

Rapid communications

FOOD-BORNE VIRUSES IN EUROPE NETWORK REPORT: THE NOROVIRUS GII.4 2006B (FOR US NAMED MINERVA-LIKE, FOR JAPAN KOBE034-LIKE, FOR UK V6) VARIANT NOW DOMINANT IN EARLY SEASONAL SURVEILLANCE

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Institutes charged with the surveillance of norovirus (NoV) outbreaks in Ireland, Germany, the Netherlands and Sweden reported high NoV activity to the European Food-borne Viruses in Europe network (FBVE) in late 2007. In these countries, the number of reported NoV outbreaks exceeds that of October and November of the previous record seasons, 2004 and 2006. A similar situation has been reported in the United Kingdom (UK) [1]. In recent years, most norovirus outbreaks have been caused by GII.4 strains. These viruses evolve rapidly by genetic mutation coupled with selective pressure. The rapid evolution of GII.4 noroviruses resulting in the successive emergence of new variants has been observed since 2002. In the norovirus outbreak season of 2006–7, two variants emerged that co-circulated. Early observations for the 2007–8 season suggest that one of these variants now dominates. The

currently circulating strains have mutations that set them apart from the older strains, leading to one amino acid change in the capsid sequence. Although we do not consider the strains that currently circulate as new variants, based on the global character of norovirus and previous experience with high numbers of reported outbreaks we are expecting high norovirus activity in other countries.

Background

Noroviruses are known as a common cause of diarrhea and vomiting, often in outbreaks and predominantly in winter. Studies across the world have shown that in recent years most outbreaks have been caused by strains belonging to a particular genotype of noroviruses, named GII.4. The GII.4 strains evolve rapidly and are further subdivided into variants. Since 1995, three variants

TABLE

Norovirus GII.4 lineages and their nomenclature

NoV season	GII.4 variant, nomenclature per country/group				
	FBVE ^a	USA ^b	Japan ^c	UK ^d	Australia ^e
<1990	Camberwell				
<1995	Bristol				
1995–6	1996		GII/4 g	Grimsby, v1	
2002–3	2002	Farmington Hills	GII/4 e	v2	
	2003/Asia			v5	
2004–5	2004		GII/4 f	v3	Hunter
2006–7	2006a	Laurens		v4	2006a
2006–7	2006b	Minerva	Kobe034	v6	2006b

^a See: <http://www.rivm.nl/ubnwww>

^b Farmington Hills: Promedmail Archive Number 20030123.0206 23-JAN-2003 Norovirus activity 2002 – USA
Minerva: Promedmail Archive Number 20070310.0849 10-MAR-2007 Norovirus - USA (multistate): new strain
Laurens: Promedmail Archive Number 20070824.2779 24-AUG-2007 Norovirus activity, 2006-2007 – USA

^c Kobe :NCBI database AB291542 Norovirus Hu/GII.4/Kobe034/2006/JP genes for nonstructural polyprotein (RNA-dependent RNA polymerase region), capsid protein, partial and complete cds.
Japanese nomenclature: Phan TG, Kaneshi K, Ueda Y, Nakaya S, Nishimura S, Yamamoto A, Sugita K, Takashi S, Okitsu S, Ushijima H. Genetic heterogeneity, evolution, and recombination in noroviruses. J Med Virol. 2007 Sep;79(9):1388-400.

^d Grimsby: Maguire AJ, Green J, Brown DW, Desselberger U, Gray JJ. Molecular epidemiology of outbreaks of gastroenteritis associated with small round-structured viruses in East Anglia, United Kingdom, during the 1996-1997 season. J Clin Microbiol. 1999 Jan;37(1):81-9.
UK variants: Gallimore CI, Iturriza-Gomara M, Xerry J, Adigwe J, Gray JJ. Inter-seasonal diversity of norovirus genotypes: emergence and selection of virus variants. Arch Virol. 2007;152(7):1295-303.

^e Hunter : Bull RA, Tu ET, McIver CJ, Rawlinson WD, White PA. Emergence of a new norovirus genotype II.4 variant associated with global outbreaks of gastroenteritis.. J Clin Microbiol. 2006 Feb;44(2):327-33

have emerged and replaced each other globally, in 1995, 2002, and 2004. In 2006, two variants emerged that co-circulated. Characterisation studies suggest that lineages evolve through selective pressure and are likely to be antigenic variants (drift variants) [2].

For international communication, standardized nomenclature of variant types is needed. This was discussed and agreed at the Third Calicivirus Meeting in Cancun, Mexico, November 2007, and a working group chaired by the Netherlands' National Institute for Public Health and the Environment (RIVM) with representatives from the United States, Canada, Australia and Japan will prepare a unifying proposal for this in the coming months. Table 1 lists the currently used names for reference for the different variants across the world.

Situation in Europe in the first part of the current season 2007–8

In the last norovirus outbreak season of 2006–7, two variants of GII.4 NoV circulated in Europe, causing the majority of viral gastroenteritis outbreaks [2]. These variants, named GII.4-2006a and GII.4-2006b in the FBVE network (Table 1), were found at approximately equal proportions in most European countries in the winter of 2006–7 [2]. Consensus sequences – the common sequences derived from multiple alignments of all strains belonging to each variant or genotype – of region A (part of the polymerase gene) and C (part of the capsid gene) and background information can be found at: <http://www.rivm.nl/bnwww>. These regions are the genome targets that are most often used for genotyping across the world. The consensus sequences are freely available from the public part of the website.

During the summer and autumn of 2007, the GII.4-2006b variant (in the United States named Minerva-like, in Japan Kobe034-like, in the UK V6) became dominant over the GII.4-2006a variant, and several countries reported a high number of outbreaks in October and November. Currently the two variants still co-circulate, but GII.4-2006b now seems more prevalent in most European countries. In the Netherlands in October 2007, 29 NoV outbreaks were reported to the RIVM, of which 26 were genotyped. Of these 3 (11.5%) were GII.4-2006a and 12 (46%) were GII.4-2006b. In November, 46 outbreaks were reported. To date, 30 of these have been genotyped, and of those 3 (10%) were GII.4-2006a and 22 (73%) were GII.4-2006b.

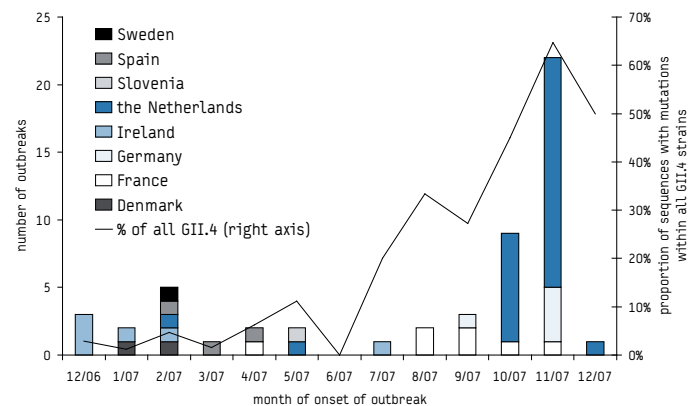
The recent GII.4-2006b strains contain two mutations in region A (T4387C and T4543C, Lordsdale numbering, X86557) and one mutation in region C (A68C, numbering starts at ATG of GII.4 capsids) discriminating them from older GII.4-2006b strains. The mutation in region C results in an amino acid mutation (N23S, numbering starts at ATG of GII.4). The sequences for these strains of region A and C are displayed in Figures 1 and 2.

In Figure 3, an overview is given of the new strains isolated from outbreaks reported so far per country and per month of onset of the outbreak. The line (right axis) represents the fraction of all GII.4 outbreak strains which hold the observed mutations.

Most countries within the network sequence region A (polymerase) of the virus, in some cases both region A and region C sequences are determined from one outbreak. Ireland and Sweden only perform region C (capsid) sequencing.

FIGURE 3

Norovirus GII.4 2006b sequences with specific mutations per country per month of onset of the outbreak



The first outbreaks with these characteristics were reported from Ireland in December 2006. From October 2007, the numbers of outbreaks rose sharply in several other European countries. The number of outbreak reports in the most recent months are expected to increase significantly because most countries in the FBVE network are only able to report sequences one or two months after the date of onset of the outbreak. Analogous to the situation in the autumn of 2004 and 2006, this indicates a highly active norovirus winter season [3,4].

Strain characterisation, capsid sequences

Additional genome sequencing of two strains that have the mutations in region A showed that the amino acid mutation in region C is the only amino acid mutation in the capsid gene. Therefore, the current high level of seasonal activity can not be explained by introduction of new antigenic variants.

The mutations we determined in regions A and C that set the latest strains apart from the earlier strains of the 2006b variant are probably not related to the changes in dominance and may simply be fixed along with other neutral mutations. We previously observed similar changes in dominance of strains and this was usually accompanied by amino acid changes in the P2 domain of the capsid protein. The earlier strains of the 2006b variant had several differences in the P2 domain compared to all other GII.4 variants circulating in previous years. However, when it first emerged, it was not able to displace the co-circulating 2006a variant, suggesting that its ability to infect and subsequently spread was not yet optimal. The observations at the start of this season suggest that the 2006b variant has gained fitness over the last year, since it has become dominant.

Conclusion

The start of the norovirus season shows a high incidence of outbreaks across Europe, caused mostly by GII.4 viruses belonging to a variant that emerged globally in 2006. It remains unclear if the record high reporting is a surveillance artifact or reflects changes in the epidemiology of GII.4 strains, although in recent years GII.4 viruses have evolved rapidly by mutation. Given the high incidence of norovirus infections in the general population, introduction into health-care settings is inevitable. Immediate action when cases

are reported and stringent hygiene measures can reduce the size of outbreaks in healthcare settings.

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