standardized

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collection of clinical specimens during norovirus outbreaks, use of two recently launched surveillance systems for reporting of norovirus outbreaks, and use of appropriate control measures focusing on hand hygiene, environmental disinfection, and exclusion of ill persons (Box). Their implementation by public health professionals is intended to guide efficient use of public health resources for effective prevention and control of norovirus disease.

Methods

These guidelines were developed by CDC subject matter experts based on a critical review of published literature and unpublished data from outbreak investigations. In June 2010, a preliminary version of these guidelines was presented at the Council of State and Territorial Epidemiologists annual conference to solicit input from state and local public health partners. A draft report was subsequently shared for comment with representatives from five state or local health departments and the U.S. Food and Drug Administration (FDA). These

recommendations complement the CDC Healthcare Infection Control Practices Advisory Committee (HICPAC) guideline for the prevention and control of norovirus gastroenteritis outbreaks in health-care settings (9), the model FDA Food Code for retail food and institutional foodservice settings (10), and other applicable state or local regulatory guidance, by providing general principles advisable across all outbreak settings.

Biology and Epidemiology

The Virus

Noroviruses are a group of nonenveloped, single-stranded RNA viruses classified into the genus *Norovirus* (previously referred to as Norwalk-like viruses [NLVs] or small round-structured viruses [SRSVs]) of the family *Caliciviridae*. Other genera within the *Caliciviridae* family include *Sapovirus* (previously referred to as Sapporo-like viruses [SLVs]), which also cause acute gastroenteritis (AGE) in persons, as well as *Lagovirus*, *Vesivirus*, and *Nebovirus*, which are not pathogenic

BOX. Key points for investigation and response to norovirus outbreaks

- Initiate investigations promptly, including collection of clinical and epidemiologic information, to help identify predominant mode of transmission and possible source.
- Promote good hand hygiene, including frequent washing with soap and running water for a minimum of 20 seconds. If available, alcohol-based hand sanitizers ($\geq 70\%$ ethanol) can be used as an adjunct in between proper handwashings but should not be considered a substitute for soap and water handwashing.
- Exclude ill staff in certain positions (e.g., food, child-care, and patient-care workers) until 48–72 hours after symptom resolution. In closed or institutional settings (e.g., long-term-care facilities, hospitals, and cruise ships), isolate ill residents, patients, and passengers until 24–48 hours after symptom resolution. In licensed food establishments, approval from the local regulatory authority might be necessary before reinstating a food employee following a required exclusion.
- Reinforce effective preventive controls and employee practices (e.g., elimination of bare-hand contact with ready-to-eat foods and proper cleaning and sanitizing of equipment and surfaces).
- After initial cleaning to remove soiling, disinfect potentially contaminated environmental surfaces using a chlorine bleach solution with a concentration of 1,000–5,000 ppm (1:50–1:10 dilution of household bleach [5.25%]) or other Environmental Protection Agency (EPA)–approved disinfectant.* In health-care settings, cleaning products and disinfectants used should be EPA-registered and have label claims for use in health care; personnel performing environmental services should adhere to the manufacturer's instructions for dilution, application, and contact time.
- Collect whole stool specimens from at least five persons during the acute phase of illness (≤ 72 hours from onset) for diagnosis by TaqMan-based real-time reverse transcription-PCR (RT-qPCR), perform genotyping on norovirus-positive stool specimens, and report results to CDC via CaliciNet (CDC's electronic norovirus outbreak surveillance network).
- Report all outbreaks of acute gastroenteritis to state and local health departments, in accordance with local regulations, and to CDC via the National Outbreak Reporting System (NORS).

* Agents registered as effective against norovirus by EPA are available at http://www.epa.gov/oppad001/list_g_norovirus.pdf. Evidence for efficacy against norovirus usually is based on studies using feline calicivirus (FCV) as a surrogate. However, FCV and norovirus exhibit different physicochemical properties, and whether inactivation of FCV reflects efficacy against norovirus is unclear.

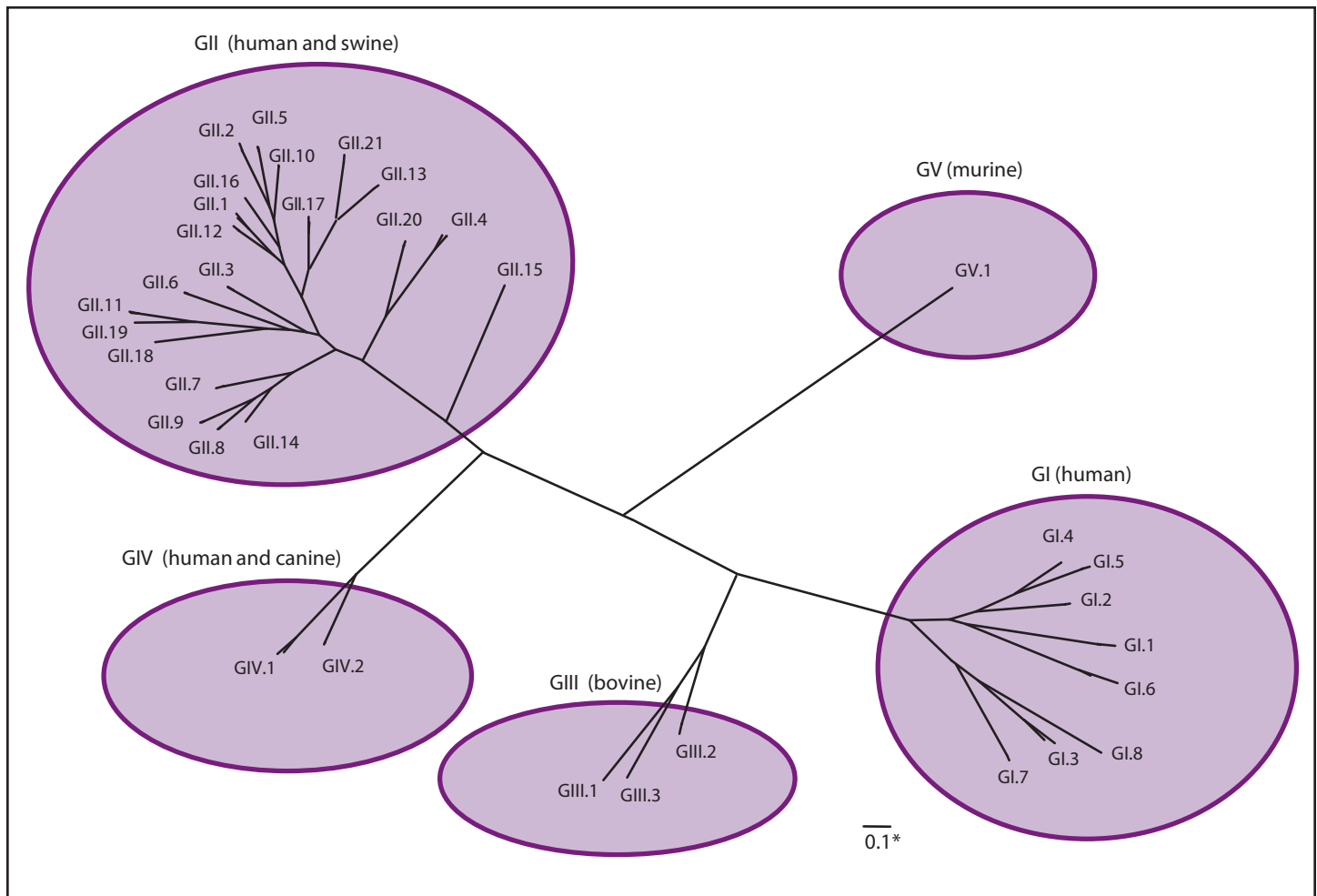
for humans (11). Noroviruses can be divided into at least five genogroups, designated GI–GV, based on amino acid identity in the major structural protein (VP1) (12). The strains that infect humans (referred to collectively as “human noroviruses”) are found in GI, GII, and GIV, whereas the strains infecting cows and mice are found in GIII and GV, respectively (Figure 1). Although interspecies transmission of noroviruses has not been documented, strains that infect pigs are found in GII (13), and a GIV norovirus was discovered recently as a cause of diarrhea in dogs (14), suggesting the potential for zoonotic transmission. On the basis of >85% sequence similarity in the complete VP1 genome, noroviruses can be classified further into genotypes, with at least eight genotypes belonging to GI and 21 genotypes belonging to GII (12,13; CDC, unpublished data, 2011). Since 2001, GII.4 viruses

have been associated with the majority of viral gastroenteritis outbreaks worldwide (15). Recent studies have demonstrated that these viruses evolve over time through serial changes in the VP1 sequence, which allow evasion of immunity in the human population (15,16).

Clinical Features

Noroviruses cause acute gastroenteritis in persons of all ages. The illness typically begins after an incubation period of 12–48 hours and is characterized by acute onset, nonbloody diarrhea, vomiting, nausea, and abdominal cramps. Some persons might experience only vomiting or diarrhea. Low-grade fever and body aches also might be associated with infection, and thus the term “stomach flu” often is used to describe the

FIGURE 1. Classification of noroviruses into 5 genogroups (GI–V) and 35 genotypes based on sequence diversity in the complete capsid protein VP1 (human strains cluster within GI, GII, and GIV)



Sources: Data from Zheng DP, Ando T, Fankhauser RL, Beard RS, Glass RI, Monroe SS. Norovirus classification and proposed strain nomenclature. *Virology* 2006;346:312–23; Wang QH, Han MG, Cheetham S, Souza M, Funk JA, Saif LJ. Porcine noroviruses related to human noroviruses. *Emerg Infect Dis* 2005;11:1874–81; CDC, unpublished data, 2011; graphic developed by Everardo Vega, PhD, CDC.

*The scale bar of 0.1 reflects the number of amino acid substitutions per site.

illness, although there is no biologic association with influenza. Although symptoms might be severe, they typically resolve without treatment after 1–3 days in otherwise healthy persons. However, more prolonged courses of illness lasting 4–6 days can occur, particularly among young children, elderly persons, and hospitalized patients (17,18). Approximately 10% of persons with norovirus gastroenteritis seek medical attention, which might include hospitalization and treatment for dehydration with oral or intravenous fluid therapy (7,19,20). Norovirus-associated deaths have been reported among elderly persons and in the context of outbreaks in long-term-care facilities (21,22). Necrotizing enterocolitis in neonates, chronic diarrhea in immunosuppressed patients, and postinfectious irritable bowel syndrome also have been reported in association with norovirus infection (23–25); however, more data from analytic studies are needed to confirm a causal link with these conditions.

Norovirus is shed primarily in the stool but also can be found in the vomitus of infected persons, although it is unclear if detection of virus alone indicates a risk for transmission. The virus can be detected in stool for an average of 4 weeks following infection, although peak viral shedding occurs 2–5 days after infection, with a viral load of approximately 100 billion viral copies per gram of feces (26). However, given the lack of a cell culture system or small animal model for human norovirus, whether these viruses represent infectious virus is unknown, and therefore the time after illness at which an infected person is no longer contagious also is unknown. Furthermore, up to 30% of norovirus infections are asymptomatic, and asymptomatic persons can shed virus, albeit at lower titers than symptomatic persons (26–28). The role of asymptomatic infection in transmission and outbreaks of norovirus remains unclear.

Immunity

Protective immunity to norovirus is complex and incompletely understood. In human challenge studies, infected volunteers were susceptible to reinfection with the same strain as well as to infection with heterologous strains (29–32). In addition, those with preexisting antibodies were not protected from infection unless repeated exposure to the same strain occurred within a short period. Two of these studies demonstrated that homologous antibody protection might last anywhere from 8 weeks to 6 months (30,31). However, the infectious dose of virus given to volunteers in these challenge studies was several-fold greater than the dose of virus capable of causing human illness, and thus immunity to a lower natural challenge dose might be greater and more cross-protective.

Because preexisting antibodies among challenged volunteers did not necessarily convey immunity, and some persons seemed

to remain uninfected despite significant exposure, both innate host factors and acquired immunity have been hypothesized to contribute to the susceptibility to infection (31). Histo-blood group antigens (HBGAs), including H type, ABO blood group, and Lewis antigens have been proposed as candidate receptors for norovirus. Expression of HBGAs is associated with strain-specific susceptibility to norovirus infection (17,33–38). Resistance to norovirus infections has been associated with mutations in the 1,2-fucosyltransferase (FUT2) gene leading to a lack of expression of HBGAs on the surface of intestinal cells (33–35,39). Thus, persons who have the normal FUT2 gene and who express these antigens are termed “secretors” whereas mutations in the FUT2 gene leading to the absence of HBGA expression result in “nonsecretor” persons who are less susceptible to infection. However, secretor status does not completely explain the differences seen among infected and uninfected persons for all strains of norovirus. Thus, additional mechanisms of immunity are likely involved, and this remains an ongoing field of research. In addition, evidence suggests that new GII.4 variants evolve to escape the build-up of acquired immunity and innate resistance in the human population (16,40).

Transmission

Norovirus is extremely contagious, with an estimated infectious dose as low as 18 viral particles (41), suggesting that approximately 5 billion infectious doses might be contained in each gram of feces during peak shedding. Humans are the only known reservoir for human norovirus infections, and transmission occurs by three general routes: person-to-person, foodborne, and waterborne. Person-to-person transmission might occur directly through the fecal-oral route, by ingestion of aerosolized vomitus, or by indirect exposure via fomites or contaminated environmental surfaces. Foodborne transmission typically occurs by contamination from infected food handlers during preparation and service but might also occur further upstream in the food distribution system through contamination with human waste, which has been demonstrated most notably by outbreaks involving raspberries and oysters as vehicles (42–46). A recent outbreak involving consumption of delicatessen meat also demonstrated the potential for norovirus contamination during processing (47). Finally, recreational and drinking water can serve as vehicles of norovirus transmission and result in large community outbreaks (48,49). These outbreaks often involve well water that becomes contaminated from septic tank leakage or sewage (50) or from breakdowns in chlorination of municipal systems (51).

Sporadic Disease

As diagnostic methods have improved and become more widely available, the role of noroviruses as the leading cause of sporadic gastroenteritis in all age groups has become clear. Approximately 21 million illnesses caused by norovirus are estimated to occur each year in the United States, approximately one quarter of which can be attributed to foodborne transmission (52). A recent systematic review of 31 community, outpatient, and hospital-based studies in both developed and developing countries estimated that noroviruses accounted for 10%–15% of severe gastroenteritis cases in children aged <5 years and for 9%–15% of mild and moderate diarrhea cases among persons of all ages (53). Although laboratory-based data on endemic norovirus disease in the United States are sparse, recent studies suggest that norovirus is the leading cause of acute gastroenteritis in the community and among persons seeking care in outpatient clinics or emergency departments across all age groups (54,55; CDC, unpublished data, 2011).

Serosurveys have demonstrated that norovirus infections are prevalent throughout the world, with initial exposure typically occurring early in life (5). In population-based studies from Australia, England, Hong Kong, and the Netherlands, norovirus infection has accounted for 9%–24% of gastroenteritis cases (19,20,56–58). In these studies, infection was more frequent in certain age groups (e.g., children aged <5 years and adults aged >65 years). In studies that have used sensitive molecular assays, a relatively high prevalence of norovirus-positive samples in asymptomatic persons has been detected, ranging from 5% in the Netherlands to 16% in England (20,56). This background rate of asymptomatic infection, coupled with innate resistance attributable to secretor status and acquired immunity, helps explain why attack rates rarely exceed 50% in outbreaks.

Outbreaks

Noroviruses are the predominant cause of gastroenteritis outbreaks worldwide. Data from the United States and European countries have demonstrated that norovirus is responsible for approximately 50% of all reported gastroenteritis outbreaks (range: 36%–59%) (5). Outbreaks occur throughout the year although there is a seasonal pattern of increased activity during the winter months. In addition, periodic increases in norovirus outbreaks tend to occur in association with the emergence of new GII.4 strains that evade population immunity (Table) (40,59). These emergent GII.4 strains rapidly replace existing strains predominating in circulation and can sometimes cause seasons with unusually high norovirus activity, as in 2002–2003 and 2006–2007. Because the virus can be transmitted by food, water, and contaminated environmental surfaces as well as directly from person to person, and because there is no long

lasting immunity to norovirus, outbreaks can occur in a variety of institutional settings (e.g., nursing homes, hospitals, and schools) and affect people of all ages. Whereas prior national estimates of outbreak attribution by mode of transmission were likely biased toward foodborne disease (60,61), more recent data from individual states indicate that the majority of norovirus outbreaks primarily involve person-to-person transmission (62,63). Multiple routes of transmission can occur within an outbreak; for example, point-source outbreaks from a food exposure often result in secondary person-to-person spread within an institution or community. Of the 660 norovirus outbreaks laboratory confirmed by CDC during 1994–2006 that indicated the setting, 234 (35.4%) were from long-term-care facilities (e.g., nursing homes); 205 (31.1%) were from restaurants, parties, and events; 135 (20.5%) were from vacation settings (including cruise ships); and 86 (13.0%) were from schools and communities (59). Although GII.4 variants predominate overall, the role of GI and other GII genotypes appears to be greater in settings that involve foodborne or waterborne transmission (Figure 2).

Long-Term Care and Other Health-Care Facilities

Health-care facilities including nursing homes and hospitals are the most commonly reported settings of norovirus outbreaks in the United States and other industrialized countries (59,60,63–65). Virus can be introduced from the community into health-care facilities by staff, visitors, and patients who might either be incubating or infected with norovirus upon admission or by contaminated food products. Outbreaks in these settings can be prolonged, sometimes lasting months (66). Illness can be more severe in hospitalized patients than for otherwise healthy persons (18), and associated deaths have been reported (21,22). Strict control measures (including isolation or cohorting of symptomatic patients, exclusion of affected staff, and restricting new admissions into affected units) are disruptive and costly but might be required to curtail outbreaks (9,67,68).

Restaurants and Catered Events

Norovirus is now recognized as the leading cause of foodborne disease outbreaks in the United States. Norovirus accounted for 822 (35%) of the 2,367 foodborne disease outbreaks reported to CDC during 2006–2007 (Figure 3) and half of the 1,641 foodborne disease outbreaks with a confirmed or suspected etiology (69,70). Food can become contaminated with norovirus at any point during production, processing, distribution, and preparation. Thus, a variety of products have been implicated in outbreak investigations; foods eaten raw (e.g., leafy vegetables, fruits, and shellfish) are identified most commonly (69,70). Handling of ready-to-eat foods by

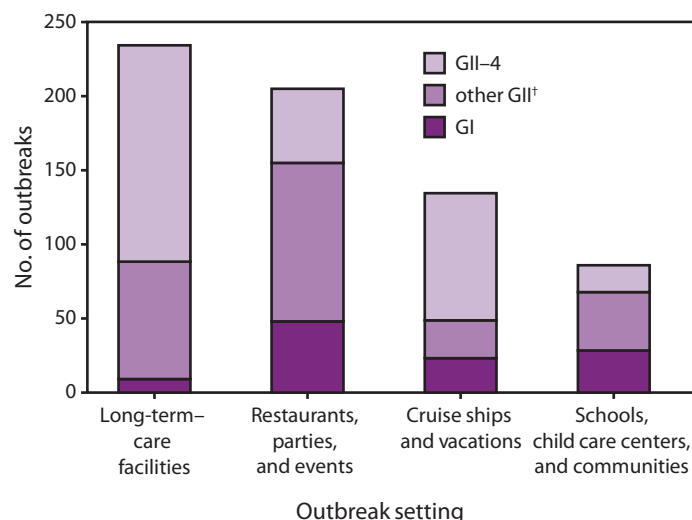
TABLE. Emergent norovirus variants of genogroup II type 4 (GII.4), including those associated with epidemic winter seasons of increased outbreaks — United States

Emergent GI.4 variant	Yrs of circulation	Epidemic Season	Other name(s)
95/96-US	1995–2002	1995–1996	Grimsby
Farmington Hills	2002–2005	2002–2003	2002 variant
Hunter	2003–2006	None	2004 variant
Yerseke	2006–2008	2006–2007	Laurens, Nijmegen, 2006a variant
Den Haag	2006–present	2006–2007	Minerva, 2006b variant
New Orleans	2009–present	None*	

Sources: Zheng DP, Widdowson MA, Glass RI, Vinje J. Molecular epidemiology of genogroup II-genotype 4 noroviruses in the United States between 1994 and 2006; J Clin Microbiol 2010;48:168–77; CDC, unpublished data, 2010.

*On the basis of data available as of September 2010, the New Orleans GI.4 variant has not been associated with an increased number of norovirus outbreaks in the United States.

FIGURE 2. Number* of norovirus outbreaks laboratory-confirmed by CDC, by setting and genotype — United States, 1994–2006



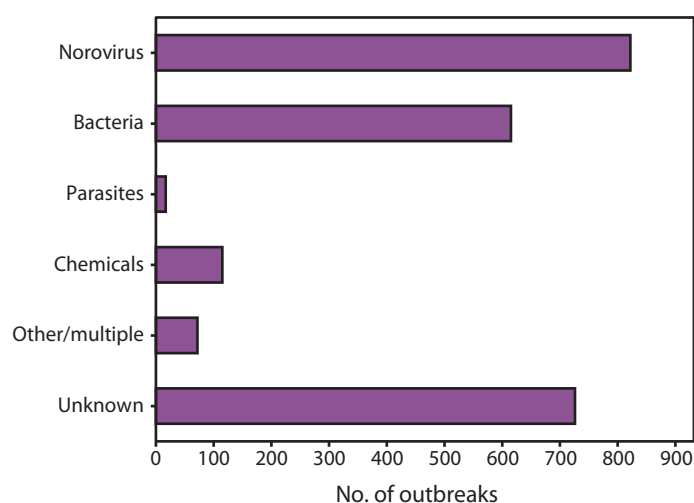
Source: Zheng DP, Widdowson MA, Glass RI, Vinje J. Molecular epidemiology of genogroup II-genotype 4 noroviruses in the United States between 1994 and 2006. J Clin Microbiol 2010;48:168–77.

*N = 660.

† Includes all other genotypes within genogroup II except genogroup II type 4 (GI.4).

infected food employees is commonly identified as a contributing factor in outbreaks of foodborne norovirus associated with food-service establishments (71,72). Norovirus outbreaks also have resulted from fecal contamination of certain food products at the source. For example, oysters harvested from fecally contaminated growing waters and raspberries irrigated with sewage-contaminated water have been implicated in outbreaks (44,73). Because gross sewage contamination will contain a collection of viruses circulating in the community, multiple norovirus genotypes often are detected in such outbreaks. Contamination with norovirus also can occur during processing, as demonstrated by a recent outbreak involving delicatessen meat (47). Only a small dose of virus is needed to cause infection, and thus infected food handlers can contaminate large quantities of product. For example, approximately 500 cases of gastroenteritis were reported during a 2006 outbreak

FIGURE 3. Number* of foodborne disease outbreaks reported to CDC, by etiology — United States, 2006–2007



Sources: CDC. Surveillance for foodborne disease outbreaks—United States, 2006. MMWR 2009;58:609–5; CDC. Surveillance for foodborne disease outbreaks—United States, 2007. MMWR 2010;59:973–9.

*No. = 2,367.

caused by a foodhandler who vomited at work (74). Drinking water or ice also might become contaminated with norovirus and result in outbreaks in food-service settings. Secondary person-to-person transmission is common following point-source food or water exposures.

Schools and Other Institutional Settings

Norovirus outbreaks occur in a range of other institutional settings including schools, child care centers, colleges, prisons, and military encampments. Outbreaks of gastroenteritis in child care centers also are caused by other pathogens, including rotavirus, sapovirus, and astrovirus, as a result of a lack of immunity to these viruses in young populations (75). Outbreaks have been reported recently from multiple universities in different states and have led to campus closures (76). An intervention study in elementary schools demonstrated that improved hand hygiene and surface disinfection can lead to lower rates of

absenteeism caused by nonspecific gastroenteritis and reduced surface contamination with norovirus (77). Norovirus was also the most common cause of gastroenteritis in U.S. marines during Operation Iraqi Freedom (78) and a common cause of outbreaks among deployed British troops (79).

Cruise Ships and Other Transportation Settings

Passengers and crew aboard cruise ships are affected frequently by norovirus outbreaks (80). Virus generally is introduced on board by passengers or crew infected before embarkation but might also result from food items contaminated before loading or persistently contaminated environmental surfaces from previous cruises. Virus also might be acquired when ships dock in countries where sanitation might be inadequate, either through contaminated food or water or passengers becoming infected while docked. Repeated outbreaks can occur in subsequent sailings as a result of environmental persistence or infected crew, particularly if control measures have not been implemented consistently and thoroughly. Genotyping of outbreak strains from repeated outbreaks has demonstrated that this can occur through the introduction of new virus or recrudescence of virus from one sailing to the next (81,82). CDC's Vessel Sanitation Program assists the cruise ship industry in preventing and controlling the introduction and transmission of gastrointestinal illness by inspecting cruise ships, monitoring gastrointestinal illnesses, and responding to outbreaks (<http://www.cdc.gov/nceh/vsp>). Outbreaks also have been reported in association with bus tours and air travel, in which environmental contamination and proximity to ill passengers facilitated norovirus transmission (83,84).

Diagnostic Methods

The majority of clinical virology laboratories perform real-time reverse transcription-polymerase chain reaction (RT-PCR) assays (specifically, TaqMan-based real-time assays) for norovirus detection. These assays have not been cleared by FDA although commercial kits are available in the United States. Positive samples can be typed subsequently by DNA sequencing of conventional RT-PCR products. FDA has recently cleared the RIDASCREEN Norovirus 3rd Generation (r-Biopharm, AG, Darmstadt, Germany) enzyme immunoassay (EIA) for preliminary identification of norovirus as the cause of an AGE outbreak. However, negative EIA results should be confirmed by RT-PCR reference methods.

Real-Time RT-PCR Assays

The ORF1-ORF2 junction region is the most conserved region of the norovirus genome, with a high level of nucleotide

sequence identity across strains within a genogroup (85,86). This feature makes this region ideal for designing broadly reactive primers and probes for TaqMan-based real-time RT-PCR (RT-qPCR) assays (Figure 4). The majority of published assays are derived from the original publication (86), which has been modified into one-step and duplex assays (87,88) for high throughput screening in clinical diagnostic laboratories. In addition to detecting norovirus RNA in clinical samples, relatively small optimizations of the primers and probes have resulted in sensitive assays to detect norovirus RNA in environmental samples (e.g., food and water) (64,89–91). The extreme analytic sensitivity of RT-qPCR permits the detection of very low titers of virus that might be present in samples from persons without disease caused by norovirus (i.e., asymptomatic infection) (28). For this reason, low titer results (i.e., high cycle threshold [CT] values) should be interpreted with caution.

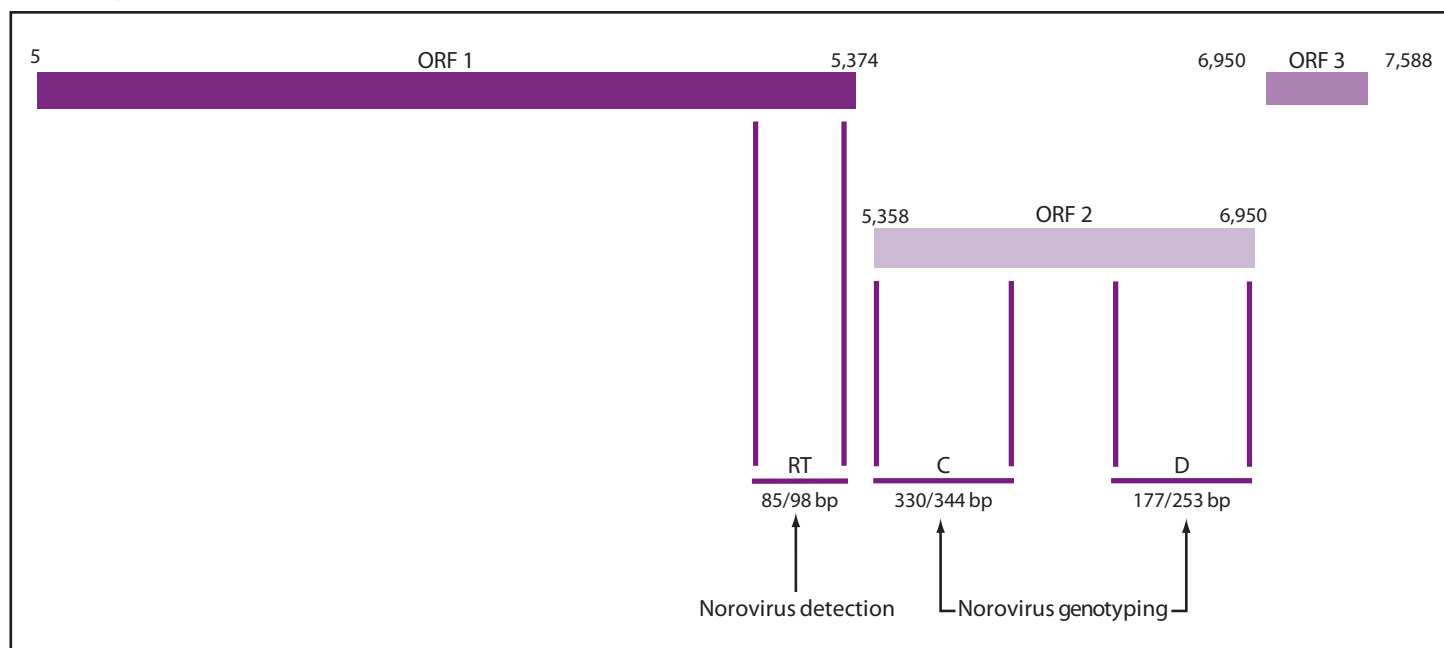
Conventional RT-PCR Assays for Genotyping

Four different regions (designated A–D) of the genome have been used successfully for genotyping of noroviruses (92,93). However, typing based on the capsid gene (region C and region D) allows for better differentiation between strains (Figure 4). Although region C sequences have been used widely for genotyping strains by clinical diagnostic laboratories in the United States, Europe, and Japan, the resolution of this region is not sufficient to distinguish differences between certain GII.4 variants, which are the predominant strains associated with outbreaks (59). The gold standard for genotyping norovirus strains is full capsid sequencing. However, for clinical samples with high copy numbers, amplifying partial capsid sequences is more practical and is only slightly less discriminatory than full capsid sequencing (92). For this reason, laboratories participating in CaliciNet, CDC's electronic norovirus outbreak surveillance network (see Reporting and Assistance), use region D genotyping.

Enzyme Immunoassays

For detection of norovirus antigen in clinical samples, rapid assays (e.g., EIA) offer an attractive alternative to expensive and technically demanding molecular detection assays. However, the development of a broadly reactive EIA for noroviruses has been challenging because of the number of antigenically distinct norovirus strains and the high viral load required for a positive signal by these assays. Commercial kits, including IDEIA Norovirus EIA (Oxoid, Ely, United Kingdom), RRSV (II)-AD (Denka Seiken Co. Ltd., Tokyo, Japan), and RIDASCREEN include pools of cross-reactive monoclonal and

FIGURE 4. Genomic regions targeted by reverse transcription-polymerase chain reaction (RT-PCR) assays used for norovirus detection and genotyping



Abbreviations: ORF = open reading frame; RT = TaqMan real-time RT-PCR region for norovirus detection (87); C = region C for norovirus genotyping (93); D = region D for norovirus genotyping (92); and bp = base pairs.

polyclonal antibodies (94–101). In evaluations, the sensitivity of these kits when compared with RT-PCR has ranged from 36% to 80%, and specificity has ranged from 47% to 100% (94–101). Because of the modest performance of these commercial kits, particularly their poor sensitivity, they are not recommended for clinical diagnosis of norovirus infection in sporadic cases of gastroenteritis. However, given their ease of use and rapid results, EIA kits with high specificity (>85%) and at least moderate sensitivity (>50%) might be useful for preliminary screening of multiple fecal samples associated with an outbreak of acute gastroenteritis. These kits are not widely available in the United States, although the RIDASCREEN Norovirus 3rd Generation EIA has been recently cleared by FDA for preliminary identification of norovirus as the cause of AGE outbreaks. Nonetheless, negative samples will have to be confirmed by a second technique such as RT-qPCR, and therefore EIA kits should not be regarded as a replacement for molecular methods during outbreak investigations.

Specimen Collection

Clinical Specimens

Whole stool specimens should be collected for laboratory diagnosis of norovirus and are preferred over rectal swabs because of the higher quantity of virus present in whole stool. Vomitus also may be collected and tested using molecular assays, although

unlike for stool, the sensitivity of these assays for vomitus is unknown. To aid in interpretation, each specimen should be accompanied with dates of symptom onset and specimen collection. An outbreak of acute gastroenteritis is considered to be laboratory-confirmed as attributable to norovirus if stool or vomitus specimens from two or more ill persons are positive for norovirus by RT-PCR, EIA, or electron microscopy (71).

Stool

Timing. Specimen collection for norovirus testing should begin as early as possible in an epidemiologic investigation. Unnecessary delays while awaiting results from testing for bacterial or parasitic agents could preclude establishment of a viral diagnosis. Ideally, whole stool specimens should be obtained during the acute phase of illness (i.e., within 48–72 hours after onset) while the stools are still liquid or semisolid and viral excretion is at its peak. When this is not possible, specimens collected later in illness or after resolution (i.e., up to 7–10 days after onset) might still provide a diagnosis and an opportunity to confirm norovirus infection in a suspected source case-patient (e.g., a food handler with a recent history of diarrhea). If specimens are collected late in the illness, the utility of viral diagnosis and interpretation of the results should be discussed with laboratory personnel before tests are conducted (see Reporting and Assistance).

Number and quantity. Obtaining a collection of high quality (i.e., sufficient volume collected during acute illness)

diagnostic specimens is crucial for laboratory confirmation. Whole stool specimens from at least five ill persons are recommended. This number should be increased if specimens are taken after the acute phase of illness, in large or protracted outbreaks, or if less sensitive EIA diagnostics are employed. On the basis of test characteristics of commercially available EIAs, six specimens are required to achieve >90% sensitivity in outbreak diagnosis (101,102). Bulk samples (i.e., 10–50 mL of whole stool placed in a stool cup or urine container) are preferred, because rectal swabs are generally insufficient (CDC, unpublished data, 2011).

Storage and transport. Whole stool specimens should be kept refrigerated at 39°F (4°C) if testing occurs within 2–3 weeks. At this temperature, specimens can be stored without compromising diagnostic yield. If the specimens have to be transported to a laboratory for testing, they should be individually bagged and sealed and kept on ice or frozen refrigerant packs in an insulated, waterproof container. If testing is expected to occur >3 weeks after collection or for archiving purposes, stool samples should be frozen at -4°F (-20°C) or -94°F (-70°C). Norovirus RNA can be detected by using molecular assays after at least 5 years when samples are stored under these conditions (59). Although it was previously recommended to avoid freezing stool specimens because of degradation of viral morphology and consequent hampering of diagnosis by electron microscopy (8), this is no longer a concern because of the widespread use of molecular assays.

Vomitus

Specimens of vomitus can be collected to supplement the diagnostic yield from stool specimens during an investigation. Recommendations for collection, storage, and shipment of vomitus specimens are the same as those for stool specimens.

Serum

Serum specimens might be useful in unique circumstances or for special studies but are not recommended for routine diagnostics. If feasible and warranted, acute- and convalescent-phase serum specimens may be obtained to test for a greater-than-fourfold rise in IgG titer to noroviruses. Acute-phase specimens should be obtained during the first 5 days after symptom onset, and the convalescent-phase specimens should be collected during the third to fourth week after resolution of symptoms. Because these assays are not available commercially, CDC may be contacted for further guidance on collection, processing, and storage of serum specimens (see Reporting and Assistance).

Environmental Specimens

Because human noroviruses cannot be grown in cell culture, current detection methods (e.g., RT-qPCR) allow detection of norovirus RNA in water, food, and environmental specimens; however, validated methods are available only for water (at CDC) and shellfish (at FDA's Gulf Coast Seafood Laboratory). If a food or a water source is strongly suspected as the source of an outbreak, a sample should be obtained as early as possible with respect to the time of exposure and preferably stored frozen at -4°F (-20°C), and CDC or FDA should be contacted for further guidance on testing. Detection of norovirus in food requires appropriate elution and concentration techniques which need to be adapted for each food vehicle. At present, these methods are not available routinely, except for shellfish. Water can be tested for noroviruses after concentration of large volumes (e.g., up to 100 L of water) through specially designed filters (103). Environmental surface swabs have also been demonstrated to detect norovirus RNA in specific outbreak settings (104,105). Depending on the specific situation, epidemiologic findings, and expected level of contamination, collection of environmental specimens might be warranted and should be pursued in consultation with CDC. (See Reporting and Assistance).

Prevention and Control

Hand Hygiene

Appropriate hand hygiene is likely the single most important method to prevent norovirus infection and control transmission. Reducing any norovirus present on hands is best accomplished by thorough handwashing with running water and plain or antiseptic soap. Washing with plain soap and water reduces the number of microbes on hands via mechanical removal of loosely adherent microorganisms (106). The efficacy of alcohol-based and other hand sanitizers against norovirus remains controversial with mixed evidence depending on the product formulation and evaluation methodology. In finger pad studies, soap and water used for 20 seconds have been demonstrated to reduce norovirus by 0.7–1.2 log₁₀ by RT-PCR assay, whereas alcohol-based hand sanitizers did not demonstrate any appreciable reduction of viral RNA (107). However, such studies cannot determine whether the residual virus remains viable given the inability to cultivate human norovirus in vitro.

Studies using cultivable surrogate viruses such as murine norovirus (MNV) or feline calicivirus (FCV) have demonstrated that ethanol has superior efficacy against FCV compared with other alcohols (e.g., propanol-1 and propanol-2), and formulations containing 70% ethanol were able to reduce

infectious MNV by $2.5 \log_{10}$ after 30 seconds (108–110). The sensitivity of FCV to low pH and the relatively high susceptibility of MNV to alcohols suggest that sanitizers that are effective against both surrogate viruses might be more likely to be effective against human norovirus, than those effective against only one of the surrogates (111). In addition, reduction of viral RNA (as opposed to reduced infectivity of cultivable surrogates) does not appear to be a reliable means of estimating the effectiveness of hand sanitizers against human norovirus (111).

Overall, studies suggest that proper hand washing with soap and running water for at least 20 seconds is the most effective way to reduce norovirus contamination on the hands, whereas hand sanitizers might serve as an effective adjunct in between proper handwashings but should not be considered a substitute for soap and water handwashing (106–111). As an additional preventive strategy, no bare-hand contact with ready-to-eat foods (foods edible without washing, cooking, or additional preparation to achieve food safety) is recommended (112; FDA, unpublished data, 2011).

Exclusion and Isolation

Considering the highly infectious nature of norovirus, exclusion and isolation of infected persons are often the most practical means of interrupting transmission of virus and limiting contamination of the environment. This is particularly important in settings where people reside or congregate such as long-term-care facilities, acute-care hospitals, cruise ships, and college dormitories. Empiric evidence for the effectiveness of exclusion and isolation strategies is limited (113); rather, strategies are based on infection-control principles. The principle underpinning isolation is to minimize contact with persons during the most infectious periods of their illness. This includes the acute phase of illness, a period following recovery while the person is still shedding virus at high levels (usually 24–72 hours), and, in some situations in health-care facilities, exclusion of exposed and potentially incubating persons. Isolation of both exposed and unexposed well persons might be useful during outbreaks in long-term-care facilities to help break the cycle of transmission and prevent additional cases. In health-care facilities, ill patients may be cohorted together in a unit or part thereof, with dedicated nursing staff providing care for infected persons (9). Analogously, passengers with gastroenteritis on cruise ships may be asked to remain isolated voluntarily in their cabins during their illness and for a period of 24–48 hours after their symptoms have resolved. Ill patients generally should not be transferred to unaffected units in the facility or to other facilities, except in the case of medical necessity and after consultation with infection-control staff. To minimize the risk of spread from incubating or asymptotically infected

patients and staff in health-care facilities, such persons should not be transferred to or work on (respectively) unaffected areas, typically for 48 hours after exposure. Ill staff members in health-care facilities and food handlers should be excluded during their illness and for 48–72 hours following resolution of symptoms. Asymptomatic food-service workers who have tested positive for norovirus, which might occur during an outbreak investigation, also should be excluded or restricted per the FDA Food Code (10). Regulatory authority approval might be required for excluded food-service workers to return to work (10), although requiring negative stool results prior to returning to work is not recommended. Sick pay and sick leave policies that do not penalize ill workers might help to facilitate such staff exclusion. Nonessential personnel, including visitors, may be screened for symptoms and excluded or, at the minimum, should be cautioned about the risks and made aware of the heightened importance of hand hygiene through washing with soap and water. In certain situations, units in a health-care facility may be closed to new admissions to prevent the introduction of new susceptible patients (113).

Environmental Disinfection

The use of chemical disinfectants is one of the key approaches to interrupt norovirus spread from contaminated environmental surfaces. Particular attention should be given to the likely areas of greatest environmental contamination such as bathrooms and high-touch surfaces (e.g., door knobs and hand rails). Sodium hypochlorite (chlorine bleach) has been widely recommended to disinfect human norovirus from surfaces, and its efficacy has been well documented (114–117). Environmental surfaces potentially contaminated with norovirus should be disinfected using a sodium hypochlorite solution or other commercial product registered with EPA as effective against norovirus. A list of EPA-approved products is available at http://www.epa.gov/oppad001/list_g_norovirus.pdf. Products containing phenolic compounds (including triclosan and quarternary ammonium compounds) are less effective against nonenveloped viruses such as human norovirus (114,118–120). Furthermore, this list should be interpreted with caution because the efficacy of these products is determined by using the surrogate FCV, which exhibits different physiochemical properties than human norovirus and therefore might not reflect a similar disinfection efficacy profile (121). In addition, several recent reports have demonstrated that FCV is not the most resistant surrogate virus to predict inactivation of human norovirus (111,122,123). Therefore, the use of multiple surrogate viruses rather than a single surrogate has been suggested to assess the efficacy of disinfectants (111).

Because of this uncertainty, whenever possible, chlorine bleach solution should be applied to hard, nonporous, environmental surfaces at a concentration of 1,000–5,000 ppm (5–25 tablespoons household bleach [5.25%] per gallon of water). Given the potential for evaporative dilution, bleach solutions should be freshly prepared for use within 24 hours, or the target concentration should be doubled (e.g., 2,000–10,000 ppm) for storage and used within 30 days. Although the upper end of this range has been recommended previously when soiling is present (124), few data are available to support the effectiveness of sodium hypochlorite on fecally soiled surfaces (125). For example, 5,000 ppm of sodium hypochlorite was not able to completely eliminate norovirus dried in 20% fecal stool suspension on surfaces (126). A recent study indicated that longer exposure times (approximately 4 minutes) of 5,000 ppm sodium hypochlorite on fecally soiled surfaces were needed to inactivate both human norovirus surrogates (MNV and FCV) by 4 log₁₀ (122), which has been proposed as a satisfactory reduction level for norovirus contamination (127). In conclusion, initial cleaning of contaminated surfaces to remove organic loads such as fecal material should be performed before sodium hypochlorite disinfection.

In health-care settings, cleaning products and disinfectants used should be EPA-registered and have label claims for use in health-care settings; personnel performing environmental services should adhere to the manufacturer's instructions for dilution, application, and contact time. Heat disinfection (i.e., pasteurization to 140°F [60°C]) has been suggested and used successfully under laboratory conditions, for items that cannot be subjected to chemical disinfectants such as chlorine bleach (128–131). Other disinfection approaches such as ozone, hydrogen peroxide, or coating surfaces with antimicrobial materials (e.g., titanium dioxide [TiO₂] film) also have been proposed for routine environmental control of noroviruses (132–134).

Reporting and Assistance

Individual cases of norovirus are not nationally notifiable; however, all outbreaks of acute gastroenteritis should be reported to the appropriate local or state health departments, in accordance with local regulations. Additional outbreak assistance, including coordination of multistate outbreak investigations, epidemiologic consultation, and laboratory support can be provided by the CDC Norovirus Program located within the Division of Viral Diseases, National Center for Immunization and Respiratory Diseases. After telephone consultation with the National Calicivirus Laboratory (404-639-1923), state or local public health laboratories can ship outbreak specimens

to CDC at National Calicivirus Laboratory, Dash Unit 75, CDC, 1600 Clifton Road, N.E., Atlanta, GA 30333.

National Outbreak Reporting System

In response to a position statement by the Council of State and Territorial Epidemiologists, CDC developed the National Outbreak Reporting System (NORS) as an integrated national surveillance system for enteric disease outbreaks that combined and expanded on the longstanding national surveillance systems for foodborne and waterborne outbreaks. Launched in February 2009, NORS provides a framework through which all outbreaks of enteric disease, regardless of transmission mode, may be reported from state and local health departments to CDC. This web-based platform includes modules for outbreaks attributable to foodborne, waterborne, and person-to-person outbreaks, thereby providing comprehensive national surveillance for all gastroenteritis outbreaks, including those caused by norovirus. Data collected through NORS will help determine the burden and trends of epidemic norovirus and attribution to settings, transmission routes, and food vehicles. Such information is critical to develop appropriate prevention and control strategies that target points of intervention most likely to yield the greatest impact. States are encouraged to contribute to this national surveillance effort by reporting all suspected and confirmed norovirus outbreaks through NORS.

CaliciNet

Genotyping of norovirus strains has been demonstrated to be useful in confirming or identifying links between clusters of norovirus illness, and direct sequencing of RT-PCR products has become the method of choice. To increase the value of national norovirus surveillance, CDC has developed and implemented an electronic norovirus outbreak surveillance network (CaliciNet) with state and local public health and food regulatory agency laboratories. CaliciNet is intended to link norovirus outbreaks to aid in identifying common (e.g., food) vehicles, identify trends, and identify emerging norovirus strains. Using standardized genotyping methods, CaliciNet-certified laboratories upload norovirus sequences and conduct rapid comparison with sequences already in the database. CaliciNet was implemented in March 2009, and as of January 2011, a total of 21 states were certified for participation. With continued development and expansion of the network, CaliciNet might help elucidate the role of food contamination throughout the continuum from production to preparation and the evolution of specific norovirus strains in causing outbreaks, which ultimately can help better target interventions.

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☆ U.S. Government Printing Office: 2011-723-011/21027 Region IV ISSN: 1057-5987