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Norovirus

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SUMMARY

Norovirus, an RNA virus of the family *Caliciviridae*, is a human enteric pathogen that causes substantial morbidity across both health care and community settings. Several factors enhance the transmissibility of norovirus, including the small inoculum required to produce infection (<100 viral particles), prolonged viral shedding, and its ability to survive in the environment. In this review, we describe the basic virology and immunology of noroviruses, the clinical disease resulting from infection and its diagnosis and management, as well as host and pathogen factors that complicate vaccine development. Additionally, we discuss overall epidemiology, infection control strategies, and global reporting efforts aimed at controlling this worldwide cause of acute gastroenteritis. Prompt implementation of infection control measures remains the mainstay of norovirus outbreak management.

INTRODUCTION

Human norovirus, previously known as Norwalk virus, was first identified in stool specimens collected during an outbreak of gastroenteritis in Norwalk, OH, and was the first viral agent shown to cause gastroenteritis (1). Illness due to this virus was initially described in 1929 as "winter vomiting disease" due to its seasonal predilection and the frequent preponderance of patients with vomiting as a primary symptom (2).

The 1968 outbreak that led to the identification of the virus affected 50% of students at an elementary school in Norwalk and manifested primarily as nausea, vomiting, diarrhea, and low-grade fever (3). Among primary cases, 98% complained of nausea, and 92% vomited, while 58% had abdominal cramps, 52% complained of lethargy, 38% had diarrhea, and 34% had fever. The occurrence of secondary cases in 32% of family contacts allowed the estimation of a 48-h incubation period. The illness lasted ~24 h, with complete recovery in all cases.

While no pathogen could be identified in the Norwalk outbreak, oral administration of filtrates prepared from rectal swabs from affected individuals to healthy adult male prisoners at the Maryland House of Correction in Jessup, MD, resulted in symptoms in 2 of 3 subjects (4). In the 2 subjects who became ill, the incubation period was 48 h, as was the duration of symptoms. Mild diarrhea, with 4 to 6 loose stools, lasted 24 h, while low-grade fever lasted only 8 to 12 h. Other symptoms were anorexia, moderately severe abdominal cramping, malaise, headache, and nausea (but no vomiting). A complete return to health occurred by 96 h. The filtrate of a stool sample from 1 of the 2 symptomatic experimentally infected volunteers was then administered to a further 9 subjects, 7 of whom became ill. Two of the seven subjects vomited (one subject, who vomited ~20 times in 24 h, required parenteral fluid replacement) but failed to develop diarrhea, while two had diarrhea without vomiting, and three had both diarrhea and vomiting. Four of the seven subjects had low-grade fever that lasted 8 to 12 h, and all seven subjects complained of malaise and headache. Symptoms resolved after a mean duration of 33 h.

While the index outbreak and the human volunteer studies that followed provided an accurate picture of the manifestations of norovirus infection in previously healthy children and adults at a time when the etiologic agent was unknown, it was an incomplete one. Further observations, discussed later in this review, have provided a more complex and nuanced view of the infection. Human noroviruses are the leading cause of epidemic gastroenteritis in all age groups and have been associated with high-profile outbreaks in hospitals, nursing homes, cruise ships, and the military (5, 6). It is estimated that each year, noroviruses are responsible for 64,000 diarrheal episodes requiring hospitalization, 900,000 clinic visits among children in industrialized nations, and ~200,000 deaths of children <5 years old in the developing world (7).

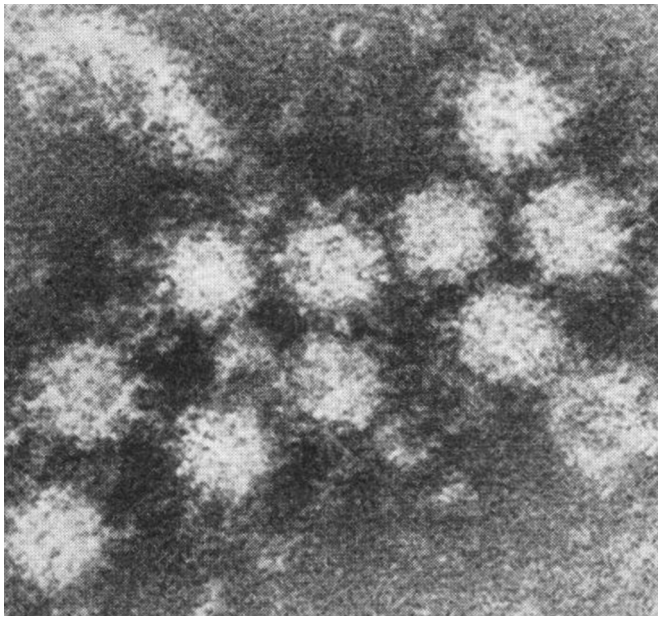

FIG 1 Immunoelectron microscopy identifies a 27-nm particle associated with acute infectious nonbacterial gastroenteritis. Shown is an aggregate observed after incubation of a second-passage stool filtrate from the original Norwalk outbreak with a 1:10 dilution of postchallenge antiserum of an experimentally infected volunteer. These particles are heavily coated with antibody. (Adapted from reference 1 with permission.)

BASIC VIROLOGY AND VIRAL DIVERSITY

The Norwalk virus agent (the original prototype virus is referred to as Norwalk virus in this review) was originally visualized by using immunoelectron microscopy (1), revealing 27-nm virus-like particles (Fig. 1). Efforts to cultivate the pathogen in cell culture and to develop an animal model were unsuccessful (8); therefore, the evolving literature focused on describing the physical characteristics of this small, round-structured virus in clinical specimens and on the serologic response to infection (9, 10). Although virion morphology, as well as protein and nucleic acid composition, was similar to that of members of the *Caliciviridae* family (10–13), clear taxonomic classification was not achieved until the whole genome sequence was obtained and compared to sequences from other caliciviruses (14, 15).

The *Caliciviridae* family of small, nonenveloped, positive-stranded RNA viruses is now comprised of five genera, including *Norovirus*, *Sapovirus*, *Lagovirus*, *Nebovirus*, and *Vesivirus* (16). The *Norovirus* and *Sapovirus* genera contain the human enteric viruses of the same names as well as a number of viruses that cause primarily enteric diseases in other animals, such as murine and canine noroviruses.

The human norovirus genome is composed of a linear, positive-sense RNA that is ~7.6 kb in length (14). The genome is covalently linked to the viral protein genome (VPg) at the 5′ end

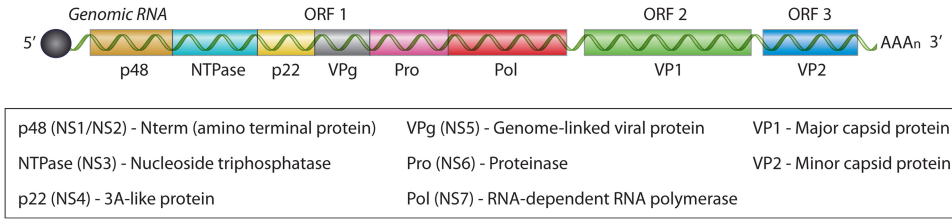

FIG 2 The human norovirus genome. The genome is comprised of a linear, positive-sense RNA, ~7.6 kb in length, covalently linked to the viral protein genome (VPg) (solid black circle) at the 5′ end and polyadenylated at the 3′ end. There are three open reading frames (ORFs), designated ORF-1, ORF-2, and ORF-3, encoding 8 viral proteins. ORF-1 encodes the 6 nonstructural (NS) proteins that are proteolytically processed by the virally encoded cysteine proteinase (Pro). ORF-2 and ORF-3 encode the structural components of the virion, viral protein 1 (VP1) and VP2, respectively.

and polyadenylated at the 3′ end (17). There are three open reading frames (ORFs), designated ORF-1, ORF-2, and ORF-3, encoding eight viral proteins (Fig. 2). ORF-2 and ORF-3 encode the structural components of the virion, viral protein 1 (VP1) and VP2, respectively. The mature virion contains 90 VP1 dimers assembled with icosahedral symmetry and arranged in such a fashion as to create hollows or cup-like structures on the virus surface. Hence, *calici* is derived from the Latin word *calyx*, or "cup" (16). ORF-1 encodes a polyprotein that is proteolytically processed into the 6 nonstructural proteins, including the norovirus protease and RNA-dependent RNA polymerase (17).

Norovirus has been likened to a "shape-shifter" (18), a mythical creature that can change form or being. This description refers to its diversity, with, as determined by the VP1 amino acid sequence, at least 6 genogroups (genogroup I [GI] to GVI) and >40 genotypes (18, 19), together with its continued evolution, apparently in response to the selective pressure exerted by the human immune system (20). Human norovirus infections are caused, in decreasing order of frequency, by GII (mostly GII.4), GI, and, to a very limited extent, GIV (some genotypes of which also infect pigs) (21, 22). In addition, antibodies to GIII, a bovine norovirus, have been detected in ~22% of humans (23), and antibodies to GVI (a genogroup that has been identified only in canines) have been detected in 22.6% of small-animal veterinarians and 5.8% of age-matched controls (24).

The genetic diversity of the human noroviruses is apparent from the observation that VP1 amino acid sequences of GII.4 strains differ by 37% to 38% from the prototypic GI.1 Norwalk virus strain and by 5% to 7% within the GII genotype alone, with as much as a 2.8% difference between strains of an individual virus (19, 25). This variability, resulting from both recombination and mutational events, is of a sufficient magnitude that it has led to the suggestion that the use of sequence difference cutoffs is no longer sufficient to classify noroviruses and that the addition of a phylogenetic approach would prove more accurate (26).

CLINICAL FEATURES OF NOROVIRUS INFECTION

Asymptomatic Infection

Fecal excretion of norovirus infection in asymptomatic individuals is common, especially in children (Table 1). Asymptomatic excretion of norovirus was detected in 19 of 163 (11.7%) children in Leon, Nicaragua (27), while in periurban Mexico City, norovirus was detected in stool samples of 31 of 63 (49.2%) asymptomatic children (28). Over a 2-year period, 37.5% of 56 children attending a day care center in central Brazil had at least one episode of asymptomatic fecal excretion of norovirus (29). Norovirus was detected as frequently in stool samples of asymptomatic as in stool samples of symptomatic children in Burkina Faso (30).

Asymptomatic infection is not limited to individuals residing in lesser-developed countries. Viral RNA was detected in fecal samples of 5 of 43 (11.6%) children who had a variety of inherited immunodeficiencies admitted to Necker Hospital in Paris, France, but who lacked gastrointestinal symptoms (31). More generally, norovirus was detected in the stool samples of 361 of 2,205 asymptomatic individuals in England, with the prevalence being highest in those <5 years of age, exceeding 25% through 3 years of age, but the prevalence was also >5% in those 35 years of age and older. The overall prevalence after adjusting for age was 12% (95% confidence interval [CI], 11% to 14%) (32).

Asymptomatic excretion of norovirus has diagnostic implications. Diarrhea due to another cause in an asymptomatic carrier may be misdiagnosed as being due to norovirus infection. Carriage also has epidemiological implications. A study in South Korea detected norovirus RNA in the stool samples of 66 of 6,441 (1.02%) asymptomatic food handlers (33). A smaller study found that 26 of 776 (3.4%) asymptomatic food handlers at elementary schools in Incheon, South Korea, were excreting the virus (34). A clear adverse consequence of asymptomatic carriage resulted in the transmission of norovirus by fecal microbiota transplantation using stool samples obtained from asymptomatic donors who had not been screened for the presence of the virus (35).

Symptomatic Infection

Incubation period. The incubation period is relatively brief in most infected individuals who develop symptoms (Table 2). Ex-

TABLE 1 Summary of selected norovirus asymptomatic infection studies

Reference	Location	Population	% of subjects with stool carriage (no. of subjects with stool carriage/total no. of subjects)
27	Nicaragua	Pediatric	11.7 (19/163)
28	Mexico	Pediatric	49.2 (31/63)
29	Brazil	Pediatric	37.5 (21/56)
30	Burkina Faso	Pediatric	24.8 (31/125)[a]
31	France	Pediatric[b]	11.6 (5/43)
32	England	Adult/pediatric	16.4 (361/2,205)[c]
33	South Korea	Food handlers	1.0 (66/6,441)
34	South Korea	Food handlers	3.4 (26/776)

[a] This percentage was 21.2% for symptomatic children.
[b] With inherited immunodeficiency.
[c] Age-adjusted prevalence of 12%

TABLE 2 Summary of selected norovirus incubation time studies

Reference	Location[c]	Time to index infection (h)	Time to secondary infection (h)
3	USA	48	
36	Sweden	34	52
37[a]	NA	29	
38	Netherlands	96[b]	

[a] Systematic review.
[b] Community onset.
[c] NA, not applicable.

TABLE 3 Summary of selected norovirus symptomatic infection studies

Reference	Location	Population	No. of patients	Symptom (% of patients)[a]
39	Taiwan	Psychiatric inpatients	179	Diarrhea (87.5) Vomiting (25.5) Abdominal pain (4.4) Fever (2.2)
40	USA	Military trainees	99	Nausea (88) Vomiting (80) Abdominal pain (76) Diarrhea (67) Fever/chills (47) Headache (22)
41	Afghanistan	Deployed British military personnel	29	Gastrointestinal symptoms (100) Headache (10) Neck stiffness (10) Photophobia (10) Obtundation (10) DIC (3)
42	UK	Hospital patients	730	Diarrhea (85) Vomiting (56) Duration of 3 days
42	UK	Hospital staff	482	Diarrhea (66) Vomiting (73) Duration of 2 days
42	UK	Nursing home residents	266	Diarrhea (73) Vomiting (66) Duration of 2 days

[a] DIC, disseminated intravascular coagulation.

amination of the onset of secondary cases in the index outbreak in 1968 led to an estimated incubation period of ~48 h (3). In a Swedish outbreak involving children and staff at day care centers, the mean incubation period after foodborne transmission was 34 h, while that for secondary person-to-person transmission to household members was ~52 h (36). A recent systematic review of the literature concluded that the median incubation period for genotype I and II infections is 1.2 days (95% CI, 1.1 to 2.2 days) (37). In contrast to these findings, Rockx and colleagues reported that the median duration of illness was 4 days in community-acquired cases (38). Longer estimates such as these may, however, be the result of misclassification of secondary transmissions as primary transmissions.

Signs, symptoms, and disease course. As seen in the index outbreak as well as in experimental passage studies, the dominant symptoms of norovirus infection are vomiting and diarrhea and are generally of a relatively short duration (Table 3). For example, in an analysis of 4 outbreaks over 3 years in an inpatient psychiatric unit in Taiwan that affected 172 patients and 7 health care workers (39), diarrhea occurred in 87.5% and vomiting occurred in 25.5% of patients, while 4.4% complained of abdominal pain and 2.2% had fever. The mean duration of symptoms was 2.1 ± 1.5 days, with a range of 1.2 to 2.8 days; 86.4% of patients had symptom resolution within 1 to 3 days.

More severe illness may, however, occasionally occur in previously medically healthy individuals. Among 99 military trainees with norovirus infection, 88% had nausea, and 80% vomited, while 76% complained of abdominal pain, 67% had diarrhea, 47% had fever or chills, and 22% had headache (40). The temperature exceeded 100.4°F in 17% of subjects, while 17% had leukocytosis and 37% had thrombocytopenia. More dramatically, in an outbreak involving 29 British military personnel deployed to Afghanistan, the first 3 patients presented not only with gastrointestinal symptoms and fever but also with headache, neck stiffness, photophobia, and obtundation (41). One patient had disseminated intravascular coagulation, and two patients required ventilatory support. It is possible, if not likely, that an undetected second infection was present.

The illness may be more severe and prolonged in individuals with medical comorbidities. An examination of norovirus outbreaks in United Kingdom health care facilities provided an opportunity to compare the clinical pictures of presumably healthy health care providers with presumably less healthy patients (42). An analysis of a large number of confirmed cases in multiple health care facilities found that 66% of affected hospital staff had diarrhea and that 73% vomited, with these proportions being reversed in nursing home residents. Among hospital patients, diarrhea dominated, being present in 85% subjects, while only 56% vomited. While the median duration of illness in hospital staff and nursing home residents was 2 days (with 3 days being at the 75th percentile of distribution for both), it was 3 days (75th percentile, 5 days) in hospital patients, and 40% of patients ≥85 years of age were still symptomatic after 4 days.

Complications: severe disease and mortality at the extremes of age. Infections occurring during outbreaks of GII.4 strains are associated with more severe outcomes, including mortality, than infections during outbreaks of non-GII.4 strains (43). Advanced age is a risk factor for a fatal outcome. Thus, in the Netherlands, norovirus outbreaks were significantly associated with excess mortality in individuals >85 years of age, coinciding with the emergence of new viral variants (44). Norovirus accounted for 0.5% of total deaths from 1999 to 2007 in individuals in this age group. A study of 82 patients with community-acquired norovirus infection with a median age of 77 years found an overall 30-day mortality rate of 7%, with elevated venous lactate levels at the time of hospital admission being predictive of mortality (45). Estimates indicate that 20% (95% CI, 13.3% to 26.8%) of deaths of persons >65 years of age caused by infectious intestinal disease other than *Clostridium difficile* in England and Wales from 2001 to 2006 were associated with norovirus infection (46). Furthermore, 13% (95% CI, 7.5% to 18.5%) of deaths caused by noninfectious intestinal disease were associated with norovirus.

Individuals at the other extreme of age are also at risk. In a study in Japan involving 71 children, the mean duration of illness was twice as long (7 days versus 3.5 days) in those <2 years of age

TABLE 4 Summary of selected studies on norovirus infection in immunocompromised hosts

Reference	Patient population	Duration of symptoms (days)	Duration of viral excretion (days)
53	HSCT recipients	6–33	
54	HSCT recipients	2–36	11–87
55	HSCT recipients	15–420	15–420
56	Pediatric HSCT recipients		13–263
57	Pediatric HSCT recipients		60–380
60	Renal transplant recipients	24–898	97–898
61	Renal transplant recipients	37–1,004	6–581

than in those 2 to 4 years of age, and the severity of illness was greater (47). Norovirus infection in term and preterm neonates causes the full range of symptoms and signs seen in other patient groups but may also be associated with very serious complications such as necrotizing enterocolitis (48). Of 8 neonates (mean gestational age, 28 weeks) who developed norovirus-associated necrotizing enterocolitis at the age of 15 to 38 days, 2 died (49). A retrospective study found that 1 of 8 neonates with a mean gestational age of 29 weeks and with norovirus infection occurring at a postnatal age ranging from 8 to 92 days developed necrotizing enterocolitis (50). Of the other 7 neonates, all had symptoms of gastroenteritis with diarrhea and abdominal distention, 4 had apnea, 3 vomited, and 3 had blood in their stool. The mean duration of illness was 5 days (range, 2 to 11 days). While neonatal necrotizing enterocolitis involves predominantly the small bowel, Pelizzo and colleagues reported 3 premature norovirus-infected infants with ischemia of the colon without involvement of the small intestine (51). A case of an adult with norovirus gastroenteritis and ischemic colitis has also been reported (52).

Norovirus in immunocompromised hosts. Norovirus infection-associated illness may also be more prolonged and severe in immunocompromised individuals and may be associated with remarkably persistent viral excretion in some of these individuals (Table 4).

(i) Hematopoietic stem cell transplant recipients. Norovirus diagnosis in hematopoietic stem cell transplant (HSCT) recipients is complicated by the frequent occurrence and multiple causes of diarrhea, including gastrointestinal graft-versus-host disease (GVHD), in these patients.

A small outbreak was confirmed to be caused by norovirus in 6 of 8 patients with watery diarrhea in a bone marrow transplant unit (53). In two of these patients, norovirus infection was superimposed on graft-versus-host disease involving the gastrointestinal tract. All patients were febrile. Gastrointestinal symptoms persisted for 8 to 33 days. No deaths were attributed to norovirus infection.

An outbreak of a norovirus GII.4 variant strain in a hematologic and transplantation unit affected 11 patients and 11 staff members (54). Six of the patients had been treated for lymphoma, and five had been treated for acute leukemia. Five patients had undergone hematopoietic stem cell transplantation (2 autologous and 3 allogeneic), while three had received chemotherapy and one had received only rituximab; seven were neutropenic. The median duration of symptoms was only 3 days in staff but was 7 days (range, 2 to 36 days) in patients. All 11 patients had diarrhea, while 8 of 11 had vomiting and 6 were febrile. Two patients who underwent abdominal computerized tomography had evidence of small bowel edema. To evaluate for the presence of gastrointestinal GVHD, the 3 patients who had undergone allogeneic HSCT had duodenal biopsy specimens that demonstrated villous blunting, slightly increased numbers of apoptotic crypt cells, and markedly increased numbers of intraepithelial $CD8^+$ T lymphocytes. Three patients died, one with aspiration and two with sepsis.

Twelve allogeneic HSCT recipients with norovirus infection had onset of diarrhea for 0.25 to 6 months prior to diagnosis (55). Eleven patients were receiving immunosuppressive therapy, including two who received it for presumed GVHD (which proved to be absent). Ten patients had vomiting of a short duration. Two patients died after 4 months of diarrhea, one of these due to malnutrition and the other for unrelated reasons. In the other 10 patients, diarrhea lasted for 0.5 to 14 months (median, 3 months), with evidence of continued viral shedding.

Over a 3-year period, of 49 HSCT patients in Hong Kong <21 years of age with diarrhea, 8 (7 allogeneic HSCT recipients and 1 autologous umbilical cord cell recipient) were found to have norovirus infection (56). The cumulative incidence at 2 years was 12.9%. Two patients were infected prior to transplantation, and the infection persisted thereafter. The median age of patients was 5.2 years, and 6 were receiving immunosuppressive therapy. Four patients also had *Clostridium difficile* infection, but diarrhea persisted after treatment. Viral excretion persisted for 13 to 263 days (median, 145 days).

Of 61 children who received HSCT at a single center, 13 were found at some time in the course of treatment to excrete norovirus in association with diarrhea and vomiting (57). Norovirus excretion persisted for 60 to 380 days (median, 150 days), and resolution of infection correlated with time to $CD3^+$ T cell recovery. All patients required prolonged enteral and parenteral nutritional support.

(ii) Solid organ transplant recipients. In an analysis of 24 immunocompromised patients (mostly pediatric), most of whom were recipients of solid organ transplants, the mean duration of norovirus-associated diarrhea was ~12 days (58). Westhoff and colleagues reported two renal transplant recipients with persistent norovirus excretion, one for >7 months and the other for 3 months (59). The first patient had resolution of symptoms after acute infection but continued to excrete the virus until spontaneous clearance occurred. The second patient had recurrent symptoms that resolved, along with norovirus excretion, with a reduction in his immunosuppressive regimen.

Over a 2-year period, 13 of 78 (16.7%) adult renal allograft recipients with prolonged or severe diarrhea were found to have norovirus infection (GII.7 and GII.17 in one patient each and GII.4 in seven patients) (60). All patients were receiving immunosuppressive therapy. Symptoms lasted for 24 to 898 days, and viral excretion lasted for 97 to 898 days. In each case, diarrhea was associated with increased serum creatinine concentrations, and 5 patients required hospitalization because of severe dehydration and allograft dysfunction. A reduction in immunosuppressive therapy was associated with symptom improvement or resolution in all cases but had no apparent effect on viral shedding, which resolved in only 3 patients.

In a retrospective study of 15 renal allograft recipients with diarrhea and norovirus infection, 14 infections were caused by GII strains, mostly GII.4 strains (61). The mean duration of diarrhea was 8.7 months. Patients lost a mean of 8.5% of their body weight.

Acute renal failure occurred in four-fifths of patients, and 5 patients had graft rejection. Four patients underwent colonoscopy with biopsy; macroscopic and histological results were all normal. Immunosuppressive therapy was reduced in all patients by lowering the mycophenylate dose or discontinuing it altogether, often by substituting azathioprine.

Norovirus was detected in stool samples during 13 of 54 (36%) severe diarrhea events in 49 kidney transplant recipients, with receipt of cyclosporine together with mycophenylate being a risk factor (62). It was associated with a mean weight loss of 3.0 kg, which was significantly greater than the weight loss associated with other causes of diarrhea. Complicating interpretation is that norovirus was detected in 10% of 30 renal transplant recipients without diarrhea.

(iii) Miscellaneous immunocompromising conditions. Two chronic lymphocytic leukemia patients with hypogammaglobulinemia and with chronic diarrhea had persistent fecal norovirus excretion (63). Chronic diarrhea in association with profound immunocompromise due to HIV infection has also been reported. In one case, the intravenous administration of human immunoglobulin was ineffective, but diarrhea resolved after improvement in the $CD4^+$ T cell response to antiretroviral therapy (64).

Unusual manifestations of norovirus infection. Norovirus GII.4 was detected in 3 of 562 (0.5%) nasopharyngeal samples of children with influenza-like illness (65). In each of the 3 patients, respiratory symptoms antedated gastrointestinal illness. Norovirus has also been detected in endotracheal aspirates of 2 preterm infants with intestinal norovirus infection, raising a question about the frequent need for oxygen supplementation in these patients (66).

Hemophagocytic lymphohistiocytosis has been described for a 24-month-old boy with chronic norovirus infection who underwent matched unrelated HSCT for relapsed acute myelogenous leukemia (67). A pediatric renal allograft recipient presented with granulocytopenia and fever, which resolved together with the resolution of symptoms of norovirus infection (68). An elderly patient with norovirus gastroenteritis developed hemolytic-uremic syndrome (69). Ischemic colitis has been reported for an adult (52) and several neonates in association with norovirus infection (51). Transient hepatocellular injury manifesting as significant elevations in transaminase levels has been reported for an adult (70) and for children with norovirus infection (71). In the 4 pediatric cases reported, the serum transaminase levels peaked a mean of 13.8 days after the onset of gastroenteritis symptoms and resolved after ~4 weeks (71).

The etiologic relationship of norovirus infection in these cases is, however, unproven. This is also true for some putative postinfectious illnesses that have been suggested to have an association with norovirus infection. Gemulla and Pessler reported 2 cases of possible postinfectious arthritis related to norovirus infection (72). Thirteen percent of patients who had been affected during a waterborne norovirus outbreak and who responded to a questionnaire reported symptoms consistent with irritable bowel syndrome 12 months after their infection (73).

A case-control study found an association of norovirus infection with exacerbations of pediatric inflammatory bowel disease (8 with ulcerative colitis and 1 with Crohn's disease) (74). However, two subsequent studies failed to identify a significant relationship between infection with this virus and exacerbations of inflammatory bowel disease (75, 76). A large case-control study of military personnel who had symptoms of acute gastroenteritis during 3 norovirus outbreaks failed to find subsequent evidence of an increased risk of irritable bowel syndrome but did detect a 1.5-fold increased incidence of constipation, dyspepsia, and symptoms of gastrointestinal reflux disease relative to controls (77).

Central nervous system manifestations have also been reported in association with norovirus infection. Encephalopathy has occurred in children and adults (78–80). While the outcome is generally benign, including in one case in which the virus was detected in cerebrospinal fluid (CSF), magnetic resonance imaging (MRI) abnormalities and permanent neurological sequelae occurred in a patient in whom the virus was detected in plasma but not cerebrospinal fluid (80). Medici and colleagues also reported finding viral RNA in the plasma of an infected child with seizures (81). Notably, a study of 39 children with uncomplicated norovirus infection detected viral RNA in the serum of 6 (15%) cases but in the CSF of none (82).

While encephalopathy has been uncommonly reported in association with norovirus infection, the occurrence of seizures appears to be more frequent. Convulsions occurred in 15 of 173 (8.7%) afebrile (≤38°C) children with norovirus gastroenteritis admitted to a hospital in Hong Kong, a frequency 5 times higher than that for children with rotavirus infection (83). In Taiwan, 19 of 64 (29.7%) children hospitalized with gastroenteritis due to norovirus developed seizures, a frequency 6 times higher than that seen in children hospitalized with rotavirus infection during the same period despite the greater severity of fever in the latter group (84). The median age of patients was 18 months (range, 15 to 21 months). Only 2 patients in the norovirus group presented with a temperature of >39°C. No subjects had neurological sequelae at follow-up in 1 year.

MANAGEMENT OF NOROVIRUS INFECTION

The treatment of norovirus gastroenteritis is supportive, involving primarily the reversal of dehydration and electrolyte abnormalities. Antiemetics and antimotility agents may play a role in some patients.

In patients with persisting symptoms, especially neonates, the elderly, and the immunocompromised, the availability of specific therapy would be of value, but no therapy has been clearly demonstrated to be effective. However, a small, blind, placebo-controlled trial of children with viral gastroenteritis found that nitazoxanide administration was associated with a reduced duration of illness, including in a subset of patients with norovirus infection (85). Siddiq and colleagues reported resolution of diarrhea in a norovirus-infected patient with refractory acute myelogenous leukemia and HSCT after administration of nitazoxanide (86).

Enteric administration of human immunoglobulin was associated with resolution of chronic diarrhea in a transplant patient (87). Florescu and colleagues performed a matched case-control study to evaluate the potential benefit of orally administered human immunoglobulin in the treatment of symptomatic norovirus infection in immunocompromised patients. Cases received 25 mg/kg of body weight of human immunoglobulin (Gamunex; Talecris Biotherapeutics, Inc., NC, USA) every 6 h for a total of 8 doses (58). Although the median age of 24 total cases plus controls was 2 years, one-third were adults, and 20 were solid organ transplant recipients. Coinfection with *Clostridium difficile* or rotavirus

was present in 8 patients. Administration of immunoglobulin was associated with a numerical decrease in stool output at 7 days ($P = 0.09$). However, while this 7-day interval was counted from the time of treatment in cases, it was counted from the time of diagnosis in controls, potentially leading to bias favoring immunoglobulin administration. Despite this potential bias, there was no significant difference in the time to resolution of diarrhea between cases and controls, with the duration being ~12 days for each group. There was a numerically greater frequency of resolution of diarrhea in cases ($P = 0.078$), without a statistically or clinically significant difference in the total time to resolution of diarrhea or length of hospital stay. Looking toward a potential future therapy, Chen and colleagues developed a set of norovirus-specific monoclonal antibodies (88).

A reduction of immunosuppressive therapy is indicated whenever feasible. In one case report, a reduction in immunosuppressive therapy together with a change from a calcineurin inhibitor (tacrolimus) to an inhibitor of mTOR (sirolimus) was associated with resolution of chronic diarrhea in a double-transplant recipient (HSCT and lung) (89). Similarly, Engelen and colleagues altered the immunosuppressive therapy of a heart transplant recipient with chronic norovirus-associated diarrhea by substituting everolimus for tacrolimus, with subsequent prompt resolution of diarrhea (90).

Attempts at prophylaxis have been unsuccessful to date. Prophylactic administration of bovine lactoferrin failed to prevent diarrhea, including that due to norovirus, in children (91). In this randomized, placebo-controlled trial in Peru, 544 previously weaned children 12 to 18 months of age were visited daily for 6 months, and stool samples were collected monthly and during episodes of diarrhea. Norovirus nucleic acid was detected in 34.2% of stool samples from lactoferrin recipients and in 35.5% of stool samples from placebo recipients. The prophylactic administration of "probiotic fermented" milk containing a strain of *Lactobacillus casei* failed to prevent norovirus infection in elderly residents of a health service facility in Japan (92).

EPIDEMIOLOGY

Norovirus is a well-described cause of epidemic gastroenteritis in both adult and pediatric populations across a wide range of geographic regions (93–97). The U.S. Centers for Disease Control and Prevention (CDC) estimates that norovirus is responsible for 60% of acute gastroenteritis cases (with a known cause), or 21 million cases, in the United States each year. With the addition of molecular methods, norovirus has also been increasingly implicated in sporadic disease (98). A systematic review of all reports of norovirus detected by reverse transcriptase PCR (RT-PCR) attributed 5 to 31% of cases of gastroenteritis in hospitalized patients and an additional 5 to 36% of cases in all patients seeking outpatient evaluation to norovirus (7). The CDC estimates that norovirus is responsible for 400,000 emergency department visits and 71,000 hospitalizations annually, although these numbers may be underestimates due to the limited number of patients who seek medical attention for viral gastroenteritis symptoms (99).

The general population is broadly vulnerable to disease across all age groups, but the majority of morbidity and mortality occurs at the extremes of age. The fecal-oral route is the main mode of transmission, although several other modalities have been described. These modalities include transmission via aerosolized viral particles in vomitus (100, 101) and through food, water, and environmental contamination (102). Some studies have associated certain norovirus genotypes with particular modes of transmission. For example, Vega and colleagues, reviewing norovirus trends in the United States from 2009 to 2013, demonstrated that GII.4 was more likely to be associated with person-to-person transmission, especially in long-term-care facilities (LTCFs) and hospital settings, whereas GI.7 and GII.12 were more frequently associated with foodborne disease (103). The environmental durability of norovirus leads to persistence of the pathogen in clinical settings and other closed-space environments, thus complicating complete disinfection and allowing for recurrent outbreaks (104, 105).

Waterborne Outbreaks

Norovirus was first reported as the causative agent of a waterborne gastrointestinal disease outbreak by Kaplan et al. in 1982. The outbreak affected ~1,500 people in a small community in Georgia, with the highest attack rates occurring in geographic areas closest to points of interconnection between industrial and municipal water systems, where the industrial water was noted to contain coliform contamination. Evidence of norovirus was determined by increased antibody titers to Norwalk virus in patient serum (106). The diversity of waterborne sources implicated in norovirus outbreaks ranges widely, indicating the ubiquitous distribution of the virus. Outbreaks have been linked to potable water sources at camps, municipal water systems, commercial ice consumption, and recreational water exposure during rafting and swimming (107–112). While much of the water contamination is thought to come from discharge of wastewater into rivers, streams, and other bodies of water, the natural distribution of noroviruses in water systems has not been thoroughly explored. Much of the difficulty in characterizing the environmental distribution of norovirus is tied to testing limitations on diverse environmental sources (113). Bivalves, such as oysters and other shellfish, often represent the link between environmental water contamination and foodborne outbreaks, as these mollusks are thought to concentrate viruses and other microbes (113).

Water contamination with norovirus, despite sewage treatment, has been documented, with viral concentrations peaking during colder months (114). Several different methods are used to remove and reduce the burden of noroviruses in water systems, including the use of waste stabilization ponds, the application of activated sludge, or the use of submerged-membrane bioreactor treatments. These modalities have been evaluated for their ability to remove viruses from wastewater (114–117). Insufficient chlorination has been linked to some outbreaks (118).

Food, Restaurants, and Catering

Food presents two distinct models for norovirus transmission. The first is direct norovirus contamination of food at the point of production, and the second is contamination of food during preparation. In a review of several hundred reported norovirus outbreaks, foodborne transmission (362/666; 54%) and foodservice settings (294/830; 35%) were most commonly implicated (102). Fruits, vegetables, and shellfish pose a significant risk for disease transmission because they are consumed raw and may be subject to norovirus contamination from water sources. Norovirus has been recovered from a variety of food products ranging from oysters to romaine lettuce, raspberries, and other produce (119–125). Additionally, the use of contaminated water for reconstituting

food products has been implicated in widespread outbreaks (e.g., custard in Bristol, United Kingdom) (126). Rebedding of shellfish and depuration with purified seawater at increased temperatures have been used to reduce the burden of norovirus from shellfish in contaminated waters (127). Various food surface decontamination strategies have been explored to enhance the produce safety and decrease viral transmission, including treatment with sodium bicarbonate and chlorine (128, 129).

Foodborne outbreaks are often linked to hygiene breaches during preparation and are often tied to ill food handlers and common source producers. Ill family members of food handlers may represent a reservoir for disease (130). Norovirus outbreaks in restaurants and canteens have been documented and have been linked to catering companies, with the extent of outbreaks varying from several isolated cases to large multistate events. In one outbreak investigated by the U.S. CDC, illnesses in 13 states among 333 people were tied to workers at a single caterer providing "boxed lunches" to series of car dealerships (131). The food preparation environment has been evaluated for reservoirs of viral persistence and methods of enhanced cleaning to reduce transmission (132).

Sporadic Disease

Caliciviruses, especially noroviruses, are important causes of sporadic gastrointestinal disease. A recent study identified norovirus as the most common causative agent in sporadic gastroenteritis as part of a multitarget PCR analysis (133). These sporadic cases may occur in individuals or within a small family cluster, and several studies documenting sporadic disease have been conducted with pediatric populations (134–138). In a study of Finnish children who developed sporadic gastroenteritis and who were being monitored as part of a rotavirus vaccine trial, human caliciviruses were isolated in 20% of placebo patients and 22% of vaccine recipients, making them the second most frequently isolated viruses in community patients with acute gastroenteritis (139). Subsequent studies in Thailand (138), Malawi (137), Chile (140), and India (134) confirmed norovirus as a common (typically first or second only to rotavirus) cause of sporadic acute gastroenteritis. A 5-year surveillance study of children <5 years old conducted in Melbourne, Australia, demonstrated that the prevalence of calicivirus infection during the study period was 9.2% (113/1,233), with 95% of the strains belonging to the norovirus genus (141).

A U.S. surveillance study of pediatric populations across three geographically distinct children's hospitals documented an 8.5% prevalence rate for caliciviruses in children with acute gastroenteritis, the vast majority of which (84%) were due to norovirus (142). These results were consistent with previous surveillance studies, although the results did not conform to seasonal trends.

OUTBREAKS

Norovirus outbreaks have been reported in a variety of settings and are uniquely suited to areas of close living quarters, shared dining facilities, and difficult environmental maintenance.

Health Care Settings

Norovirus is frequently implicated in hospital ward and nursing home outbreaks. These closed-space outbreaks can present both a logistic challenge in terms of eradicating the source and a financial burden to health care institutions. One Swiss study attributed substantial direct costs to reduced capacity due to bed closures from staff illness rather than the actual cost of outbreak investigation and expanded laboratory testing (143). Beyond the financial burden, ward closure due to norovirus outbreaks can also have a negative impact on patient care due to staff shuffling and the potential for transferring patients to units without appropriate specialized nursing care.

Within hospitals, person-to-person transmission is the primary mode of transmission and can occur between both patients and staff. In one review of reported nosocomial outbreaks, researchers estimated that more cases are involved in outbreaks tied to patient index cases than in staff-originated outbreaks and that patient-indexed outbreaks require more aggressive hygiene interventions in order to disrupt viral transmission (144).

While hospitalized patients represent one reservoir for possible transmission due to nosocomial transmission, the patients themselves are also subject to many of the same traditional risk factors as community patients. Pether and Caul described an outbreak of norovirus in patients due to chicken sandwiches served by an infected health care worker at two hospitals (145).

Schools

Schools and day care settings are frequently implicated in acute gastrointestinal outbreaks. Reports of norovirus outbreaks have been documented across the spectrum of age from day care to college settings (36, 146–148). Multiple modes of transmission, including person-to-person, foodborne, and aerosolized vomitus modes, have been described in these outbreaks, and control can be complicated by asymptomatic viral excretion (29).

Military

Norovirus is a major cause of morbidity in military training centers and fields of operation for many of the same reasons that it causes disease in civilian settings: close living quarters, the low viral inoculum required for infection, persistent viral shedding, viral resistance to disinfection, and environmental durability (41, 149). Reports of noroviral disease among military personnel have been documented in a French parachuting unit, British military forces in Afghanistan, the U.S. Air Force Academy, and the Israeli army (41, 150, 151).

Cruise Ships and Resorts

Numerous well-publicized norovirus outbreaks have been associated with cruise ships dating back several decades (152–155). The CDC Vessel Sanitation Program maintains a list of gastrointestinal outbreaks of public health significance in vessels sailing for 3 to 21 days, carrying 100 or more passengers, and on which 3% or more of passengers or crew report diarrheal symptoms to onboard medical staff during the voyage (156). Shared living and dining quarters, in addition to passenger and crew disincentives for reporting illness, have been implicated in outbreaks (101). Norovirus outbreaks have also been reported in land-based resorts (157, 158). Risk factors for disease acquisition are similar to those reported during cruise ship outbreaks, such as sharing rooms with previously affected persons and witnessing episodes of public vomiting (101, 158).

Outbreak Reporting Systems

Once norovirus was recognized as a major etiologic agent of acute gastroenteritis and a significant cause of morbidity and cost within health care systems, several countries developed robust surveil-

lance networks to monitor norovirus activity and outbreaks. These systems range from stand-alone norovirus data collection tools to broader electronic surveillance systems for all types of infectious diseases. In terms of geographic scope, reporting systems can be either single-country electronic reporting systems, such as Germany's SurvNet@RKI, which integrates nosocomial norovirus outbreak information into a larger infectious disease surveillance system (159), to multinational molecular epidemiologic surveillance efforts such as NoroNet. Spearheaded by the National Institute for Public Health and the Environment of the Netherlands (RIVM), NoroNet is an informal network of university and public health scientists, which maintains a database of norovirus sequences and monitors outbreak activity. NoroNet is comprised of reporting members across Europe, Asia, and Australia and has been helpful in identifying the emergence of new variant strains (160). A centralized European system for monitoring foodborne outbreaks, the Food-Borne Viruses in Europe Network, or FBVE, also includes norovirus reporting (161).

In the United States, a multifaceted surveillance network was developed by the CDC for monitoring enteric pathogens. Bacterial pathogens are monitored via PulseNet and typed by using pulsed-field gel electrophoresis methodology (162), whereas enhanced surveillance for noroviruses was launched in 2009 through a network called CaliciNet. While all states had the ability to perform norovirus testing by 2008, strain typing was not uniformly performed and was typically supported through the CDC National Calicivirus Laboratory (NCL). In an effort to provide robust, epidemiologically accurate data collection and dissemination, the CDC deployed a standardized method of strain typing to certified state and local laboratory members of CaliciNet to perform strain identifications and collaborate on outbreaks. Member laboratories are required to pass a yearly proficiency test in typing methodologies (163). CaliciNet proved useful in documenting the emergence of a new strain in 2012 (164).

Beyond the identification of new strains, norovirus outbreak reporting has demonstrated the significant financial and staff resource burdens placed on hospitals as a result of norovirus outbreaks. Launched in 2009 by the United Kingdom Department of Health, the Hospital Norovirus Outbreak Reporting System (HNORS) collects direct reports from infection preventionists about suspected and confirmed norovirus outbreaks. A 2013 review of the system's first full season demonstrated that more outbreaks were documented in that period than in the previous 17 years of norovirus reporting (1,884 versus 1,817) and helped document the significant financial implications of norovirus outbreaks within the National Health Service (165). Outbreak surveillance networks dedicated specifically to foodborne sources (e.g., FoodNet [United States] and OzFoodNet [Australia]) may prove useful in identifying small-scale norovirus transmission events (102, 166, 167).

CLINICAL DIAGNOSIS AND ENVIRONMENTAL DETECTION

Rapid identification of an outbreak is the key to effective infection control. While molecular methods offer a definitive way to establish etiology, these diagnostic tests may not be available in some clinical settings due to time delays or resource limitations. Kaplan's clinical and epidemiologic criteria (Table 5), developed prior to the advent of molecular methods, can be used to rapidly identify norovirus outbreaks (168). The utility of Kaplan's criteria was reevaluated in 2006, and these criteria continued to prove useful in identifying norovirus outbreaks where molecular diagnostics were not easily accessible (169).

TABLE 5 Kaplan's criteria

Criterion	Description
1	Vomiting in more than half of symptomatic cases
2	Mean (or median) incubation period of 24 to 48 h
3	Mean (or median) duration of illness of 12 to 60 h
4	No bacterial pathogen isolated in stool culture

Specimen Collection

Interpretation of norovirus diagnostic testing relies upon the quality of the specimens submitted for analysis and therefore requires that appropriate specimens are properly collected and handled (170). The optimal specimen for the diagnosis of norovirus infection is diarrheal stool. Specimens should be collected in a closed container within 48 to 72 h of the onset of symptoms, although norovirus may be detected in stool samples for 7 to 10 days or longer. Specimens should be refrigerated at 4°C prior to testing and frozen at −20°C or −70°C for long-term storage. Vomitus is an alternative specimen type that may be used to supplement stool sample testing during outbreak investigations. Collection and handling are the same as for stool specimens. Serum specimens are not recommended for routine diagnosis.

Norovirus Antigen Detection

Enzyme immunoassays. A number of enzyme immunoassays (EIAs) are commercially available for the detection of norovirus GI and GII antigens in stool specimens. The most commonly performed EIAs are IDEIA Norovirus (Oxoid Ltd., Hampshire, United Kingdom) and Ridascreen Norovirus (R-Biopharm, Darmstadt, Germany). These solid-phase, sandwich-type immunoassays demonstrate a wide range of sensitivities and specificities (Table 6). For example, the sensitivities and specificities for IDEIA Norovirus range from 38.0 to 78.9% and 85.0 to 100.0%, respectively. Similarly, the sensitivities and specificities for Ridascreen Norovirus range from 31.6 to 92.0% and 65.3 to 100.0%, respectively. Factors contributing to these differences in performance include the viral load present in the stool specimen and the viral genotypes represented in the sample set, as the assay antibodies show differential genotype affinities. These characteristics in turn may be affected by the clinical context of collection (outbreak versus sporadic cases), the timing of collection relative to symptom onset, and patient demographics (pediatric versus adult). Further sources of variability include the use of different EIA kit lots and assay iterations, known as generations (at least two generations for IDEIA and three for Ridascreen), and the use of different nucleic acid amplification tests (NAATs) as reference methods.

Several studies that have evaluated the performance of EIA for detection of norovirus in outbreak investigations compared to sporadic gastroenteritis cases have shown that these assays are more sensitive in the outbreak setting, particularly if multiple samples are collected (171, 172). For example, in a large European multicenter study reported by Gray et al. (172), IDEIA had a 33.3% sensitivity and Ridascreen had a 44.4% sensitivity when two specimens per outbreak were tested. Sensitivity increased to 80.0% for both methods if >7 specimens per outbreak were

TABLE 6 Performance of norovirus antigen enzyme immunoassays

Study reference	Test	Study location(s)	Case context	Population(s)	Sensitivity (%)	Specificity (%)	Reference method (reference[s])
363	IDEIA[a]	UK	Outbreak	Not specified	55.5	98.3	Conventional RT-PCR (180, 364)
365	IDEIA	USA	Outbreak, sporadic	Pediatric, adult	39.0	100.0	Conventional RT-PCR[d]
	SRSV(II)-AD[b]				80.0	69.0	
193	Ridascreen[c]	Germany	Outbreak, sporadic	Pediatric, adult	34.6	65.3	Nested RT-PCR (366)
367	Ridascreen	Australia	Outbreak	Not specified	47.0	71.0	Conventional RT-PCR (368)
369	IDEIA	Australia	Outbreak	Not specified	66.0	85.0	Conventional RT-PCR (368)
370	IDEIA	Netherlands		Not specified	38.0	96.0	Conventional RT-PCR (189)
	Ridascreen				36.0	88.0	
371	Ridascreen	Venezuela	Sporadic	Pediatric	60.0	97.5	Conventional RT-PCR (364)
372	IDEIA	Canada	Outbreak	Pediatric, adult	60.6	100.0	Composite[e]
	Ridascreen				80.3	100.0	
172	IDEIA	European	Sporadic	Not specified	46.2	95.7	Conventional RT-PCR[f]
	IDEIA	Multicenter	Outbreak		65.9	95.7	
	Ridascreen		Sporadic		31.6	99.5	
	Ridascreen		Outbreak		55.3	97.1	
373	IDEIA	Spain	Sporadic	Pediatric	76.9	85.9	Conventional RT-PCR (189, 374)
	Ridascreen				59.0	73.1	
171	IDEIA	USA, UK	Sporadic	Pediatric, adult	59.0	93.3	Composite[g]
			Outbreak		58.7	88.9	
375	IDEIA	Brazil	Sporadic	Pediatric	45.0	100.0	Real-time/conventional RT-PCR (184, 198)
	Ridascreen				63.0	100.0	
213	IDEIA	Hungary	Sporadic	Pediatric, adult	78.9	100.0	Composite[h]
376	Ridascreen[i]	Brazil	Sporadic	Pediatric, adult	49.5	93.9	Conventional RT-PCR (377)
			Outbreak		87.9	83.8	
378	Ridascreen[i]	Brazil	Sporadic	Pediatric	92.0	83.3	Conventional RT-PCR (377)
379	Ridascreen[i]	Germany	Sporadic	Not specified	77.0	96.0	Composite[j]
380	Ridascreen[i]	Italy	Sporadic	Pediatric, adult	40.0	96.0	Real-time RT-PCR (116)

[a] Oxoid Ltd, Hampshire, United Kingdom.
[b] Denka Seiken Co. Ltd., Tokyo, Japan.
[c] R-Biopharm, Darmstadt, Germany.
[d] RT-PCR primers were not specified.
[e] At least 2 positive test results by RT-PCR (88), electron microscopy, and 2 enzyme immunoassays are considered a true-positive result.
[f] Multiple RT-PCR assays were utilized in this study (76).
[g] Utilizes a diagnostic algorithm (171) that takes into account electron microscopy, conventional RT-PCR/bidirectional sequencing (131, 184, 211, 381), and real-time RT-PCR (202).
[h] At least 1 positive real-time RT-PCR test result by Argene Calici/Astrovirus Consensus (bioMérieux, Marcy l'Etoile, France) and SmartNorovirus (Cepheid, Sunnyvale, CA) is considered a true-positive result.
[i] The third-generation Ridascreen Norovirus assay was used in this study.
[j] At least 2 positive real-time RT-PCR test results by SmartNorovirus (Cepheid, Sunnyvale, CA), Ridagene Norovirus LC (R-Biopharm, Darmstadt, Germany), and an assay developed at the Robert Koch Institute (195) are considered a true-positive result.

tested. Similarly, Costantini et al. (171) reported that IDEIA had a 44.1% sensitivity when three specimens per outbreak were tested and a 77.8% sensitivity when >5 specimens per outbreak were tested. Based on statistical modeling, it has been estimated that at least six samples must be tested by EIA to achieve a 90% probability of detecting a norovirus outbreak (173). This minimum threshold of 6 outbreak samples has been adopted by the U.S. CDC and is recommended for outbreak management (174).

In 2011, the Ridascreen Norovirus third-generation test received Food and Drug Administration (FDA) approval for use in norovirus outbreak investigations. Notably, the intended use does not include the diagnosis of sporadic norovirus gastroenteritis cases. The package insert also acknowledges the relative insensitivity of EIA testing of limited sample numbers in outbreak settings. Compared to nucleic acid amplification tests, EIAs are generally simple to perform, do not require special molecular diagnostic laboratory facilities, and typically have a short turnaround time. For these reasons, the EIA is an attractive method for outbreak investigations, particularly in laboratories that lack molecular diagnostic capabilities. However, as nucleic acid amplification testing becomes commonplace in diagnostic and public health laboratories worldwide, real-time RT-PCR and other NAATs may replace the EIA entirely for outbreak investigation. This transition may be further hastened by the development of near-care and point-of-care molecular platforms capable of rapid sample-to-answer detection of norovirus RNA.

Rapid immunochromatographic assays. Rapid norovirus antigen detection via lateral-flow immunochromatographic assays may provide an alternative to standard EIAs for stool screening in near-care or point-of-care settings. Several commercial rapid antigen assays are available for the rapid detection of GI and GII noroviruses, including Ridaquick Norovirus (R-Biopharm, Darmstadt, Germany) and SD Bioline Norovirus (Standard Diagnostics, Inc., Kyonggi-do, South Korea). Similar to the EIA literature, there is a wide range of reported sensitivities (Table 7), and the assays and study designs are subject to the same sources of variability. Ridaquick sensitivities range from 17.0 to 83.0%, and SD Bioline sensitivities range from 23.0 to 92.0%. Both of these

TABLE 7 Performance of norovirus rapid antigen immunochromatographic assays

Study reference	Test	Study location	Case context	Population(s)	Sensitivity (%)	Specificity (%)	Reference method (reference[s])
382	Laboratory developed	Japan	Sporadic	Pediatric	69.8	93.7	Conventional RT-PCR (383)
384	Ridaquick[a]	Australia	Not specified	Not specified	82.0	100.0	Real-time RT-PCR (198)
385	Ridaquick	Netherlands	Not specified	Not specified	57.1	99.1	Real-time RT-PCR (195)
375	Ridaquick	Brazil	Sporadic	Pediatric	69.0	98.0	Real-time/conventional RT-PCR (284, 298)
386	Ridaquick	Australia	Sporadic, outbreak	Not specified	83.0	100.0	Composite[b]
387	Ridaquick	USA	Not specified	Not specified	61.4	100.0	Real-time RT-PCR (387)
379	Ridaquick	Germany	Sporadic	Not specified	69.0	97.0	Composite[c]
388	SD Bioline[d]	South Korea	Not specified	Pediatric, adult	90.2	100.0	Real-time RT-PCR[e]
389	SD Bioline	South Korea	Sporadic	Pediatric, adult	76.5	99.7	Real-time RT-PCR[f]
390	Ridaquick	Thailand	Sporadic	Not specified	48.2	87.5	Nested/real-time RT-PCR[g]
391	Ridaquick	France	Not specified	Not specified	17.0	100.0	Conventional RT-PCR (392)
	ImmunoCardSTAT![h]				26.0	100.0	
	Norotop[i]				52.0	100.0	
	SD Bioline				23.0	100.0	

[a] R-Biopharm, Darmstadt, Germany.
[b] Utilizes a diagnostic algorithm that takes into account electron microscopy and six conventional RT-PCR assays (386).
[c] At least 2 positive real-time RT-PCR test results by SmartNorovirus (Cepheid, Sunnyvale, CA), Ridagene Norovirus LC (R-Biopharm, Darmstadt, Germany), and an assay developed at the Robert Koch Institute (195) are considered a true-positive result.
[d] Standard Diagnostics, Inc., Kyonggi-do, South Korea.
[e] Ridagene Norovirus (R-Biopharm, Darmstadt, Germany) and AccuPower Norovirus real-time RT-PCR kit (Bioneer, Daejeon, South Korea).
[f] AccuPower Norovirus real-time RT-PCR kit (Bioneer, Daejeon, South Korea).
[g] Norovirus real-time RT-PCR kit (Shanghai ZJ Bio-Tech, Shanghai, China) and nested RT-PCR (393).
[h] Meridian Bioscience Europe, Nice, France.
[i] All.Diag SA, Strasbourg, France.

tests show high specificity: 87.5 to 100.0% for Ridaquick and 99.7 to 100.0% for SD Bioline. Given these performance characteristics, positive test results are reliable, although negative test results may require follow-up with a more sensitive NAAT.

Molecular Diagnostic Tests

Conventional RT-PCR. RT-PCR is the gold standard for the detection and typing of norovirus, and numerous conventional and real-time norovirus RT-PCR assays have been developed. The first-generation norovirus assays utilized a variety of primers based solely on the first described Norwalk virus genome and required RT in a separate tube prior to PCR (12, 175–178). These assays underestimated norovirus genetic diversity and therefore did not perform well when applied to clinical specimens. The second-generation assays took advantage of sequences from additional norovirus strains and for the most part used primers directed at conserved regions of the viral polymerase (179–182). Importantly, these assays required post-PCR analysis via hybridization probes or sequencing to improve sensitivity and specificity. The difficulty in designing broadly reactive primers to accommodate norovirus diversity was illustrated in a study comparing a set of five additional second-generation, conventional RT-PCR assays tested against a panel of stool specimens selected to cover a range of norovirus genogroups/genotypes (183). Although 84% of the specimens were detected by at least one assay, the sensitivity of individual assays ranged from just 52 to 73%. These conventional assays were optimized in a variety of different ways to improve detection (184–189); however, there remained issues of assay complexity and postamplification specimen handling.

Real-time RT-PCR. These limitations were addressed with the development of real-time RT-PCR for norovirus diagnostics. These assays used numerous detection methods, including SYBR green (190–193), hydrolysis (TaqMan) (194–202), and hybridization probes (203, 204). While many of these assays were directed at the viral polymerase gene, further sequence analysis revealed that a conserved region at the ORF1-ORF2 polymerase-capsid junction could also be used as an effective target for detection. Kageyama et al. described the first of these junction-targeting assays, which used two reactions to detect both GI and GII noroviruses (198). Similarly, Hohne and Schreier designed a two-reaction, real-time assay for GI and GII viruses using their own ORF1-ORF2 primer-probe sets (196). Importantly, this assay did not require a separate RT reaction.

To further minimize the reaction setup time and the potential for carryover contamination, GI and GII ORF1-ORF2 primer-probe sets were optimized for use in a single, multiplex TaqMan reaction (195, 197). In these assays, the probes were differentially fluorescently labeled to allow simultaneous detection and genogrouping. This multiplex, multiprobe approach directed at ORF1-ORF2 has also been used with GII/GIV TaqMan probes (199), GI/GII/GIII TaqMan probes (205), and GI/GII hybridization probes (204). It remains unclear, however, whether immediate norovirus genogrouping is important for outbreak control or clinical management. Simple, broadly reactive assays (177, 206) may be more important in the acute setting. Alternatively, the routine use of assays that detect and type norovirus may simultaneously allow laboratories to more rapidly monitor epidemiological patterns and highlight geographic regions or communities requiring further investigation (207).

Given the numerous real-time RT-PCR assays available for norovirus detection and genotyping, well-controlled, comparative studies similar to earlier work by Vinje et al. (183) are required to accurately determine the relative performance characteristics of

TABLE 8 Commercial norovirus RT-PCR assays

Assay	Company	Method
Argene Calici/Astrovirus Consensus	bioMérieux, Marcy l'Etoile, France	RT-PCR ELOSA[a]
SmartNorovirus	Cepheid, Sunnyvale, CA	Real-time RT-PCR
RealStar Norovirus	Altona Diagnostics, Hamburg, Germany	Real-time RT-PCR
Ridagene Norovirus	R-Biopharm, Darmstadt, Germany	Real-time RT-PCR
AccuPower Norovirus	Bioneer, Daejeon, South Korea	Real-time RT-PCR
Norovirus real-time RT-PCR	Shanghai ZJ Bio-Tech, Shanghai, China	Real-time RT-PCR

[a] ELOSA, enzyme-linked oligosorbent assay.

these assays. Vainio and Myrmel (208) provided the first of these studies, by looking at two assays described above (192, 196) as well as two assays initially designed for screening of shellfish (209, 210). After a detailed analysis, the duplex, GI/GII, real-time TaqMan RT-PCR assay designed by Jothikumar et al. (209) was selected for in-house use. Compared to a conventional nested approach (208, 211), this assay, which employs modifications of the primer-probe sets reported by Kageyama et al. (198), had a clinical sensitivity of 91%. These results were superior to those of the SYBR green assay reported by Richards et al. (80%) and slightly inferior to those of the TaqMan assay reported by Hohne and Schreier (93%) but with the advantage of detection of GI and GII noroviruses in a single reaction. This study was performed on specimens from norovirus outbreaks in Norway, so additional work will be required to account for norovirus diversity in different populations. Furthermore, this assay was selected based on both clinical and practical considerations, yet it was the only assay evaluated that was capable of single-tube identification of multiple genogroups. Future work is required to provide a more comprehensive analysis of the numerous real-time norovirus assays now available with these characteristics.

Commercial RT-PCR assays. Several commercial RT-PCR reagents are available for norovirus RNA detection (Table 8), although comparisons with one another or the large number of laboratory-developed norovirus RT-PCRs are not widely available. The Argene Calicivirus/Astrovirus consensus test (bioMérieux, Marcy l'Etoile, France) is a second-generation RT-PCR assay that requires a detection step via microplate hybridization using biotinylated probes. This test can identify caliciviruses and astroviruses but cannot distinguish between noroviruses and sapoviruses (212). Kele et al. used selected samples from sporadic cases of gastroenteritis in Hungary to evaluate the performance of Argene Calicivirus/Astrovirus Consensus and SmartNorovirus (Cepheid, Sunnyvale, CA), a set of primers and differentially labeled probes that allow real-time PCR detection and differentiation of GI and GII noroviruses by real-time RT-PCR (213). When true positives were defined as at least one positive RT-PCR result, the sensitivities of Argene Consensus and SmartNorovirus were 92.8% and 91.2%, respectively.

R-Biopharm (Darmstadt, Germany) offers two internally controlled, norovirus real-time PCR assays, Ridagene Norovirus, for qualitative detection of GI and GII noroviruses, and Ridagene Norovirus I&II, which both detects and differentiates GI and GII noroviruses in a single reaction. When the AccuPower Norovirus real-time PCR assay (Bioneer Co., Daejeon, South Korea), another internally controlled assay for detection of G1 and GII noroviruses, was compared to Ridagene Norovirus, there was 99.0% (96/97) positive agreement and 95.1% (175/184) negative agreement (214). Similarly, comparison of the Ridagene Norovirus I&II assay with conventional RT-PCR using stool specimens from distinct outbreaks in Victoria, Australia, in 2012 and 2013 revealed 98% sensitivity (85% [11/13] for GI and 100% [87/87] for GII) and 98% (98/100) specificity (215).

Future comparative studies with large, globally distributed sets of stool samples from sporadic gastroenteritis cases and outbreak settings will be required to better define the performance characteristics of these commercial reagents.

Multiplex PCR/RT-PCR tests for diarrheal pathogens. The development and widespread use of commercial, highly multiplexed molecular diagnostic technologies have revolutionized testing for infectious diseases. Although initial efforts were dedicated to the design of respiratory virus panels, the focus has now shifted to gastrointestinal pathogens, with a number of manufacturers developing multiplex panels for diarrheal disease. The first of these panels is the xTAG Gastrointestinal Pathogen Panel (GPP) (Luminex, Austin, TX). In addition to norovirus genogroups I and II, this assay detects rotavirus A, adenovirus 40/41, *Giardia*, *Cryptosporidium*, *Entamoeba histolytica*, *Campylobacter*, *C. difficile* toxin A/B, *Salmonella*, *Shigella*, *Vibrio cholerae*, *Escherichia coli* O157:H7, as well as enterotoxigenic and Shiga-like toxin-producing *E. coli*. This method utilizes multiplex RT-PCR followed by target-specific primer extension for the addition of oligonucleotide hybridization tags. The tagged amplicons are then specifically hybridized to a set of microspheres with unique spectral signatures and coupled to capture sequences complementary to the tag sequence. Finally, the captured amplicons are labeled with a detection reagent, and bead-bound amplicons are counted via flow cytometry. This liquid-based array approach allows a significant level of multiplexing; however, it is laborious, it has a long turnaround time, and, because several steps require the handling of amplicons, there is a high risk of contamination.

A number of studies utilizing the xTAG GPP have been carried out, and the performance characteristics of the norovirus component of the assay are summarized in Table 9. Claas et al. demonstrated good sensitivity (GI, 100% [9/9]; GII, 92.5% [62/67]) and specificity (GI, 100% [642/642]; GII, 97.6% [570/584]) compared to real-time RT-PCR, although it is important to note that all xTAG GPP testing in this study was performed by the manufacturer (216). Wessels et al. also showed good sensitivity (94.4% [17/18]) and specificity (100% [375/375]) compared to real-time RT-PCR (217, 218). Studies by Mengelle et al. and Navidad et al. are difficult to interpret, as very few norovirus reference method-positive specimens (six total) were identified (219, 220). Finally, although Kahlau et al. had a large number of xTAG GPP norovirus-positive specimens, confirmatory RT-PCR testing was performed on only a subset of positive specimens, and none of the xTAG GPP-negative specimens were tested with the reference method (221).

Another multiplexing approach involves the use of TaqMan Low Density arrays (Life Technologies, Grand Island, NY), microfluidic cards comprised of 384 wells divided into 8 zones of 48 wells that are preloaded with a panel of singleplex TaqMan assay mixtures. Ports on the array allow extracted nucleic acids from 8 samples to be delivered to each zone for testing. Liu et al. (222)

TABLE 9 Norovirus detection using multiplex gastrointestinal pathogen panels

Study reference	Test	Study location(s)	Case context(s)	Population(s)	Genogroup	Sensitivity[c] (%)	Specificity (%)	Reference method(s) (reference)
216	xTAG GPP[a]	International Multisite	Sporadic	Pediatric, adult	I	100.0	100.0	Real-time RT-PCR (218)
					II	92.5	97.6	
219	xTAG GPP	France	Sporadic	Pediatric, adult	I or II	0.0	93.6	ImmunoCardSTAT![b]
220	xTAG GPP	United States	Sporadic, outbreak	Pediatric, adult	I	NA	100.0	Real-time RT-PCR (202)
					II	100.0	100.0	
217	xTAG GPP	Netherlands	Sporadic	Not specified	I	NA	100.0	Real-time RT-PCR (218)
					II	94.4	100.0	
222	TaqMan Array	Tanzania, Bangladesh	Not specified	Pediatric	II	100.0	96.2	RT-PCR Luminex (223)
224	BioFire FilmArray GI Panel[e]	United States	Not specified	Not specified	I or II	96.2[d]	99.8	xTAG GPP,[f] real-time RT-PCR (202)

[a] Luminex, Austin, TX.
[b] Meridian Bioscience Europe, Nice, France.
[c] NA, not applicable; genogroup I-positive samples were not detected by the reference method.
[d] The composite reference requires at least two positive tests to be considered positive. Sensitivity and specificity were calculated by using both prospective and retrospective samples.
[e] bioMérieux, Marcy l'Etoile, France.
[f] Utilized stool specimens collected in Carey-Blair medium rather than the manufacturer-recommended raw stool specimens.

developed a gastrointestinal TaqMan array that detects 19 enteropathogens and includes the norovirus GII primer-probe set reported by Kageyama et al. (198). Compared to a laboratory-developed RT-PCR Luminex assay that also utilizes the GII primer and probe sequences of Kageyama et al. (223), the TaqMan array demonstrated 100% (31/31) sensitivity and 96.2% (75/78) specificity for norovirus GII.

While the xTAG GPP and TaqMan array methods are of high complexity and require separate nucleic acid extraction prior to amplification and detection, the BioFire FilmArray (bioMérieux, Marcy l'Etoile, France) is a moderate-complexity, 60-min sample-to-answer system that performs sample preparation, amplification, and detection in a single disposable pouch. The FilmArray GI panel detects 22 bacterial, protozoan, and viral targets, including norovirus GI/GII, although like the xTAG GPP, the FilmArray assay does not distinguish between genogroups. Khare et al. evaluated the FilmArray GI panel and showed 96.2% (52/56) sensitivity and 99.8% (441/442) specificity for norovirus GI/GII compared to a composite reference that included the xTAG GPP (224).

Additional large independent studies will be required to further characterize the norovirus component of these panels as well as other multiplex gastrointestinal panels currently in development. An important preliminary finding in these initial studies is the identification of infections with multiple pathogens. The evaluation of the clinical consequences of these coinfections will be an important area of future investigation.

Isothermal amplification. In addition to the wide variety of RT-PCR-based amplification assays, isothermal PCR alternatives have also been developed for norovirus detection. Several groups have designed nucleic acid sequence-based amplification (NASBA) strategies by using previously reported primer pairs modified for NASBA compatibility (225–228). A small study by Houde et al. (226) determined that NASBA and RT-PCR using the GII primer sets described by Kageyama et al. (198) showed equivalent analytical sensitivities but that the NASBA assay provided less consistent signals. Many NASBA formats, including those described above, require an additional product detection step. However, Patterson et al. (229) designed a NASBA assay using a molecular beacon probe that allowed real-time detection. This assay was 88% sensitive compared to conventional RT-PCR, suggesting that the assay requires further optimization. A norovirus NASBA assay, Swiftgene Norovirus GI/GII, is commercially available in Japan (Kainos Laboratories, Tokyo, Japan).

The final, real-time, non-PCR, nucleic acid-based approach for norovirus diagnosis is RT–loop-mediated isothermal amplification (RT-LAMP) (230–232). Fukuda et al. (230) described a two-reaction, GI- and GII-specific RT-LAMP assay also using primers directed at the ORF1-ORF2 junction. Compared to conventional RT-PCR (184), the RT-LAMP assay had 100% clinical sensitivity. Based on this work, a commercial assay, Loopamp Norovirus GI and GII, was developed (Eiken Chemical, Tokyo, Japan) (232). One advantage of this approach is that detection is performed via inexpensive, real-time turbidimetry or simple, endpoint, visual examination. Future work will be required to compare the performance characteristics of RT-LAMP to those of real-time RT-PCR.

NOROVIRUS PREVENTION AND CONTROL

Several studies, with various degrees of evidence quality, on infection prevention and control practices to interrupt the transmission of norovirus in health care settings have been reported. Many of these results are summarized in the HICPAC (Healthcare Infection Control Practices Advisory Committee) guidelines for the prevention and control of norovirus gastroenteritis outbreaks in health care settings published in 2011 and in a recent review of norovirus infection control measures (233, 234). The three main strategic areas included staff and patient policy development, hand hygiene, and proper environmental disinfection. Despite the breadth of existing literature on norovirus outbreaks and mitigation strategies, a recent survey of infection preventionists showed clear room for improvement in their knowledge of both prevention and control practices (235).

Staff and Patient Policies

An efficient response to a suspected norovirus outbreak is predicated on preexisting staff training and the rapid initiation of out-

break management policies, although evidence in support of these practices is minimal and based substantially on descriptive studies and single-institution reports. Lynn and colleagues described two norovirus outbreaks in elderly care wards occurring 18 months apart (236). Lessons learned from a review of the first outbreak were used to develop policies for staff absenteeism, financial compensation, and patient movement, among other outbreak response behaviors, in advance of the second outbreak. Applications of these polices resulted in a reduced duration of hospital ward closure (from 11 to 6 days) and a reduced staff attack rate (from 41% to 18%). In a Hong Kong health system of seven hospitals with an already low incidence of nosocomial norovirus transmission, investigators demonstrated that targeted infection control measures, coupled with rapid accurate surveillance screening with PCR testing, were able to further reduce the incidence of norovirus compared to control health care systems (237). These measures included additional staff training sessions on infection control practices, which reached 91.6% of the professional staff over the study period. In order to disrupt a norovirus outbreak in a Canadian tertiary-care facility, one Alberta hospital established an outbreak management committee to reinforce routine infection prevention practices and implement infection control strategies. This was coupled with a comprehensive communication strategy for informing staff, patients, and visitors of up-to-date outbreak information (238). No studies have definitely demonstrated which education policies and practices are most effective in sustaining good infection control practice, although the HICPAC recommends staff, patient, and visitor education on symptoms, transmission, and prevention strategies during suspected or confirmed norovirus outbreaks (233).

Ward closure is another oft-employed control strategy with limited supporting evidence. It became the mainstay of infection prevention strategies in the United Kingdom in the early 2000s following publication of Health Protection Agency (HPA) guidelines which stipulated that wards should be closed for at least 72 h after the last case of norovirus and only after a thorough terminal cleaning has been performed (239). The goal of ward closure is to prevent the transfer of new susceptible patients into an affected ward and the transfer of potentially ill patients out to other unaffected wards. This costly infection control intervention is thought to be necessary to control viral gastroenteritis outbreaks because of the ease of transmissibility (240). The majority of evidence in favor of ward restriction or closure has been reported in descriptive studies (241–243). While many of these studies reported early interruption of transmission, it was at substantial cost to the affected health care systems.

The decision to implement aggressive norovirus control strategies, such as restricting ward admissions, has been evaluated from an economic standpoint in a few studies. Estimates of the cost of single-institution nosocomial norovirus outbreaks reported in the literature range from US$40,000 to more than US$650,000 (143, 244). An Austrian hospital norovirus outbreak from December 2006 to February 2007 involved 3 separate ward closures, 90 patients, and an estimated cost of €80,138 (245). Lopman and colleagues estimated the direct cost, due to bed closure and staff absences, of nosocomial gastroenteritis outbreaks to the National Health Service in the United Kingdom to be approximately US$1 million per 1,000 hospital bed-days, and >60% of viral gastroenteritis outbreaks were attributed to norovirus (241).

Evidence that complete ward closure may be an overly conservative reaction to nosocomial norovirus outbreaks at too high an opportunity cost is beginning to emerge. Beginning in 2007 to 2008, several investigators evaluated partial ward closure as a means of restricting nosocomial spread and limiting service disruptions. Cohorting by bay, as opposed to total-ward closure, resulted in decreased total closure time and improved the outbreak management efficiency in one study (246). Additionally, in a before-and-after-program implementation study conducted by the Lancashire Teaching Hospitals, the modified bay closure strategy resulted in a significant decrease in the ratio of hospital to community outbreaks, with the number of confirmed outbreaks in hospitals decreasing from 42 to 25 during the 2 study points, while the number of community outbreaks increased from 46 to 81 ($r = 0.317$; $P = 0.025$). The number of days of restricted admissions on hospital wards per outbreak also decreased from 8 days to 6 days ($r = 0.742$; $P = 0.041$). Finally, the number of hospital bed-days lost per outbreak decreased from 29 to 5 between the two norovirus seasons ($r = 0.344$; $P < 0.001$) (247). That study did not show any significant change in the number of patients or staff affected during each outbreak, although fewer lost bed-days resulted in cost savings. Currently, ward closure and limiting transfers of symptomatic patients are category II HICPAC recommendations (233).

Several studies describe visitor-specific policies that were implemented during outbreaks in an effort to reduce the number of transmissions among patients and staff. In 2004, 24 norovirus outbreaks were reported in the city of Baltimore, MD. Infection control staff at Johns Hopkins Hospital reported their efforts to thwart the epidemic at their institution with several enhanced infection control policies. These policies included screening of all visitors for gastrointestinal symptoms by nurse managers. Any visitors who screened positive were blocked from visiting patients in the units for 72 h (244). Ultimately, visitors were banned entirely due to the persistence of the outbreak. In another acute-care setting, visitors were registered for 14 days during an outbreak and administered a standard sign-and-symptom questionnaire to uncover possible cases of gastroenteritis among visitors to a pediatric ward (248). The total number of visitors per inpatient was also limited to 2.

Staff and patient cohorting is one of the most frequently reported control actions during outbreaks (249). This is achieved by several means, as reported in descriptive studies of nosocomial norovirus outbreaks (236, 243, 244, 248, 250). In one setting, nurses were divided into teams, with one team being assigned to symptomatic patients and an alternate team caring for asymptomatic patients only (244). In another example, staff who had worked in affected areas were restricted to those areas and not assigned to unaffected patient units (248).

In essentially all reported outbreaks in both acute-care and long-term-care settings, ill health care workers have been placed on mandatory leave if they exhibit symptoms of gastroenteritis. Staff members are typically prohibited from returning to work for 48 to 72 h after the resolution of symptoms. In one report, a New Zealand hospital instituted additional paid sick leave during a norovirus outbreak to increase compliance with the mandatory 48-h work restriction (236).

Patient activity restrictions are another common infection control strategy used to limit norovirus outbreaks (243). In the literature, this has primarily involved prioritizing diagnostic studies and therapy sessions to only the most urgent cases during out-

breaks. For example, in an outbreak at the Johns Hopkins Hospital affecting an inpatient psychiatric unit, group therapy sessions were suspended during the norovirus outbreak, and this was informally tied to therapeutic delays for some patients (244).

Long-Term-Care and Other Facilities

The policies employed in acute-care settings, such as patient cohorting, activity restrictions, and work restrictions for ill and exposed staff members, have been adapted to long-term-care facilities (251). Additionally, some institutions may offer delayed admission to prospective long-term-care residents during ongoing outbreaks (252). In a prospective study of 49 Dutch nursing homes, investigators demonstrated that infection control measures were most effective when initiated within 3 days of the identification of an index case (253). Visitor restrictions have also been utilized in a number of reports of outbreaks in long-term-care or other extended-care settings. These restrictions have been centered primarily on restricting visiting privileges to immediate family only and prohibiting or discouraging children from visiting during outbreaks (243, 251).

Hand Hygiene

One of the primary recommended control strategies to interrupt norovirus transmission during outbreaks is appropriate hand hygiene, although this is based primarily on descriptive data (254). Use of soap and running water for a minimum of 20 s is recommended after patient contact with confirmed or suspected cases at a category IB level (strong recommendation and low-quality evidence) (233). Evaluation of disinfectants has proven challenging due to the limited ability to cultivate human norovirus in cell culture. Several viral proxies have been evaluated, including feline calicivirus (FCV) and murine noroviruses (MNVs), to assess the effectiveness of various disinfectants in hand contamination models (255). Researches in Germany, using FCV as a surrogate for human noroviruses, measured the virus-inhibitory effect of three types of alcohol (ethanol, 1-propanol, and 2-propanol) *in vitro* and *in vivo* with artificially contaminated fingertips. This study showed that ethanol and 1-propanol had higher $\log_{10}$ viral reduction values than did 2-propanol, which was not considered adequate by those authors (256). This study also demonstrated declining $\log_{10}$ viral reductions with increased concentrations of alcohol in each type of solution, which the authors theorized was related to the minimum amount of water necessary to achieve viral inactivation. Additionally, an FCV fecal hand contamination model supported the use of higher-concentration ethanol-based hand rubs rather than propan-1-ol-containing products (257). In one study of experimental human norovirus hand contamination, liquid soap wash and water rinse were superior to ethanol-based sanitizers based on viral recovery through quantitative RT-PCR (258). Triclosan-containing soaps and several other alcohol based-hand rubs showed inadequate levels of virus reduction (259). Overall, additional research on specific human noroviral inactivation by various common cleaning and sanitizing products is needed (233).

Isolation and Personal Protective Equipment Procedures

Symptomatic patients with vomiting and/or diarrhea should be placed in contact isolation (single room, gowns, and gloves) pending results of testing. After confirmation of norovirus infection, several descriptive studies support the use of continued contact precautions until some time period after the resolution of diarrhea, typically 48 h (236, 250, 251, 260). Enforcement of standard precautions throughout health care settings experiencing a nosocomial norovirus outbreak is thought to reduce transmission (244). The data in favor of gown and glove use for the prevention of norovirus transmission are derived primarily from observational or descriptive studies. Mask use is recommended only for staff who anticipate exposure to vomitus (143, 244).

Environmental Disinfection

Environmental persistence of norovirus has been reported in several settings, and its role in propagating outbreaks has been described in settings ranging from health care environments to food products and preparation sites to a concert hall (261–264). A large proportion of the evidence on environmental disinfection is derived from studies using FCV or other surrogate viruses, and direct correlation with success in disinfecting human noroviruses is unknown (233, 265). In general, hypochlorite (bleach) solutions of at least 1,000 ppm are the preferred disinfectants for contaminated surfaces and objects and must be used for an appropriate contact time (233, 266, 267). Quaternary ammonium compounds are also under investigation but have been somewhat less effective than bleach solutions (234, 267). Both the type of sanitizer and method of application can have an impact on virucidal success (268). In health care and non-health care settings, studies have focused on cleaning of high-touch surfaces, such as patient bathrooms, tables, chairs, computers, and commodes, in addition to floors and carpets (146, 243, 244, 261). Descriptive evidence supports rapid attention to and remediation of contaminated floors and patient care items and steam cleaning of carpets, although these data are of limited generalizability (233, 236, 244, 248). Additional steps, such as discarding all unused patient care items after discharge of a norovirus patient, disposing of curtains, and changing mop heads and cleaning solution after every three rooms, have been described and may be performed, but these steps are without direct correlation to a shortening of the duration of nosocomial outbreaks (233, 236, 243, 244, 265).

NOROVIRUS IMMUNOLOGY

An inability to cultivate norovirus *in vitro* until very recently and the absence of an animal model that closely resembles human disease, together with viral and human host diversity, have represented major obstacles to our understanding of the pathogenesis of and immune response to norovirus infection. As a consequence, much of our knowledge of the immunology of this highly species-specific virus revolves around studies of MNV and the use of virus-like particles (VLPs) of human norovirus. VLPs are the product of self-assembling viral structures derived from the expression of recombinant VP1. They are structurally and antigenically similar to their corresponding wild virions but lack genomic material.

Animal Models

Although no animal model to date has been entirely satisfactory, it has been demonstrated that chimpanzees can be successfully infected with GI.1 norovirus (269), while gnotobiotic pigs (270) and gnotobiotic calves (271) can be successfully infected with GII.4 norovirus. The development of a norovirus replicon that expresses nonstructural viral proteins in human hepatoma cells (272) and a reverse-genetics system driven by human elongation

factor 1 alpha that produces progeny virus containing infectious viral RNA (273) may provide insights into virus-host interactions at the cellular level. Furthermore, the development of a humanized immunodeficient murine model of human norovirus infection (274) may also prove useful although perhaps only to a limited extent. For example, Taube and colleagues reconstituted *Rag1*$^{-/-}$ *yc*$^{-/-}$ BALB/c mice (yc is the γ chain of receptors for interleukin-2 [IL-2], IL-4, IL-7, IL-9, and IL-15) with human CD34^{+} human hematopoietic stem cells after neonatal irradiation (275). Despite this manipulation, infection by the oral route was entirely unsuccessful, and intraperitoneal inoculation with a strain of human norovirus GII.4 was required but with no evidence of associated illness.

Some insights into norovirus infection may, however, be obtained from studies of murine models utilizing MNVs. MNVs are widespread in laboratory mice, and in contrast to human noroviruses, they can be propagated in tissue culture (276). Although MNV produces little or no outward signs of infection in wild-type laboratory mice (277), knockout studies indicate that both innate and adaptive immunity play critical roles in the control of MNV infection. Particularly important are type 1 and type 2 interferons (278–282), dendritic cell functions (283–285), and the production of neutralizing antibody (286–288). As such, MNVs may provide some important understanding of human norovirus infection that would not otherwise be possible to obtain (286).

Human Host Factors in Susceptibility and Resistance to Norovirus Infection

Almost 4 decades ago, Parrino and colleagues challenged and then rechallenged, after an interval of 27 to 42 months, 12 volunteers with stool filtrates containing the norovirus (GI.1) from the index outbreak that had been serially passaged through other human volunteers (289). Six subjects developed symptoms of gastroenteritis after the initial challenge, and each of these subjects also became ill upon rechallenge. In contrast, none of the 6 subjects who remained asymptomatic upon initial challenge became ill after rechallenge. Four of the six patients who developed symptoms were challenged a third time 4 to 8 weeks after the second challenge, and only one patient became ill. The investigators concluded that they had demonstrated the presence of short-term but the absence of long-term immunity to Norwalk virus infection. This conclusion does not, however, address the 6 subjects who failed to become ill after either the first or second challenge, a finding that suggested the possibility that some individuals are intrinsically resistant to Norwalk virus infection. Five years later, the discovery of familial clustering of infection, with some related groups having apparent resistance, was also observed in a large community outbreak traced to a swimming pool (111). These observations suggested the possibility that some individuals possess inherited protection against norovirus infection. Subsequent investigations determined that the reason for this inherited resistance lies in the natural variability of histo-blood group antigens (HBGAs) and their expression on the mucosal epithelial surface of the gastrointestinal tract (290).

HBGAs are oligosaccharide epitopes whose diversity results from the sequential addition of monosaccharides to glycan precursors (291, 292). The A and B red cell antigens are synthesized from a common intermediate molecule, the H substance, of which there are 3 types, but with the final fucosylated product having the same terminal disaccharide. There is no "O antigen": group O erythrocytes express the H antigen; hence, the ABO system is better labeled the ABO(H) system.

The fucosyltransferases FUT1 and FUT2 each add a fucose to the precursor disaccharides of the H substance. While the *FUT1* gene is expressed in erythroid progenitor cells, *FUT2* is expressed mostly in mucosal epithelial cells from which the enzymatic gene product is secreted into surrounding secretions such as saliva and breast milk. While also produced by FUT2, Lewis (Le) antigens are predominantly the result of fucosylation by a third enzyme, FUT3. Approximately 5% of the white population are homozygous for inactive *FUT3* alleles and, as a consequence, lack Le^{a} and Le^{b} and are termed Lewis negative (291). Lewis antigens are also present on mucosal surfaces and are secreted into the surrounding milieu.

The presence of H, Le^{b}, A, or B antigens in saliva and other secretions operationally defines the secretor phenotype and is evidence of an active *FUT2*, or "secretor," gene. Approximately 20% of individuals of European descent have, however, inherited two null *FUT2* alleles as a result, in 99% of cases, of a G428A mutation that introduces a stop codon (293). The resultant absence of HBGAs at mucosal surfaces and in surrounding secretions that characterize the nonsecretor phenotype plays a key role in protection against infection by most noroviruses, as demonstrated in challenge studies (294–296) and analyses of outbreaks, as reviewed by Rydell and colleagues (297).

Norwalk virus-derived VLPs bind to H antigen *in vitro* (298) and also hemagglutinate type A, AB, O, and, much more weakly, B red blood cells (295). They also bind to epithelial cells of the gastroduodenal mucosa of individuals who are secretors but not to those of nonsecretors (290). Thus, it appears that norovirus is among organisms, such as *Helicobacter pylori* (299), that utilize HBGAs expressed in the gastrointestinal tract as cell surface receptors (300).

Given the multiplicity of viral strains and of HBGAs, it is not surprising that there are diverse patterns of individual strain associations with individual HBGAs. In a study involving 14 norovirus strains, Huang et al. reported having identified 7 different patterns that could be classified into 2 groupings: one group of viruses recognized A and/or B and H antigens, while the second group reacted only with Lewis and/or H antigens (301). While there was some clustering of binding patterns depending on the phylogenetic relatedness of the viruses, both patterns could be found among both GI and GII viruses. GII.4 VLPs bind strongly to saliva of secretor-positive individuals regardless of the ABO(H) blood group (302), while strong binding of GI.1 VLPs is observed only with secretions of type A, AB, or O secretors (22, 294, 301, 303–306).

While initial studies indicated that a nonsecretor status seemed to provide total resistance to norovirus-associated illness, the degree of protection has now been demonstrated to be less than absolute. Examples of infection in nonsecretors include ones due to norovirus GII.2 Snow Mountain (307), GII.4 (308, 309), and GI.3 (310, 311). In fact, combining the data from two GI.3 outbreaks, it can be calculated that 11 of 22 (50%) nonsecretors and 46 of 90 (51%) secretors were infected (310, 311). In addition, binding to human Caco-2 intestinal cells by GII.6 norovirus strain VLPs is independent of HBGAs and is instead associated with cell maturity (312), as is that by the GII.4 Desert Shield strain (313). The receptors for these viruses remain unknown. In addition, inherited factors other than HBGAs may affect susceptibility to norovirus infection. For example, travelers to Mexico who have the lactoferrin T/T genotype may be protected against norovirus in-

fection despite being at an increased risk of all-cause traveler's diarrhea (314).

In addition to resistance to infection based on secretor status, norovirus infection results in adaptive immunity to homotypic viral challenge, albeit of relatively short duration, as was first reported by Parrino and colleagues in 1977 (289) and subsequently confirmed (294). For instance, a multiple-challenge experiment with Norwalk virus found evidence of protection for ≥6 months (315), and it is commonly stated that immunity lasts as long as 2 years (316). However, the relevance of many challenge experiments has been questioned because the inocula used in this and many other studies were likely several orders of magnitude higher (317) than that required for infection, and as a consequence, the duration of immunity in the natural setting may be significantly longer than that estimated from these experiments. Thus, Teunis and colleagues estimated the 50% infectious dose (ID_{50}) to be between 18 and 1,015 genomic equivalents (317). Atmar and colleagues found that the Norwalk virus ID_{50}s were estimated to be ≈1,320 genomic equivalents (≈3.3 RT-PCR units) in subjects who proved to be secretor-positive blood group O or A persons and ≈2,800 (≈7.9 RT-PCR units) for all secretor-positive persons (318, 319). On the other hand, the potential for natural exposure to much larger numbers of viral particles is significant. Thus, 1 ml of virus-containing vomitus from symptomatically infected subjects contained a median of 41,000 genomic equivalents (319). The norovirus load in feces is much higher and appears to be genogroup dependent, with reported medians of 8.4×10^5 cDNA copies per g in individuals with GI infection and 3.0×10^8 cDNA copies per g in individuals with GII infection (320). It is therefore possible that estimates from observational studies of natural infection may provide the best estimates of the duration of immunity. Thus, mathematical modeling taking into account observational data describing the age-specific incidence of norovirus disease, seasonality, and population immunity led to an estimated duration of immunity of 4.1 years (95% CI, 3.2 to 5.1 years) to 8.7 years (95% CI, 6.8 to 11.3 years) (316).

Complicating the determination of immunity duration by examination of naturally acquired infections is the fact that immunity may be strain specific, and any analysis is potentially confounded by the multiple genogroups, genotypes, and strains of virus, together with the continuing evolution of the virus. Thus, administration of stool filtrates from two distinct outbreaks to prison volunteers led to a lack of cross-protection between the Norwalk and Hawaii strains (321), now known to be prototypes of GI and GII noroviruses, respectively. A prospective study of diarrhea in infants in the first weeks of life (the median age at recruitment was 19 days) to the age of 2 years found evidence of protection that was genotype specific: 97% of repeat infections were due to a genotype that differed from that of a previous infection (322).

Although IgG antibody directed against norovirus antigens is present in the serum of >90% of individuals by the time they reach adulthood, and they nonetheless remain at risk of repeat norovirus infection (323), evidence indicates that blocking antibody plays a role in immunity to reinfection. While the inability to culture the virus *in vitro* precludes the ability to detect neutralizing antibody by classical methods, the prevention of binding of norovirus-derived VLPs or P particles to HBGA (blocking antibody) is believed to be an accurate surrogate of neutralization (324, 325).

In a volunteer study, preexisting antibody did not protect against disease resulting from an initial challenge, but a correlation with protection emerged after subsequent rechallenges (315). However, others have reported that preexisting antibody provides at least partial protection against naturally acquired infection (326, 327). The appearance of IgA antibody against norovirus in saliva by day 5 after challenge of genetically susceptible individuals correlated with protection (294), as did an early Th1 lymphocyte response (307). High prechallenge titers of blocking antibodies also correlate with protection against experimental challenge (325). Volunteers challenged with a GII.2 strain (Snow Mountain) elicited serum IgG antibody responses that were cross-reactive with another GII.1 viral strain (Hawaii), but lesser cross-reactivity was noted with salivary IgA, and neither antibody type was cross-reactive with GI.1 (307). A similar pattern of cross-reactivity was seen with T cells exposed to Snow Mountain virus, which elicited a predominantly Th1 response. Passive protection from a maternal source occurs, as demonstrated by the observation that exclusive breastfeeding of infants from the ages of 3 to 5 months was associated with protection, and infections that did occur in the first 6 months of life were more likely to be asymptomatic than were those that occurred at 6 to 11 months of age (55% versus 36%; $P < 0.001$) (322).

The IgG antibody response to challenge with different GI strains results in variable heterotypic responses that are likely determined by an individual's history of natural exposure to noroviruses and deceptive imprinting (e.g., by development of "decoy epitopes") (328).

Antibodies to antigens other than those of the viral capsid also result from viral challenge. Three-fourths of volunteers challenged with GI.1 virus had an antibody response to viral protease from either the homologous virus or GII.4 virus (Houston) (329), but these antibodies are not believed to be protective.

Immune Selection and Development of Viral Diversity

The viral capsid protein VP1 has 3 structural domains, with the shell (S) being the core from which 2 other domains, P1 and P2, protrude (330). P2 is the most exposed portion and is likely the major point of contact with HBGA ligands and with neutralizing antibody (22, 88, 331–333). In addition, mutations and recombination events involving P2 can significantly affect antigen properties and interactions with HBGAs (334). GII.4 strains, in particular, are undergoing rapid evolution that affects receptor binding by changes in surface-exposed P2 and antigenic expression, resulting in the emergence of new epidemic strains of the virus (25, 335–340). In contrast, there has been only limited evolution of GI viruses over the last 4 decades (334).

GII.4, although first recognized as a major epidemic strain in the middle of the last decade of the 20th century, has been circulating since at least 1974 (25). GII.4 undergoes epochal evolution characterized by periods of stasis followed by the emergence of a new epidemic strain. There have been 7 different GII.4 variants associated with global epidemics since the 1990s, which occurred in 1996, 2002, 2004, 2007 to 2008 (2 variant strains), 2009 to 2012, and 2012 onward (the Sydney strain) (341). Thus, on average, new variants of GII.4 have appeared every 2 to 3 years.

Evidence indicates that new variants emerge under positive selection (25), likely as a result of the pressure exerted by the development of herd immunity as larger portions of the population experience infection, with resultant viral antigenic drift (20, 342–345). GII.4 2012 Sydney, which has, to a large extent, replaced previously circulating GII.4 variants, had undergone changes in at least 2 epitopes recognized by blocking antibodies (344).

TABLE 10 Obstacles to norovirus vaccine development

Obstacle to norovirus vaccine development
Inability to cultivate norovirus *in vitro*
Inability to directly measure neutralizing antibody
Inherited host variability, especially with regard to HBGA
Multiple viral genogroups and genotypes and their continued evolution
Limited heterotypic immunity
Likely need for continuing vaccine reformulation
Uncertain duration of immunity
Incomplete understanding of the role of cellular immunity
Possible acceleration of viral evolution in response to a vaccinated population
Uncertain efficacy in most vulnerable individuals, including young children, the elderly, and the immunocompromised

While norovirus evolution is believed to result from the selective pressure of the immune system, Schorn and colleagues demonstrated amino acid changes in P2 and P1-2 during individual chronic infections due to GII.4 in renal transplant recipients and due to GII.7 and GII.17 in an additional patient each (60). Others evaluating two hematopoietic stem cell transplant recipients and one small bowel transplant recipient chronically infected with GII.4 or GII.7 found evidence of positive selection, with accumulation of an average of 5 to 9 mostly nonsynonymous mutations per 100 days in the hypervariable region of the P2 domain of the VP1 capsid gene (346).

The immune selection of norovirus variants has important implications for vaccine development.

NOROVIRUS VACCINE

There are strong public health and economic arguments in support of the potential benefits of the development of an effective norovirus vaccine. Using a simulation model, it was concluded that a vaccine with 50% protective efficacy for 12 months and costing US$50 would save US$1,000 to US$2,000 per case averted in the United States (347). Thus, despite the biological obstacles to vaccine development, which require dealing with the complex matrix of inherited human traits and variability among noroviruses (Table 10), the potential benefits would appear to be well worth the effort. Table 11 summarizes clinical studies on norovirus vaccines.

Most efforts at vaccine development are now focusing on the use of VLPs as the immunogen (348). GII.4 P particles are immunogenic in mice (284, 349), but evidence indicates that GII.4 VLPs are superior to homologous P particles (350). Furthermore, VLP vaccines have a successful history in the prevention of hepatitis B virus and of human papillomavirus infection (351).

Intravenous administration of Norwalk virus to chimpanzees led to the appearance of virus in feces (along with liver and duodenal and jejunal tissues), but all animals remained asymptomatic (25). Animals were resistant to rechallenge with Norwalk virus ≥4 months later, and this appeared to correlate with the antibody response to the virus. Intramuscular inoculation of other chimpanzees with VLPs derived from Norwalk virus protected against intravenous challenge with the same virus 6 and 18 months later, together with the development of blockade antibodies. These data provide evidence of homologous but not heterologous resistance and indicate that norovirus-derived VLP inoculation may produce homologous immunity.

Despite all the potential obstacles to the development of an effective vaccine, the interest is high, and by 2010, Herbst-Kralovetz and colleagues were able to list 12 phase 1 trials that had reported the immunogenicity of plant or insect cell-derived norovirus VLPs after mucosal delivery (352). Both oral and intranasal administrations have been shown to elicit antibody responses (353–355). El-Kamary and colleagues reported the results of two of these trials in that same year (355). These investigators administered GI.1-derived VLPs with the Toll-like receptor 4 (TLR4) agonist monophosphoryl lipid A (MLA) and mucoadherent chitosan formulated as a dry powder by the intranasal route and found evidence of safety and dose-dependent immunogenicity, both mucosal and systemic (355). The majority of circulating IgA norovirus antigen-specific cells carried markers indicative of homing to mucosal tissues alone or to mucosal and lymphoid tissues. Furthermore, subjects developed significant norovirus IgA and IgG memory B-cell responses (356).

This GI.1-derived VLP vaccine was subsequently further evaluated. Healthy adults with a functional *FUT2* gene, as evidenced by the presence of FUT2 detected by the presence of HBGAs in saliva, were randomized to receive either placebo or the adjuvanted GI.1 VLP vaccine (357). Two doses of each vaccine were administered intranasally 3 weeks apart. Participants were then challenged orally with a dose of Norwalk virus (48 RT-PCR units) that was ~10-fold higher than the ID_{50}. The vaccine was well tolerated, and 70% of 47 vaccine recipients had a ≥4-fold increase in the serum concentration of Norwalk virus-specific IgA antibody levels, as measured by an enzyme immunoassay. Changes in IgG and IgM antibody levels were limited, as was the level of HBGA blocking antibody. The vaccine was modestly protective against infection after challenge, with 81% of placebo recipients showing evidence of infection compared to 62% ($P = 0.05$) of those who received the vaccine, and it also reduced virus-specific gastrointestinal symptoms (69% of placebo patients versus 37% of vaccine recipients; $P = 0.009$). A *post hoc* analysis found evidence that a serum HBGA blocking antibody titer of ≥1:200 was associated with a >50% relative reduction in the frequency of both viral infection and illness. In addition, antigen-specific memory T cells

TABLE 11 Summary of selected norovirus vaccine studies

Reference	VLP genotype	Adjuvant(s)[a]	Route	Dose (μg)	Regimen	Challenge dose (RT-PCR units)
353	GI.1	None	Oral	100 or 250	2 doses 21 days apart	None
354	GI.1	None	Oral	250, 500, or 2,000	2 doses 21 days apart	None
355	GI.1	MLA, chitosan	Intranasal	5, 15, 50, or 100	2 doses 21 days apart	None
357	GI.1	MLA, chitosan	Intranasal	100	2 doses 21 days apart	48 (GI.1 virus)
358	GI.1/GII.4	MLA, alum	Intramuscular		2 doses 28 days apart	4,000 (GII.4 virus)

[a] MLA, monophosphoryl lipid A.

were generated in all subjects who received the highest dose (100 μg) of vaccine. Thus, this proof-of-concept trial demonstrated the ability of an intranasal vaccine to provide a degree of short-term protection against illness after homotypic challenge.

A systemically administered bivalent vaccine has also been evaluated in humans. Healthy adults were randomized to receive either placebo or a bivalent GI.1/GII.4-derived VLP vaccine with MLA and alum (358). The GII.4 component was a consensus product designed by alignment of the VP1 sequence of 3 GII.4 strains and was shown to be antigenically similar to GII.4 strains that have been circulating for 3 decades (359). Each vaccine was administered in 2 intramuscular doses at an interval of ≥28 days, and subjects were then challenged at least 28 days later with 4,000 RT-PCR genome equivalents of a heterologous GII.4 strain. The primary composite endpoint of reduction in any type of gastroenteritis or norovirus case ascertainment was not achieved. However, fewer of the vaccine recipients ($n = 56$) than placebo recipients ($n = 48$) reported vomiting and/or diarrhea of any severity after challenge (20% versus 41.7%; 52% reduction; $P = 0.028$).

There is interest in the development of norovirus vaccines to be given in combination with other immunogens. A vaccine containing human rotavirus recombinant VP6 as well as VLPs derived from GII.4, GII.12 New Orleans, and GI.3 was immunogenic for all components in BALB/c mice (360, 361). In addition, a bivalent norovirus/hepatitis E virus vaccine has been demonstrated to be immunogenic in mice (362).

Many factors will need to be effectively addressed for the development of a useful norovirus vaccine (318). Given our current understanding of the virus and the host response to it, such a vaccine will almost certainly be multivalent and, as is the case with influenza virus, may require frequent reformulations in response to viral evolution.

CONCLUSIONS

Norovirus is an important cause of morbidity due to acute gastroenteritis both within health care institutions and in the broader community. Although mortality is typically limited to the extremes of age, the disease exacts a significant toll on the health care system. Therapeutic management is usually supportive, and advances in molecular diagnostics may lead to the earlier identification of outbreaks and a reduction in person-to-person transmissions, particularly in vulnerable patient populations. Ongoing global reporting initiatives will be enhanced by improved diagnostic methods. Additionally, global control efforts will benefit from the growing knowledge of the clinical implications of various norovirus strains. Several advances into understanding the relationship among the viral strain, the host human blood group antigen type, and disease susceptibility have recently been elucidated, but this work has not yet been extended to clinical practice. The interplay of norovirus and host immunity still poses many unanswered questions. Areas of future research may overcome technical limitations, such as the inability to cultivate norovirus *in vitro*, and may elucidate a way to directly measure neutralizing antibodies, which could pave the way for vaccine development. The recent demonstration of infectability of B cells by the human norovirus GII.4 Sydney due to the presence of *Enterobacter cloacae* expressing H antigen may represent an important advance in our ability to understand norovirus replication (394). Several additional factors, such as inherited host variability, noroviral genogroup diversity, and ongoing viral evolution, will continue to complicate the process of vaccine development. Until a broadly effective, sustainable vaccine is developed, outbreak management will depend primarily on infection control efforts.

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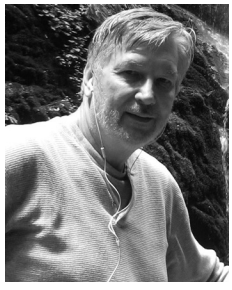

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