Epidemiologic and Molecular Trends of "Norwalk-like Viruses" Associated with Outbreaks of Gastroenteritis in the United States

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Between July 1997 and June 2000, fecal specimens from 284 outbreaks of nonbacterial gastroenteritis were submitted to the Centers for Disease Control and Prevention for testing for "Norwalk-like viruses" (NLVs). Specimens were examined by reverse-transcription polymerase chain reaction and direct electron microscopy for the presence of NLVs. Adequate descriptive data were available from 233 of the outbreaks, and, of these, 217 (93%) were positive for NLVs. Restaurants and events with catered food were the most common settings, and contaminated food was the most common mode of transmission. Genogroup II (GII) strains were the predominant type (73%), with genogroup I strains causing 26% of all NLV-positive outbreaks. Certain GII clusters (GII/1,4,j) were more commonly associated with outbreaks in nursing home settings than with outbreaks in other settings. Strain diversity was great: one potential new sequence cluster was implicated in multiple outbreaks, and strains belonging to a tentative new genogroup were identified.

"Norwalk-like viruses" (NLVs), also called small round structured viruses (SRSVs), are a genus of genetically diverse, single-stranded RNA viruses belonging to the family *Caliciviridae* [1–3]. In industrialized countries, NLVs may be responsible for 68%–80% of all outbreaks of gastroenteritis [4–8]. These outbreaks occur in all age groups and in many settings, including schools, nursing homes, hospitals, cruise ships, restaurants, and events with catered meals. NLVs are spread through contaminated food and water or by direct person-to-person contact [5–11].

Three genogroups of NLVs have been described: genogroups I (GI) and II (GII) infect humans, whereas genogroup III (GIII) strains have been detected only in cattle. The 3 genogroups can be further divided into at least 17 genetic clusters on the basis of the amino acid sequences from the entire capsid gene. GI and GII presently consist of 7 and 8 genetic clusters, respectively, whereas GIII contains 2 tentative clusters [3, 12]. Strains belonging to GI and GII genetic clusters have been shown to cocirculate [8, 9, 13–16], whereas at least 1 strain has been identified in a global epidemic [6, 17]. GII was the predominant strain type identified in the 1990s; few GI strains were reported [4, 6, 8–10]. Strains from particular genetic clusters have been shown to change in predominance over time, with similar patterns seen in different parts of the world. For example, GII/3 (Toronto virus) was reported as being epidemic in outbreaks in both The Netherlands and the United Kingdom in 1994 [6, 18]; GII/4 (Bristol virus) was reported to be epidemic in many parts of the world, including the United States, the United Kingdom, The Netherlands, Australia, and elsewhere in 1995–1996 [4, 6, 10, 17], and the Venlo strain caused a small epidemic in The Netherlands in the fall and winter of 1996 [6].

In this study, we describe laboratory and epidemiologic data from outbreaks of acute nonbacterial gastroenteritis reported to the Centers for Disease Control and Prevention (CDC) over the 3-year period from July 1997 through June 2000. We used this data set to identify the epidemiologic trends in reported outbreaks of nonbacterial gastroenteritis in the United States, to determine the prevalence of NLVs as a causative agent in these outbreaks, and to examine the genetic diversity of NLV strains circulating in the United States, as determined on the basis of genetic sequence analysis. We compared these data with those from our previous report that reviewed NLV strains detected in outbreaks of acute gastroenteritis between January 1996 and June 1997 [9] and with that of reports from other laboratories [4–8, 10, 11], to gain a more global view of the importance of NLV infections and the circulation patterns of common NLV strains.

Materials and Methods

Outbreaks of suspected nonbacterial acute gastroenteritis are reported to the CDC by investigators at state or local health departments, generally when investigators are seeking laboratory as-

Received 25 October 2001; revised 5 March 2002; electronically published 10 June 2002.

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The Journal of Infectious Diseases 2002; 186:1–7
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0022-1899/2002/18601-0001$15.00

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sistance to test for enteric pathogens [19]. As many as 10 samples from each outbreak are first tested for the presence of NLVs and then, if tests for NLVs are negative, examined for other viral pathogens. In this study, we examined fecal specimens submitted to the CDC for viral testing for all reported outbreaks that occurred in the United States or aboard cruise ships docking at US ports during the 3-year period from July 1997 to June 2000 for which no bacterial pathogen was identified and ⩾4 fecal specimens were available for testing.

Epidemiologic data for each outbreak were collected on a standardized form and submitted to the CDC with each group of specimens. For this study, we examined the setting of the outbreak, the implicated or suspected mode of transmission of the infectious agent, the size of the outbreak, including both the actual number of persons ill and the number at risk, and the age of affected persons. Data were not available for all categories in all outbreaks.

The samples were processed as follows: a 10%–20% suspension of stool in sterile water was mixed with 1,1,2-trichloro-1,2,2-trifluoroethane and centrifuged at 1700 *g* for 10 min. RNA was then extracted from the stool suspensions, using either the UltraSpec-3 RNA kit (Biotecx Laboratories), as directed by the manufacturer's instructions for RNA precipitation, or a NucliSens Extractor (BioMérieux), as directed for small sample volumes. Reverse-transcription polymerase chain reaction (RT-PCR) was done using the G1 and G2 primer set (now referred to as region A primers), as described by Ando et al. [20], the region B primers (R.L.F., unpublished data), or both sets. Amplified products were detected on a 3% (region A) or 2% (region B) ethidium bromide–stained agarose gel. At least 2 samples from each positive outbreak were chosen for nucleotide sequencing, prepared as described elsewhere [20], and sequenced on an automated sequencer (model 377; Applied Biosystems) using a BigDye Terminator Cycle Sequencing Ready Reaction kit with AmpliTaq DNA Polymerase FS (PE Applied Biosystems). All sequences were analyzed by use of the GCG suite of programs [21], including the DISTANCES program using uncorrected distances and the GROWTREE program with the neighbor-joining method to create a phylogram. On the basis of the resulting phylogram, strains were placed into a genetic cluster, using, with modifications, the nomenclature system of Ando et al. [12].

Because the region of sequence determined in this study is small (81 bp for region A and 172 bp for region B), the sequences have not been individually submitted to GenBank but are available from the authors upon request. GenBank accession numbers for reference strains are as follows: GI-1-Norwalk, M87661; GI-2-Southampton, L07418; GI-3-Desert Shield, U04469; GI-4-Chiba, AB022679; GI-4-New Orleans, AF414402; GI-5-Musgrove, AJ277614; GI-5-Appalachicola Bay, AF414406; GI-6-Hesse, AF093797; GII-1-Hawaii, U07611; GII-1b-Wortley, AJ277618; GII-2-Melksham, X81879; GII-3-Toronto, U02030; GII-4-Bristol, X76716; GII-5-Hillingdon, AJ277607; GII-5-White River, AF414423; GII-6-Seacroft, AJ277620; GII-6-Florida, AF414410; GII-7-Leeds, AJ277608; GII-7-Gwynedd, AF414409; GII-8-Amsterdam, AF195848; GII-8-Idaho Falls, AYO54299; GII-n-Erfurt, AF427118; GIII-1-Jena, AJ011099; GIV-1-Alphatron, AF195847; and GIV-1-Fort Lauderdale, AF414426. GenBank accession numbers for sequences described in this study are AF493117–AF493231.

Results

Outbreaks. In total, 284 outbreaks were reported to the CDC between July 1997 and June 2000 with requests for NLV testing. Of these, 233 met the criteria for this study, and 51 were excluded: 38 had inadequate numbers of specimens, 6 consisted of only serum or emesis samples, 5 were from outbreaks abroad, and 2 outbreaks had samples that were improperly collected or stored. The 233 outbreaks that met the criteria for study included 2709 stool and emesis samples, of which 2391 were tested by RT-PCR.

The 233 outbreaks were reported from 29 states, the District of Columbia, the US Virgin Islands, and from cruise ships docking at American ports (figure 1). Although some states submitted specimens from many outbreaks (e.g., Ohio, 61; Florida, 29; and Maryland, 22), most states provided specimens from ⩽5 outbreaks, and 16 states submitted no specimens for testing. Ten state laboratories performed RT-PCR diagnostics for NLVs during the study period, and outbreaks investigated by these laboratories are not included in this analysis.

Epidemiologic characteristics. The setting of the outbreak was provided for 221 (95%) of the outbreaks reported to the CDC (table 1). The most common settings reported were restaurants or events with catered meals (90 outbreaks [39%]), followed by nursing homes and hospitals (59 outbreaks [25%]). Outbreaks were also reported in schools, day care centers, and camps (31 outbreaks [13%]) and in vacation destinations, including cruise ships (24 outbreaks [10%]). The median number of persons affected in outbreaks was 40, with outbreaks ranging in size from as few as 4 to 800 persons. Contaminated food was the most commonly reported vehicle of infection (57%), whereas infection by person-to-person contact (16%) and contaminated water (3%) were less common. No mode of transmission could be determined for 42 outbreaks (24%). Information on age was available for 1484 of the 2945 patients, and the mean age was 43 years (range, 2 months to 104 years). Of 1568 patients for whom information on their sex was available, 55% were female.

No distinct seasonality of outbreaks was observed. Illness peaked in July and November 1997, November 1998, December 1999, and February to March 2000 (figure 2). Both GI and GII strains occurred throughout each season of the year, and no seasonal difference was observed between outbreaks that were NLV positive versus those that were NLV negative.

Molecular characteristics. In total, 201 (86%) of the 233 outbreaks were positive for NLVs, as determined using either the region A or region B primers or both. Region A primers detected the implicated strain in 77 outbreaks, region B primers detected 98 implicated outbreak strains, and both primer sets detected the implicated strain in 26 outbreaks, although not all outbreaks were tested with both primer sets. Of the 29 outbreaks that were negative for NLVs by RT-PCR, 28 were examined by electron microscopy, and 16 (55%) of these were positive for SRSVs. Combining these 2 methods of detection,

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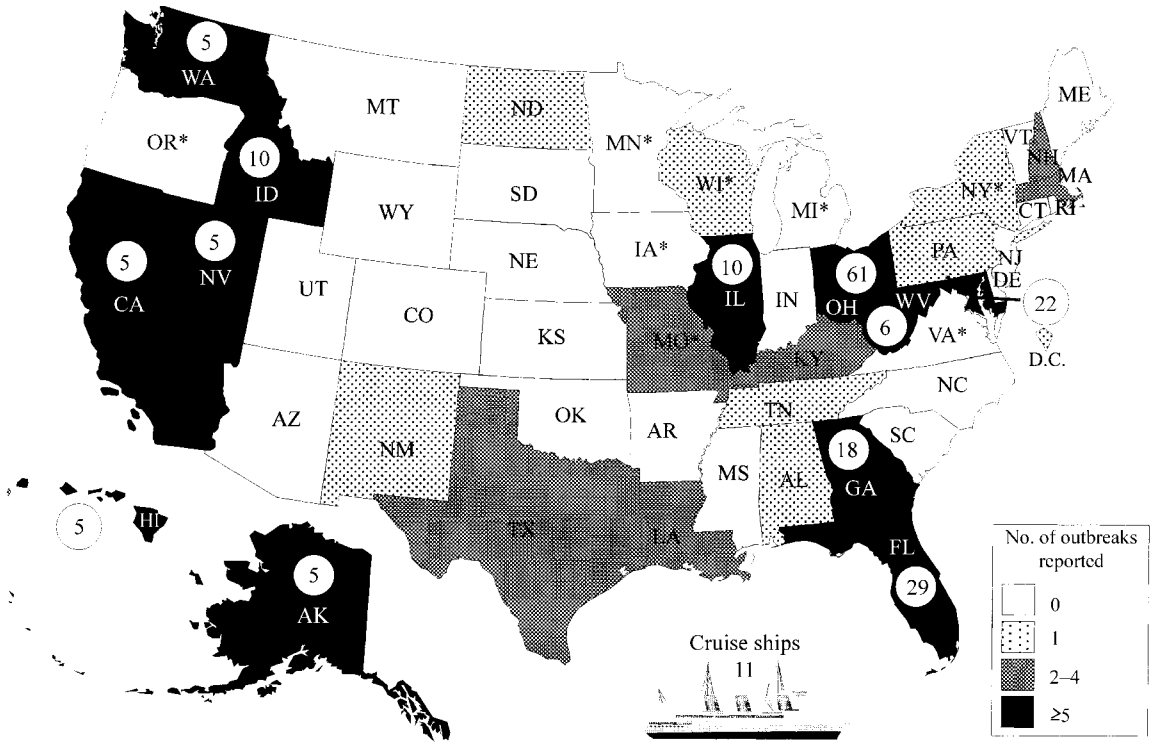

Figure 1. Map of the United States showing distribution of outbreaks of nonbacterial gastroenteritis reported to the Centers for Disease Control and Prevention between July 1997 and June 2000. Nos. of outbreaks are shown in white circles for all states reporting ⩾5 outbreaks. *States routinely performing diagnostic testing for "Norwalk-like viruses"; data from outbreaks tested in these states are not included in this report.

217 (93%) of 233 outbreaks reported to the CDC were positive for NLVs. Of note, rotavirus was identified in 3 outbreaks that were negative for NLVs (1.3%) [22].

Some outbreaks were associated with multiple strains of virus, and, overall, 213 strains of NLV were detected and sequenced during this study. The strains were grouped into genogroups and clusters, as determined on the basis of nucleotide sequence comparisons. Within a genogroup, clusters are assigned numbers sequentially on the basis of the reporting of complete capsid protein gene sequences that differ by ⩾20% in amino acid sequence identity [3, 12]. Amsterdam virus (AF195848) was not previously assigned a cluster number [3], but, on the basis of the above criteria, we have designated it GII/8. For this study, clusters suggested on the basis of comparisons of partial capsid sequence have been assigned letters to distinguish them from those based on comparisons of complete capsid sequences. Thus, strains previously classified as GII/8 and GII/10 [12] have been designated GII/j and GII/k, respectively. In a similar manner, 2 new tentative clusters identified from partial capsid sequences determined in this study were temporarily assigned GII/m and GII/n. Several clusters could not be distinguished from one another by comparison of nucleotide sequences from regions A and B alone (figure 3) but required data from the capsid gene for differentiation. Because these data are not available for all strains included in this study, outbreak strains have been grouped on the basis of region A and B sequences. For example, strains belonging to clusters GII/1, GII/4, and GII/j are not well resolved in region B and were collectively designated GII/1,4,j, whereas strains from clusters GII/6, GII/7, and GII/8 are designated GII/6,7,8 for this study.

Several strains were detected that could not be placed into a previously defined cluster, including a group that caused 24 outbreaks during this period. Sequence analysis of a 277-bp region of open reading frame (ORF) 2 [17] of several of these strains supports their differentiation into a new GII cluster (figure 3), tentatively referred to as GII/m, pending completion of the sequence of the complete capsid gene. Strains from 2 outbreaks, 642 and 762, were closely related to GII-1-Hawaii, on the basis of the region B sequence, but were quite distinct on the basis of the partial ORF2 sequence and were designated cluster GII/n (figure 3). These sequences are >98% identical to the corresponding region from the recently described Erfurt virus (AF427118). In addition, 1 GII and 2 GI strains could not be placed into a defined cluster and are considered undefined until the capsid gene is sequenced and analyzed. Finally, on the basis of sequence analysis of the entire capsid gene, we have assigned 2 strains into genogroup IV (GIV) because of

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Table 1. Epidemiologic characteristics of 233 outbreaks of gastroenteritis investigated in the United States, July 1997 to June 2000.

Setting	No. (%) of outbreaks	Mode of transmission of virus, no. of outbreaks					No. of persons affected[a]	No. of persons at risk[a]
		F	PP	W	U	No data		
Nursing homes, retirement centers, and hospitals	59 (25)	3	15	0	19	22	41 (4–88)	139 (8–2000)
Restaurants and events with catered meals	90 (39)	72	6	1	7	4	33 (5–800)	60 (6–3000)
Schools and day care centers	31 (13)	14	3	0	10	4	56 (6–200)	500 (20–2054)
Vacation settings, including cruise ships	24 (10)	6	2	2	4	9	61 (13–270)	82 (36–2318)
Other[b]	17 (7)	6	2	2	2	5	30 (13–99)	600 (15–7000)
Not specified	12 (5)	0	0	0	0	12	9[c]	35[c]
Total (%)[d]	233 (100)	101 (57)	28 (16)	5 (3)	42 (24)	57	40 (4–800)	120 (6–7000)

NOTE. Data were not available in all categories for all outbreaks. F, foodborne; PP, person-to-person; U, undetermined; W, waterborne.

[a] Data are median (range).

[b] "Other" includes 5 outbreaks in camps, 4 in prisons, 2 in communities, 2 on a military base, and 1 each in an office, a physician's office, a fire department, and a health department.

[c] Data were available for only 1 outbreak.

[d] For each mode of transmission, percentages were determined using only outbreaks for which data were available and excluding those in the category "no data."

their relationship to other existing GI, GII, and GIII strains and using the criteria described by Ando et al. [12].

The distribution of strains was examined by epidemiologic setting to look for possible clustering effects. Overall, GII strains were identified in 73% of outbreaks, GI strains in 26% of outbreaks, and a tentative new genogroup (GIV) was detected in 1% of outbreaks. Strains from clusters GII/1,4,j were the most common (37%), followed by GII/6,7,8 (13%), GI/3 (12%), and GII/m (11%). All 17 clusters previously defined by Ando et al. [12] were detected in this study, with the exception of GI/1 (Norwalk virus), GI/5 (Musgrove virus), GII/k, and GIII clusters.

GII/1,4,j strains were significantly more common in outbreaks in nursing homes than in other settings, causing 60% of outbreaks in nursing homes and only 26% of outbreaks in other settings ($P < .001$). GI/3 strains were not implicated in any outbreaks occurring in nursing homes, despite being responsible for 12% of all outbreaks. All other settings had a distribution of strains similar to that seen for all outbreaks. Of note, all 4 reported outbreaks associated with prisons were negative for NLVs by RT-PCR.

Discussion

Although NLVs are recognized to be the leading cause of outbreaks of nonbacterial gastroenteritis, most outbreaks of gastroenteritis still go without an etiologic diagnosis because detection methods used here are not widely available. In this study, 93% of outbreaks of nonbacterial gastroenteritis reported to the CDC were associated with infection with NLVs, by use of RT-PCR and electron microscopy for diagnosis. Combining these data with those from our previous report [9], 323 outbreaks have been examined over a 4.5-year period; NLVs were associated with 303 (94%) of these outbreaks, confirming that NLVs are the leading cause of outbreaks of nonbacterial gastroenteritis in the United States. These data and those recently reported from laboratories in other countries [5–7] confirm that NLVs are the leading cause of nonbacterial outbreaks of gastroenteritis in developed countries.

Among the NLV outbreaks, the variability between strain types detected throughout the world is considerable. GII/1,4,j strains were predominant in our previous study and remain the most commonly detected strain type, a trend that has been reported in other countries as well, including The Netherlands and Australia [6, 10, 17]. We also saw an increase in detection of strains in the GII/6,7,8 clusters, which is consistent with a similar observation in The Netherlands [6]. In addition, in the United States, the number of GI strains detected increased from only 4% of outbreaks in 1996–1997 to 26% between July 1997 and June 2000; however, other laboratories that previously reported a low prevalence of GI strains [4, 6, 10] have not reported a similar increase. This increase in GI detection may be due in part to the application of newly designed primers, called region B primers, that are highly effective at detecting GI strains previously missed with the region A primers (R.L.F., unpublished data). We also detected several strains that did not fall into one of the described clusters, including one that caused 24 outbreaks during this period. Finally, we detected 2 strains from a potential fourth genogroup whose sequences are as distant from both GI and GII strains as GI and GII strains are from each other (data not shown).

GII/1,4,j strains were significantly more common in nursing home settings, as opposed to other settings in this study, which suggests that the elderly may be most susceptible to this particular strain of virus. This could explain the overwhelming predominance of outbreaks in nursing home and hospital settings that was observed when the GII/4 strains were epidemic worldwide in 1995–1997 [4, 6, 10, 17]. Outbreaks in other settings were caused by an unremarkable distribution of different strain types, and we could not identify any unique epidemiologic patterns or links between setting, mode of transmission, or severity with strain types.

The most common setting for outbreaks during the past 3 years included restaurants and events with catered meals, followed by nursing homes and hospitals. In our previous report

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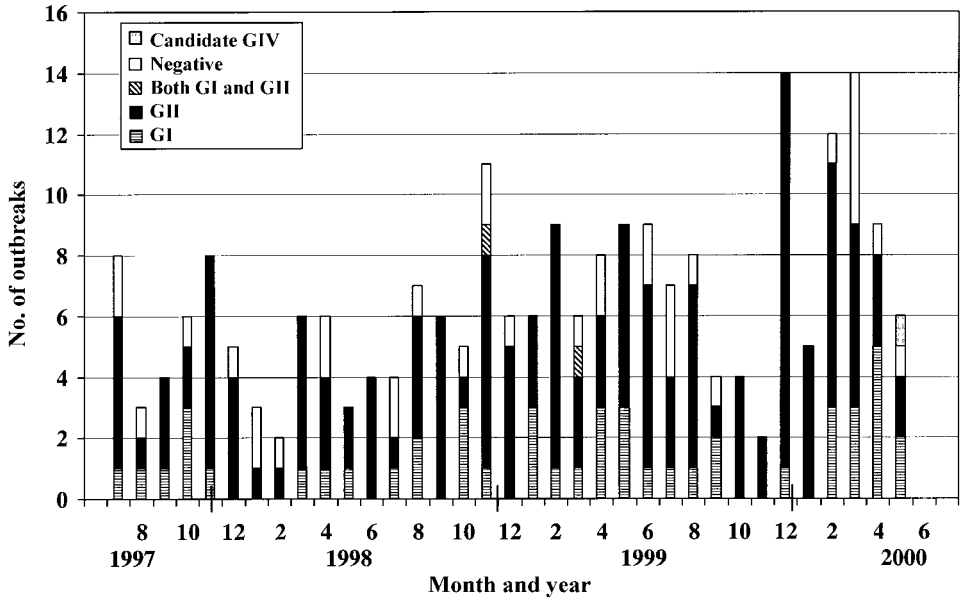

Figure 2. Distribution of nonbacterial gastroenteritis outbreaks, by month. Genogroup of implicated strains are shown, and outbreaks negative by use of reverse-transcription polymerase chain reaction are indicated. "Both GI and GII" bars refer to those outbreaks for which 2 strains, 1 genogroup I and 1 genogroup II, were implicated. "Candidate GIV" refers to the tentative new genogroup detected in this study.

and in those from other countries, nursing homes and hospitals have been the most commonly reported setting [6, 7]. This change may be explained by the fact that Florida, which had many nursing home outbreaks in the past, introduced testing for NLVs by the state laboratory in 1999 and has since reported fewer outbreaks to the CDC. Contaminated food, which was reported as the cause in 57% of outbreaks in which the mode was investigated, was the most commonly suspected vehicle of infection (up from 37% reported in our previous report), and none of these infections was related to the consumption of contaminated oysters. The mean age for patients in NLV-positive outbreaks was 43 years (range, 6 months to 104 years), which is significantly younger than what has been reported elsewhere [7, 9]. We were concerned that the decrease in age might be due to fewer reports of outbreaks from nursing homes in Florida, but, when patient ages were analyzed from both studies, with the exclusion of all outbreaks from Florida, the median ages did not change significantly, which suggests that this result is not a reporting artifact.

This study has some limitations that could affect our interpretation of results. We are dependent upon reporting of outbreaks and forwarding of specimens to the CDC, and so these data are biased toward certain states, settings, and number of persons affected. The CDC receives reports of outbreaks where no etiology has been identified and where clinical symptoms may be consistent with NLV illness. This potential selection bias in our passive surveillance system may explain why our detection rates are higher than those reported in other countries. A greater problem is that passive surveillance undoubtedly results in gross underreporting of outbreaks, so the true extent of morbidity from NLV infection is not known. Small outbreaks most likely go unreported in most cases, and even large outbreaks may not be reported because the illness is usually not life threatening and the duration of sickness is only a few days. Finally, many states have begun to introduce diagnostics for NLVs, and the results of these investigations are not included in this dataset.

Improved diagnostics for NLVs have allowed for surveillance of NLV infection in outbreaks of gastroenteritis and characterization of the strain types involved. CaliciNet, an Internet-based sequence comparison system recently established at the CDC, allows any laboratory to rapidly compare its NLV sequences to all others placed in the database (for more information in regard to CaliciNet, please send requests to CaliciNet@cdc.gov). This technology should be very useful in recognizing multistate or international outbreaks in a timely manner so that efforts can be made to stop the spread of the virus. This will require more-rapid methods to allow for real-time comparison of strain types in circulation. The data presented here confirm that NLVs are overwhelmingly the most common cause of outbreaks of nonbacterial gastroenteritis worldwide. Little is known, however, about the predominance of NLVs in all cases of gastroenteritis in the United States because no studies have thoroughly examined cases of gastroenteritis for bacteria, parasites, and viruses together. Such studies are needed to understand the true prevalence of NLVs in acute gastrointestinal illness, both in outbreak settings and in hospitalized patients. Because our data currently rely on passive reporting of outbreaks, it is also important that small setting surveillance studies be conducted in communities in which all

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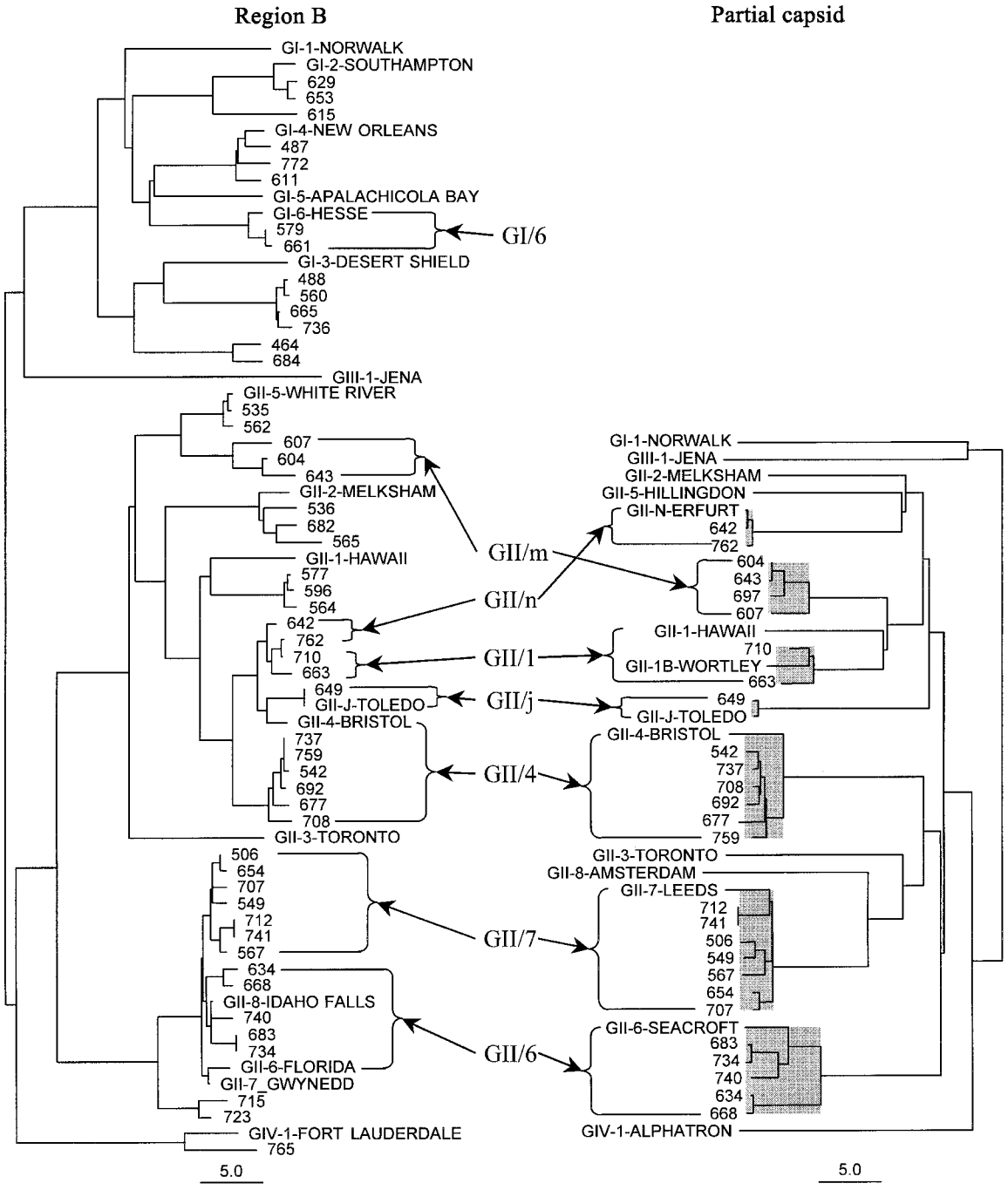

Figure 3. Phylogenetic analysis of selected "Norwalk-like virus" strains. Dendrograms were generated by neighbor-joining on the basis of uncorrected distances calculated for 172 nt from region B *(left)* or 277 nt from the capsid gene *(right)*, using the DISTANCES and GROWTREE programs of the GCG sequence analysis suite [21]. Sequences from representative outbreak strains from this study plus 1 prototype strain from each previously defined cluster [3, 12] were analyzed in region B *(left)*. For those clusters for which sequence information corresponding to region B has not been reported for the prototype strain, prototypes were selected from the review by Ando et al. [12]. The clusters GII/j, GII/m, and GII/n are tentative assignments pending analysis of complete capsid genes. A subset of strains belonging to those clusters that are not well resolved in region B (i.e., GII/1,4,j and GII/6,7,8) were independently analyzed using partial sequences from the capsid gene *(right)*. Strains having <15% difference in nucleotide identity in the partial capsid sequence are indicated by shading. G, genogroup.

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outbreaks of gastroenteritis can be reported and thoroughly investigated. This would enable a more accurate assessment of the causes of gastroenteritis outbreaks and their epidemiologic characteristics.

Acknowledgments

We thank all the epidemiologists at the state and local health departments, for the investigation of the outbreaks and the collection of specimens, and Eva Quiroz, Chris Zimmerman, and Alicia Anderson, for their epidemiologic investigations, assistance, and helpful discussions. Carl Kirkwood, Jennifer Tai, Suzanne Beard, and Brad Barkin provided laboratory assistance with this project; Aaron Curns assisted with graphics; and John O'Connor provided editorial comments.

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