Emergence of a novel GII.17 norovirus – End of the GII.4 era?

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In the winter of 2014/15 a novel GII.P17-GII.17 norovirus strain (GII.17 Kawasaki 2014) emerged, as a major cause of gastroenteritis outbreaks in China and Japan. Since their emergence these novel GII.P17-GII.17 viruses have replaced the previously dominant GII.4 genotype Sydney 2012 variant in some areas in Asia but were only detected in a limited number of cases on other continents. This perspective provides an overview of the available information on GII.17 viruses in order to gain insight in the viral and host characteristics of this norovirus genotype. We further discuss the emergence of this novel GII.P17-GII.17 norovirus in context of current knowledge on the epidemiology of noroviruses. It remains to be seen if the currently dominant norovirus strain GII.4 Sydney 2012 will be replaced in other parts of the world. Nevertheless, the public health community and surveillance systems need to be prepared in case of a potential increase of norovirus activity in the next seasons caused by this novel GII.P17-GII.17 norovirus.

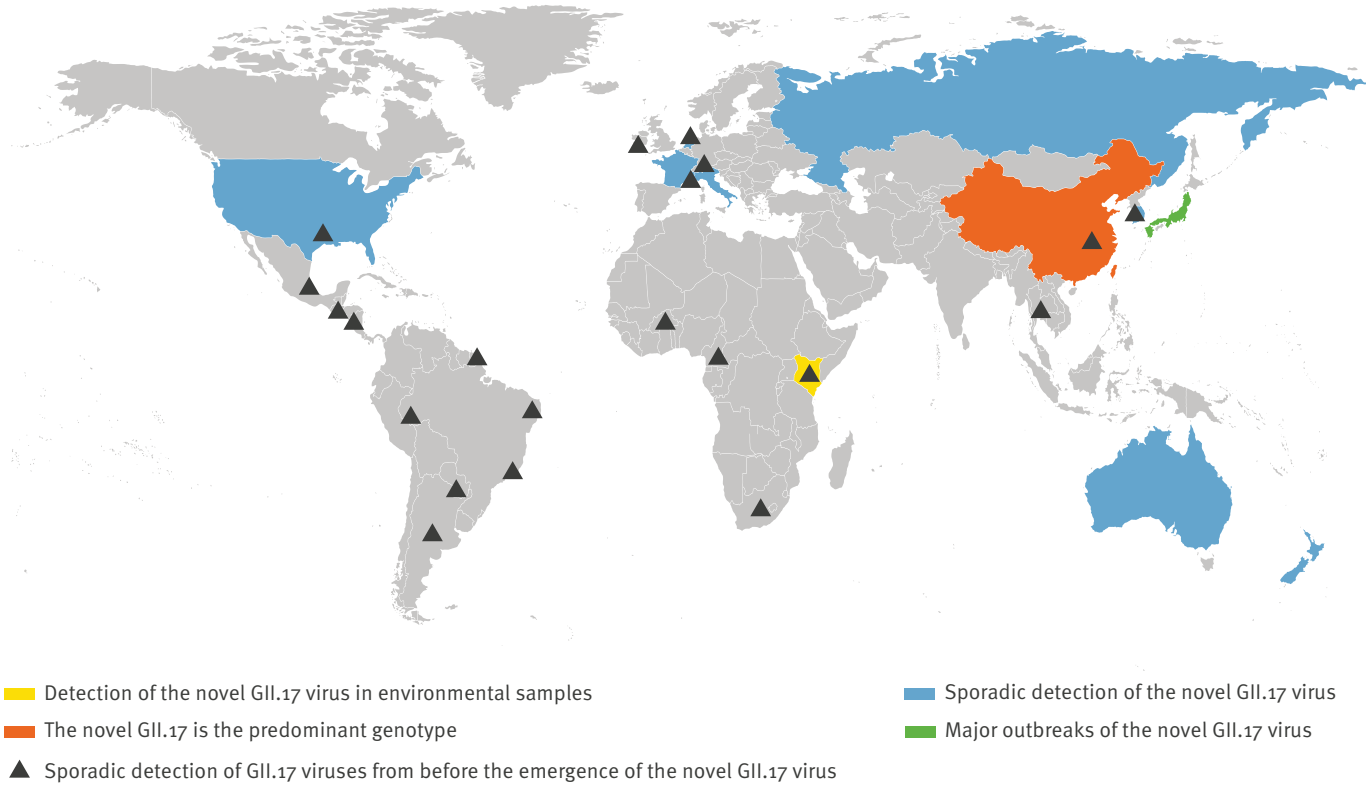
In this issue of *Eurosurveillance*, observations from Japan are reported on an unusual prevalence of a previously rare norovirus genotype, GII.17, in diarrheal disease outbreaks at the end of the 2014/15 winter season [1], similar to what was observed for China [2,3]. Norovirus is a leading cause of gastroenteritis [4]. Although the infection is self-limiting in healthy individuals, clinical symptoms are much more severe and can last longer in immunocompromised individuals, the elderly and young children [5,6].

The *Norovirus* genus comprises seven genogroups (G), which can be subdivided in more than 30 genotypes [7]. Viruses belonging to the GI, GII and GIV genogroups can infect humans, but since the mid-1990s GII.4 viruses have caused the majority (ca 70–80%) of all norovirus-associated gastroenteritis outbreaks worldwide [8-10].

GII.4 viruses can continue to cause widespread disease in the human population because they evolve through accumulations of mutations into so-called drift variants that escape immunity from previous exposures [11]. Contemporary GII.4 noroviruses also demonstrate intra-genotype recombination near the junction of open reading frame (ORF) 1 and ORF2, which is likely to foster the emergence of novel GII.4 variants [12]. In addition, the binding properties of GII.4 viruses have altered over time, resulting in a larger susceptible host population [13].

Figure 1

World map showing areas where GII.17 norovirus strains have been detected, 1978–2015



Emergence and geographical spread of GII.17 genotype noroviruses

Viruses of the GII.17 genotype have been circulating in the human population for at least 37 years; the first GII.17 strain in the National Center for Biotechnology Information (NCBI) databank is from 1978 [14]. Since then viruses with a GII.17 capsid genotype have sporadically been detected in Africa, Asia, Europe, North America and South America (Table, Figure 1). The virus appears to be clinically relevant, as it has been associated with acute gastroenteritis (AGE) in children and adults, and with chronic infection in an immunocompromised renal transplant patient [15] and a leukaemia patient (unpublished data). In the United States (US), only four GII.17 outbreaks were reported between 2009 to 2013 through CaliciNet, with a median of 11.5 people affected by each outbreak [16]. In Noronet, an informal international network of scientists working in public health institutes or universities sharing virological, epidemiological and molecular data on norovirus, GII.17 cases were also sporadically reported in Denmark and South Africa during this period [17].

More widespread circulation of GII.17 was first reported for environmental samples in Korea from 2004 to 2006. This information was published in a report in 2010 by the Korean Food and Drug Administration (KFDA) and was cited by Lee et al. [18], but the original document describing this finding is not publicly available and there are no matching clinical reports. From 2012 to 2013 a novel GII.17 virus accounted for 76% of all detected norovirus strains in rivers in rural and urban areas in Kenya [19]. In the winter of 2014/15, genetically closely related GII.17 viruses were first detected in AGE outbreaks in the Guangdong province in China in schools, colleges, factories and kindergartens [3]. Sequence analyses demonstrated that 24 of the 29 reported outbreaks during that winter were caused by GII.17. A large increase in the incidence of AGE outbreaks was also reported; 29 outbreaks associated with 2,340 cases compared with nine outbreaks and 949 cases in the previous winter when GII.4 Sydney 2012 still was the dominant genotype [3].

During the same winter there was also an increase in outbreak activity in Jiangsu province, which could be attributed to the emergence of this novel GII.17 [2]. This triggered us to investigate the prevalence of GII.17 in other parts of the world by means of a literature study and by inviting researchers collaborating within Noronet to share their data on GII.17. Currently, in Asia, in addition to Guangdong and Jiangsu [2,3], the novel GII.17 is also the predominant genotype in Hong Kong (unpublished data) and Taiwan [20], while in Japan, a sharp increase in the number of cases caused by this novel virus has been observed during the 2014/15 winter season [1]. Related viruses have been detected sporadically in the US [21] (http://www.cdc.gov/norovirus/reporting/calicinet/index.html), Australia, France, Italy, Netherlands, New-Zealand and Russia (unpublished data, www.noronet.nl) (Figure 1). In France the novel GII.17 virus appeared at the beginning of 2013,

Table A

Overview of detected GII.17 norovirus strains worldwide, 1978–2015

Country	Geographical spread GII.17[a]	Year[b]	ORF1	ORF2	Study population	Proportions of typed strains or outbreaks[c]	Suspected source of infection	Description of the sequence (size)	Accession number	References
French Guiana	Single location	1978	GII.P4	GII.17	Children with AGE	1 strain	–	Partial genome (7,441 bp)	KC597139, JN699043	[14]
Brazil	Rio de Janeiro	1997 (1994–2008)	–	GII.17	Children with AGE	3/52 strains	–	5'-end ORF2 (300 bp)	JN600531	[31]
Kenya	Nairobi	1999–2000	–	GII.17	HIV positive children with or without AGE	1/11 strains	–	5'-end ORF2 (309 bp)	KF279387	[32]
France	Briançon	2004	GII.P13	GII.17	Child with AGE	1 strain	–	Partial ORF1/2 (1,361 bp)	EF529741	Data not shown
Paraguay	Asuncion	2004–2005	–	GII.17	AGE in children (<5 years)	5/29 strains	–	3'-end ORF2 (255 bp)	KC736582, KC736580, KC736578, KC736569	[33]
Brazil	States of Acre (Brazil)	2005 (2005–2009)	–	GII.17	AGE	2/62 strains	–	3'-end ORF2 (215 bp)	JN587118 JN587117	[34]
United States	Houston	2005	–	GII.17	AGE evacuees hurricane Katrina	Predominant genotype in an outbreak	Sewage	ORF2 and 3 (2,459 bp)	DQ438972	[35]
Argentina	Single location (Argentina)	2005–2006	–	GII.17	River samples	1/33 strains	–	–	–	[36]
Brazil	State of Rio de Janeiro	2005–2006 (2004–2011)	–	GII.17	Outbreaks of AGE	3/112 outbreaks	–	3'-end ORF2 (214 bp)	KJ179752, KJ179753, KJ179754	[37]
Nicaragua	Léon	2005–2006	–	GII.17	AGE	1 strain	–	5'-end ORF2 (244 bp)	EU780764	[26]
France	Sommières	2006	GII.P13	GII.17	AGE	1 strain	Foodborne	Partial ORF1/2 (1,056 bp)	EF529742	Data not shown
Thailand	Lopburi	2006–2007	–	GII.17	AGE	2 strains	–	5'-end ORF2 (209 bp)	GQ325666, GQ325670,	[38]
China	Wuhan	2007 (2007–2010)	GII.P13	GII.17	AGE	1/488 strains	–	Partial ORF1/2 (1,096 bp)	JQ751044	[39]
Mexico	Mexico City	2007	–	GII.17	–	–	Waterborne	5'-end ORF2 (1,337 bp)	JF970609	NCBI[d]
Switzerland	Zürich	2008	–	GII.17	Renal transplant patient	1/9 strains	–	ORF2 (1,599 bp)	GQ266696	[15]
Nicaragua	Léon	2008	–	GII.17	AGE in children (<5 years)	2/38 strains	–	5'-end ORF2 (244 bp)	EU780764	[40]
South Korea	Seoul	2010 (2008–2011)	–	GII.17	AGE	1/710 strains	–	5'-end ORF2 (209)	JQ944348	[41]
Brazil	Quilombola	2009 (2008–2010)	–	GII.17	Children (<10 years)	2/16 strains	–	3'-end ORF2 (215 bp)	JX047021, JX047022	[42]

Table B

Overview of detected GII.17 norovirus strains worldwide, 1978–2015

Country	Geographical spread GII.17[a]	Year[b]	ORF1	ORF2	Study population	Proportions of typed strains or outbreaks[c]	Suspected source of infection	Description of the sequence (size)	Accession number	References
Cameroon	Southwestern region of Cameroon	2009	GII.P13	GII.17	Healthy children and HIV positive adults	4/15 strains	–	Partials ORF1/2 (1,024 bp)	JF802504–JF802507	[43]
Guatemala	Tecpan	2009	–	GII.17	Children after waterborne outbreak	1/18 strains	Waterborne	–	–	[44]
Burkina Faso	Ouagadougou	2009–2010	–	GII.17	AGE in children (<5 years)	1/36 strains	–	5'-end ORF2 (287 bp)	JX416405	[27]
Netherlands	Single location	2002–2007	–	GII.17	Nosocomial	3/264 strains	Nosocomial	–	–	[45]
South Korea	South Korea	2010	–	GII.17	Groundwater samples	2/7 strains	–	5'-end ORF2 (311 bp)	KC915021–KC915022	[18]
Ireland	Ireland	2010	–	GII.17	Influent waste water	4/24 strains	–	5'-end (302 bp)	JQ362530	[46]
South Africa	South Africa	2010–2011	–	GII.17	Waste water	9/69 strains	–	5'-end ORF2 (305 bp)	KC495680, KC495686, KC495672–KC495674, KC495664, KC495657, KC495655, KC495640	[47]
South Korea	Jinhae Bay	2010–2011	–	GII.17	Oysters	1 strain	–	–	–	[48]
Morocco	Oujda (Morocco)	2011	–	GII.17	AGE in children (<5 years)	1/42 strains	–	5'-end (205 bp)	KJ162374	[49]
South Africa	Johannesburg (South Africa)	2011	GII.P16	GII.17	AGE	–		Partial ORF1/2 (1,010 bp)	KC962460	[50]
Cameroon	Limbe	2011–2012	GII.P3	GII.17	Healthy adults and Children	4/100 strains	–	Partial ORF1/2 (653 bp)	KJ946403	[51]
Kenya	Kenya	2012–2013	–	GII.17	Surface water	16/21 strains	–	5'-end ORF2 (306 bp)	KF916584–KF916585, KF808227–KF808254	[19]
South Korea	Gyeonggi	2012	–	GII.17	AGE outbreak	1 strain	Waterborne	5'-end (205 bp)	KC413386 KC413399–KC413403	[22]
China	Guangdong province	2014–2015	–	GII.17	AGE outbreaks	24/29 outbreaks	–	5'-end (249 bp)	KP718638–KP718738	[3]
United States	Gaithersburg	2014	GII.P17	GII.17	AGE in child of 3 years	1 strain	–	Partial genome (7,527 bp)	KR083017	[21]
China	Jiangsu province	2014–2015	GII.P17	GII.17	Outbreaks of AGE	16/23 outbreaks	–	–	KR270442–KR270449	[2]

Table C

Overview of detected GII.17 norovirus strains worldwide, 1978–2015

Country	Geographical spread GII.17[a]	Year[b]	ORF1	ORF2	Study population	Proportions of typed strains or outbreaks[c]	Suspected source of infection	Description of the sequence (size)	Accession number	References
Japan	Japan	2014–2015	GII.P17	GII.17	Outbreaks of AGE	100/2,133 strains	–	Partial genome (7,534–7,555 bp)	AB983218, LC037415, LC043139, LC043167, LC043168, LC043305	[1]

AGE: acute gastroenteritis; HIV: human immunodeficiency virus; NCBI: National Center for Biotechnology Information; ORF: open reading frame.

[a] GII.17 detection location with study location between brackets (when different from GII.17 detection location).

[b] GII.17 detection year(s) with study years between brackets.

[c] Either the proportion of strains that was typed as GII.17 or the proportion of outbreaks that was caused by GII.17 is given.

[d] Information derived from the GenBank entry related to the accession number of the sequence.

but since then, it has not resulted in an increase in AGE outbreaks as observed in China, nor replaced the predominant GII.4 in the last seasons (data not shown).

Based on sequence analyses of the ORF1-ORF2 junction region, most diagnostic real-time transcription polymerase chain reactions (PCRs) will be able to detect this novel GII.17 virus, but it is not known whether the same holds true for immunoassays. However, only a small portion of norovirus outbreaks are typed beyond the GI and GII classification, therefore it is possible that GII.17 is more prevalent than we currently suspect.

Phylogenetic analyses and molecular characterisation of the novel GII.17 viruses

Phylogenetic analysis of the viral protein 1 (VP1) of GII.17 strains in the NCBI database demonstrated at least two clusters, with the novel Asian GII.17 strains grouping together with the GII.17 strains detected in the surface water in Kenya (Figure 2,[21]) and in an outbreak in 2012 in Korea [22]. Although the novel GII.17 clusters away from previously identified GII.17 strains, the amino acids changes in VP1 are not sufficient to separate it into a different genotype. For only a limited number of GII.17 strains the full VP1 has been sequenced, which demonstrated three deletions and at least one insertion compared with previous GII.17 strains (comprehensive alignments are given in Fu et al. and Parra et al. [2,21]). The majority of these changes could be mapped in or near major epitopes of the VP1 protein and potentially result in antigenic drift or altered receptor-binding properties [21]. Most publicly available GII.17 sequences only comprise the VP1, and most frequently the 5'-end of VP1 (C region), while most of the observed diversity within the GII.17 genotype is observed in the 3'-end of VP1 (D region) [23].

Previously, viruses with a GII.17 VP1 genotype contained a GII.P13 ORF1 genotype, although recombinants with an ORF1 GII.P16, GII.P3 and GII.P4 genotype have also been identified (Table). Sequence comparison showed that the ORF1 region of the novel GII.17 viruses was not detected before and cluster between GII.P3 and GII.P13 viruses [21]. Since this is the first orphan ORF1 sequence associated with GII.17, it has been designated GII.P17 according to the criteria of the proposal for a unified norovirus nomenclature and genotyping [24]. The novel GII.17 virus was termed Kawasaki 2014 after the first near complete genome sequence (AB983218) submitted to GenBank. Noronet provides a publicly available and widely used tool for the typing of norovirus sequences (http://www.rivm.nl/mpf/norovirus/typingtool). This typing tool was updated to ensure correct classification of both ORF1 and ORF2 sequences of the newly emerged GII.P17-GII.17 viruses.

The acquisition of a novel ORF1 could potentially result in an increase in replication efficiency and may – in part – explain the increase of the AGE outbreak activity. Histo-blood group antigens (HBGAs) function as (co-) receptors for noroviruses. Alpha(1,2)fucosyltransferase

Figure 2

Unrooted maximum likelihood phylogenetic tree based on the 5'-end of virus protein 1 (VP1) sequences (C region) of GII.17 noroviruses, available from the National Center for Biotechnology Information (NCBI)

The tree was estimated under the general time reversible model using PhyML. Bootstrap values above 70% are given. Sequences from Kenya are depicted in red and those from the recent outbreaks (2013–1015) reported in Asia in blue. The scale bar represents nucleotide substitutions per site.

2 (FUT2) adds an alpha-1,2 linked fucose on HBGAs, and individuals lacking the FUT2 gene are referred to as 'non-secretors', while those with a functional FUT2 gene are called 'secretors'. Non-secretors have been shown to be less susceptible to infection with several norovirus genotypes [25]. In studies investigating the genetic susceptibility to norovirus genotypes, a secretor patient with blood type O Lewis phenotype Le^{a-b+} and a secretor patient with blood type B Lewis phenotype Le^{a-b-} were positive for previously identified GII.17 viruses and no non-secretors were found positive [26,27], suggesting that there could be genetic restrictions for GII.17 viruses in infection of humans. How the observed genetic changes have affected the antigenic and binding properties of the novel GII.17 strains, and hereby the susceptible host population, remains to be discovered.

Public health implications

Based on the emergence and spread of new GII.4 variants, we know that noroviruses are able to rapidly spread around the globe [28,29]. The novel GII.17 virus has been detected in sporadic cases throughout the world, but until now it has not resulted in an increase

in outbreak activity or replacement of GII.4 Sydney 2012 viruses outside of Asia. Following the patterns observed in the past years for GII.4 noroviruses and based on the data from China and Japan, an increase in norovirus outbreak activity can be expected if the currently dominant GII.4 is replaced by GII.17. Another possibility – however – would be some restriction to global expansion, as has been observed previously for the norovirus variant GII.4 Asia 2003 [29]. Such restrictions could be due to differences in pre-existing immunity, but could also be the result of differences between populations in the expression of norovirus receptors [29]. Based on current literature on the novel GII.17 virus there is no indication that it will be more virulent compared with GII.4. Nevertheless, the public health community and surveillance systems need to be prepared in case of a potential increase of norovirus activity by this novel GII.17 virus.

Conclusions

Understanding the epidemiology of norovirus genotypes is important given the development of vaccines that are entering clinical trials. Current candidate vaccines have targeted the most common norovirus genotypes, and it remains to be seen if vaccine immunity is cross-reactive with GII.17 viruses [30]. Contemporary norovirus diagnostic assays may not have been developed to detect genotype GII.17 viruses since this genotype was previously only rarely found during routine surveillance. These assays need to be evaluated and updated if necessary to correctly diagnose norovirus outbreaks caused by the emerging GII.17 virus. Norovirus strain typing ideally should include ORF1 sequences and the variable VP1 'D' region as well as metadata on the host, like clinical symptoms, immune status and blood group. This will allow us to better study and monitor the genetic disposition, pathogenesis, evolution and epidemiology of this newly emerged virus.

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Conflict of interest

None declared.

Authors' contributions

MG, JB, HV: compiling the data, drafting the manuscript; AP, FB, KT, MC, JM, JN, GR, ML, LDR, NI JH, VM, KAB, JV, PW: collecting field data, critical review of the manuscript; MK: initiation of study, providing data, critical review of the manuscript.

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