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Differences in clinical presentation between norovirus genotypes in nursing homes

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ABSTRACT

Background: In healthcare settings, norovirus (NoV) outbreaks are predominated by genotype II.4 (GII.4) strains. Periodically, new variants of GII.4 emerge, causing a temporary increase of outbreaks.
Objectives: To study the relationship between symptoms and NoV genotype.
Study design: Data of 49 nursing homes which were monitored for NoV outbreaks in the winter seasons of 2005/2006 and/or 2006/2007 were used.
Results: Data on symptoms and duration of illness were available for 465 residents and 174 staff members from 28 NoV outbreaks. Genotype GII.4 was responsible for 21 outbreaks. Attack rates for residents seemed to be higher in GII.4 outbreaks compared to other genotypes. In outbreaks caused by GII.4, residents vomited more often than in outbreaks with other genotypes. They also had more often complaints of nausea, abdominal cramps, fever, and mucus in stool. The GII.4 2004 variant outbreaks showed higher percentages of nausea, stomach ache, and fever than outbreaks with the GII.4 2006a variant. Differences in duration of illness were not found. In nursing home staff, no clear differences were found between outbreaks caused by GII.4 and non-GII.4 NoVs.
Conclusions: Genotype GII.4 was found to be related to more symptomatic disease, including more residents vomiting, and to a lesser extent, higher attack rates among residents.

1. Introduction

Noroviruses are the most common cause of gastroenteritis both in the community and in outbreaks. In Dutch residential settings, noroviruses were detected as causative agent in 86% of gastroenteritis outbreaks of suspected viral etiology[1] and in 70% of all gastroenteritis outbreaks.[2] As noroviruses are highly contagious and difficult to eradicate, it spreads rapidly within closed settings.[3,4] In most cases, infection with norovirus is relatively mild, mostly lasting 12–60 h,[5] but prolonged diarrhea and serious complications, including death, have been reported.[6,7] Main symptoms are diarrhea and/or vomiting, accompanied by nausea and abdominal cramps. Noroviruses have been classified in five genogroups (GI–GV) of which three genogroups have been found in humans (GI, GII, and GIV).[8,9] Norovirus strains can be further subdivided into genotypes. Currently, at least 26 genotypes have been identified in humans.[9] In healthcare settings, outbreaks of norovirus are predominated by GII.4 strains.[10–12] Periodically, new variants of GII.4 emerge, causing a temporary increase in the number of outbreaks.[12–14] These new variants are often referred to using the year of detection, for example the GII.4 2004 variant was a genogroup II.4 variant first found in 2004. The new GII.4 variants that have caused epidemics since 1995 have a preferential accumulation of mutations in the protruding part of the capsid protein which suggests that population immunity plays a role in the evolution of GII.4 norovirus strains.[12] This does, however, not explain why GII.4 strains are dominant over other genotypes. Whether different norovirus strains also show differences in illness severity has not been investigated yet. In the present study, the relationship between symptoms and genotype was studied during norovirus outbreaks in nursing homes. It offers the opportunity to search for factors that may contribute to the successful spread of GII.4 noroviruses.

2. Methods

2.1. Design and setting

The present study was embedded in a larger study evaluating the effect of different infection control protocols during norovirus

Abbreviations: RIVM, National Institute for Public Health and the Environment; RT-PCR, reverse transcription-polymerase chain reaction.

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Table 1
Number of outbreaks, ill residents and staff per genotype in norovirus seasons 2005/2006 and 2006/2007.

Genotype	Outbreaks, *n*	Residents		Staff	
		Number ill	With info (%)	Number ill	With info (%)
GII.4	19	475	318 (66.9)	253	95 (37.5)
GII.4 2004	6	165	109 (66.1)	99	24 (24.2)
GII.4 2006a	9	216	166 (76.9)	85	61 (71.8)
GII.4 2006b	4	94	43 (45.7)	69	10 (14.5)
Other	7	162	141 (87.0)	137	77 (56.2)
GI.3 Birmingham	1	4	4 (100)	0	0
GI.6 Mikkeli	1	4	4 (100)	6	6 (100)
GII.b Hilversum	1	20	20 (100)	5	5 (100)
GII.3 Toronto	1	28	28 (100)	12	11 (91.7)
GII.7 Leeds	3	106	85 (80.2)	114	55 (48.2)
Total	26	637	459 (72.1)	390	172 (44.1)
Available questionnaires[a]	28		465[a]		174[b]

[a] Eight patient questionnaires of two outbreaks (GII.4 2004 and 2006a) where no data was available about total number of ill residents and staff were also included.

outbreaks in nursing homes.[15] Between November 2005 and April 2006 and November 2006 and April 2007, the National Institute for Public Health and the Environment (RIVM) performed this larger study in collaboration with five (2005/2006) and six (2006/2007) local health services throughout the Netherlands. All nursing homes and rest homes with a nursing ward within these health service regions were contacted. During both winter seasons all participating homes were asked to report a (suspected) norovirus outbreak as soon as possible to the local health service, send in stool samples from 5 to 10 patients to the RIVM, and start the infection control protocol assigned. An outbreak was defined as two or more cases of gastroenteritis within 3 days of one another on one ward within a home, and lasted up to the day the last case went ill on the involved ward. During the outbreak, staff was asked to fill in a patient questionnaire for each gastroenteritis patient (residents and staff). This patient questionnaire included date of onset, last day of illness, and presence of clinical symptoms, namely diarrhea, vomiting, stomach ache, abdominal cramps, nausea, fever and mucus in stool. Furthermore, information was gathered about hospital admission, death, and contacts with other patients. At the end of an outbreak, all affected wards received a questionnaire about the total number of ill residents and staff, and the actual implementation of the protocol during the outbreak.

2.2. Norovirus detection and genotyping

The collected stool samples were tested for norovirus by reverse transcription-polymerase chain reaction (RT-PCR). At least one positive sample per outbreak was genotyped. Diagnostic testing and genotyping were performed as described by Svraka et al.[1]

2.3. Analysis

Analyses were performed using SAS 9.1 for Windows (SAS Institute Inc., USA). The relationship between symptoms and genotype was examined using Chi-square and Fisher exact tests. Associations are presented by odds ratios with 95% confidence intervals. Number of symptoms per case was analyzed using Wilcoxon rank sum tests. Finally, attack rates were calculated and differences in these attack rates by genotypes were tested with a Wilcoxon rank sum test. All comparisons were made between infections by GII.4 strains and the other genotypes, and also between GII.4 2004 and GII.4 2006a strain variants. Comparison with GII.4 2006b variant was not possible, due to too few available questionnaires. Mean Cp values, obtained in the real time RT-PCR assay, were compared for GII.4 2004, GII.4 2006a and GII.4 2006b as indication of the virus shedding level per genotype.

Table 2
Symptoms reported during norovirus outbreaks in nursing homes by genotype, separate for residents and staff.

	GII.4 (%)	Other (%)	OR[a]	GII.4 2006a (%)	GII.4 2004 (%)	OR[b]
Residents						
Diarrhea	82.8	85.5	0.8 (0.5–1.4)	83.6	77.0	1.5 (0.8–2.8)
Vomiting	57.8	41.6	1.9 (1.3–2.9)	58.4	57.9	1.0 (0.6–1.7)
Diarrhea and vomiting	43.3	29.2	1.9 (1.2–2.9)	43.0	41.1	1.1 (0.7–1.8)
Nausea	50.4	35.3	1.9 (1.1–3.1)	42.9	67.2	0.4 (0.2–0.7)
Stomach ache	29.9	22.4	1.5 (0.8–2.7)	23.6	41.8	0.4 (0.2–0.8)
Abdominal cramps	23.5	9.4	3.0 (1.3–6.5)	25.7	19.4	1.4 (0.7–2.9)
Fever	19.2	7.1	3.1 (1.3–7.6)	13.6	32.8	0.3 (0.2–0.7)
Mucus in stool	7.3	0	$p = 0.009$	10.0	3.0	3.6 (0.8–16.4)
Number of symptoms: median	2.0	1.0	$p < 0.001$	2.0	2.0	$p = 0.93$
Staff						
Diarrhea	85.7	78.4	1.7 (0.7–3.7)	86.0	80.0	1.5 (0.4–5.3)
Vomiting	78.7	80.0	0.9 (0.4–2.0)	80.7	72.7	1.6 (0.5–4.9)
Diarrhea and vomiting	71.3	65.3	1.3 (0.7–2.5)	71.7	66.7	1.3 (0.5–3.5)
Nausea	81.8	81.5	1.0 (0.1–2.4)	81.1	81.0	1.0 (0.3–3.7)
Stomach ache	41.6	49.2	0.7 (0.4–1.4)	39.6	42.9	0.9 (0.3–2.4)
Abdominal cramps	61.0	66.2	0.8 (0.4–1.6)	58.5	61.9	0.9 (0.3–2.4)
Fever	18.2	30.8	0.5 (0.2–1.1)	20.8	14.3	1.6 (0.4–6.3)
Mucus in stool	3.4	1.5	2.6 (0.3–25.6)	3.8	4.8	0.8 (0.1–9.1)
Number of symptoms: median	3.0	3.0	$p = 0.21$	4.0	3.0	$p = 0.26$

[a] Odds ratio (95% confidence interval) of GII.4 versus other.
[b] Odds ratio (95% confidence interval) of GII.4 2006a versus GII.4 2004.