Norovirus outbreaks in long-term care facilities. Catalonia, 2017-2018

Ignacio Parrón (IParron@gencat.cat)
Sub-Direcció Regional a Barcelona del Departament de Salut, Barcelona
Irene Barrabeig
Sub-Direcció Regional a Barcelona del Departament de Salut, Barcelona
Miquel Alseda
Sub-Direcció Regional a Lleida del Departament de Salut, Lleida
Cristina Rius
Agència de Salut Pública de Barcelona, Barcelona
Thais Cornejo-Sánchez
Departament de Microbiologia, Vall d'Hebrón Hospital, Barcelona
Mireia Jané
Sub-Direcció General de Vigilància i Resposta a Emergències de Salut Pública, Barcelona
Cristina Pérez
Sub-Direcció Regional a Barcelona del Departament de Salut, Barcelona
Susanna Guix
Departament de Genètica, Grup de Virus Entérics, Microbiología i Estadística, Universitat de Barcelona, Barcelona
Àngela Domínguez
Departament de Medicina, Universitat de Barcelona, Barcelona
Working Group
CIBER Epidemiologia y Salud Pública, Instituto de Salud Carlos III, Madrid

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Abstract

Norovirus is the leading cause of outbreaks of acute viral gastroenteritis. We carried out this study to investigate outbreaks in long-term care facilities reported in 2017 and 2018 in Catalonia (Spain).

The characteristics of the centres, exposed persons and the genogroups responsible were analyzed. Viral loads were estimated.

The attack rate (AR), rate ratios (RR) or the odds ratio (OR) and its 95% confidence intervals were calculated. The mean cycle thresholds (Cq) were compared using the t-test for independent means.

We included 30 outbreaks (4,631 exposed people). The global AR was 25.9%. The RR of residents vs. staff was 2.28 (95%CI 2.0-2.6). In residents with total or severe dependence the attack rate was 85.16% and in residents with moderate and low dependence or independent was 69.13% (RR 1.23, 95% CI 1.05–1.45). ARs were higher in smaller centres than in larger ones (34.4% vs 19.5%; RR 1.76 (95%CI 1.60–1.94). GII was responsible for 70% of outbreaks and 78.5% of identifications. No association was found between the genogroup and presenting symptoms (OR 0.96; 95% CI 0.41 to 2.26). Viral loads were higher in symptomatic than in asymptomatic patients (p = 0.001).

Because norovirus was detected in asymptomatic persons, control measures should be applied not only to people with symptoms but to all persons in LTCF where norovirus outbreaks occur.

Introduction

Norovirus, an RNA virus of the *Caliciviridae* family with 6 genogroups, of which genogroup I, II and IV are human pathogens[1], usually produces symptoms of nausea, vomiting and diarrhoea, with a self-limiting evolution of 48-72h[2].

Norovirus is estimated to be responsible for 20% of cases of all-cause diarrhoea worldwide[3] and may cause up to 90% of outbreaks of acute gastroenteritis (AGE) of viral aetiology[4].

Inns et al., in a review of norovirus reports worldwide between 1995 and 2015, found an incidence of up to 60 cases per 1000 person-years and a hospitalization rate of up to 1.04 per 1000 person-years[5]. Kreidieh et al. in a similar study in the Middle East and North Africa between 2000 and 2015 found that between 0.82% and 36.84% of AGE outbreaks in children aged < 5 years treated in hospital emergency rooms were caused by norovirus[6].

Of the more than 1,000 outbreaks of AGE reported annually in 2009 and 2010 in the United States, norovirus was confirmed as the aetiological agent in 86% and 90% of norovirus-associated deaths in the same period occurred in people aged ≥ 65 years[7].

In long-term care facilities (LTCF), the attack rate of AGE outbreaks due to norovirus varies between 3% and 45%, with a case fatality rate ranging from 0.3–1.6%[8]. In these institutions, norovirus is the second leading cause of outbreaks, after the flu virus[9]. In England an incidence of 30 outbreaks per 100 LTCF per year has been reported during the period 2014-2016[10]. In France in 2011, more than 70% of AGE outbreaks in such facilities were due to norovirus[11] and in the United States > 60% of norovirus outbreaks between 2009 and 2013 occurred in these facilities[12]. Although norovirus infection is usually mild, it may be more severe in older people. In developed countries, norovirus is responsible for between 10% and 20% of hospitalizations due to AGE in residents of LTCF and between 10% and 15% of deaths[8].

Genogroup GII is the most frequently identified genogroup of norovirus in outbreaks[13]. In Spain, this genogroup has also been the most prevalent in recent years[14].

Asymptomatic affected people may contribute to transmission of norovirus[15] and to a longer duration of outbreaks, which has important repercussions for disease control.

Symptomatic persons have a higher viral load than asymptomatic ones[16], but no value has been established to predict the level of shedding associated with clinical manifestations[17].

In symptomatic patients, it has not been possible to associate the duration of symptoms with the viral load, although the duration of viral shedding has been shown to be longer in those with a higher load and in older people[18,19].

In patients with AGE, the viral load has been shown to be higher when symptoms are due to genogroup GII rather than GI, and the higher load of GII, which has been linked to increased ease of transmission[20], has also been observed in patients co-infected with GI and GII[16,18,21,22].

Objective

The objective of this study was to investigate attack rates in AGE outbreaks due to norovirus that occurred in LTCF and their association to the type of exposed person, size of the centre, type of transmission, genogroup involved, and viral load.

Material And Method

A prospective study of outbreaks of AGE due to norovirus in LTCF reported between January 2017 and December 2018 was made in Catalonia, a region in North-western Spain with a population of 7,496,276 in January 2017, of which 18.6% were aged ≥ 65 years[23]. Outbreaks of any aetiology must be reported to the Public Health Agency of Catalonia, which studies the causes and establishes control measures[24].

AGE was defined as sudden-onset diarrhoea that may be accompanied by fever, nausea, vomiting, or abdominal pain. The involvement of two or more people with a common exposure (or possible person-to-

person transmission) was considered as an outbreak of AGE. A confirmed outbreak of norovirus was defined as the identification of norovirus in stool samples by real-time RTqPCR.

Data collection

Norovirus outbreaks occurring in LTCF confirmed by RTqPCR were included. The numbers of residents and staff, the capacity of the centre and whether transmission was person-to-person or by a common vehicle were collected. A survey was designed for all exposed (affected and unaffected) persons including sociodemographic data, the degree of dependence (estimated using the Barthel index), the medical history, the date and time of symptom onset and the symptoms presented.

For staff, information on the type of work was collected. Stool samples were collected to identify the cause of the outbreak. Norovirus was tested for using quantitative reverse transcription PCR (RTqPCR) and identifying the genogroup detected, as described above[17]. The semi-quantitative value given by the RTqPCR cycle of quantification (Cq) was used to measure the viral load in samples positive for norovirus. Stool samples were obtained from both symptomatic and asymptomatic staff and residents and, in outbreaks where a foodborne transmission was suspected, from food handlers.

Statistical analysis

The overall attack rates and the rates by age group, sex, relation with the center (residents or staff), type of transmission (common vehicle or person-to-person), degree of dependency and, in staff, type of work activity were calculated. The rate ratio (RR) and 95% confidence intervals (CI) were calculated to estimate the risk of being affected (resident vs. staff), globally and separately for outbreaks of person-to-person transmission and foodborne transmission, according to the capacity of the center (< 100 residents or ≥ 100).

To assess the seasonality we compared outbreaks occurred in autumn and winter months and those occurred in spring and winter months using a chi square test.

The association between genogroup and the presence of symptoms was assessed by odds ratio (OR) and its 95% confidence interval.

The mean Cq as an approximation to viral loads was compared using the t-test for independent means. The Student's t-test and its 95% CI was used to calculate the degree of significance of the difference between means.

Data collection and management was made using the MS-Office 2013 Access 12.0 database and the statistical analysis using the PASW Statistics 18.0.2 statistical package and Epi Info™ for Windows 7.2.

Ethics statement

All data used in the study were collected during routine public health surveillance activities as part of the legislated mandate of the Health Department of Catalonia, the competent authority for surveillance of

communicable diseases according to Decree 203/2015 of the 15 September which created the epidemiological surveillance network of Catalonia[24]. Health Department of Catalonia is officially authorized to receive, treat and temporarily store personal data on infectious disease cases and outbreaks. Access to data was restricted to personnel involved in data collection and analysis. Established measures were used to protect the confidentiality of personal data and all were fully anonymized.

This article does not contain any studies with human participants or animal performed by any of the authors.

The study was approved by the University of Barcelona Bioethics Commission (Institutional Review Board IRB00003099) on April 12, 2016 in accordance with research regulations, guidelines, and ethical protocols established.

Results

During 2017 and 2018, 213 AGE outbreaks were reported to the Public Health Agency of Catalonia, of which 40 (18.8%) occurred in LTCF. Norovirus was identified as the causal agent in 89 of the reported outbreaks, 30 of which (33.7%) were in LTCF. Norovirus was identified as the causative agent in 75% of outbreaks in LTCF.

The transmission mechanism was person-to-person in 27 of the 30 outbreaks in LTCF and foodborne in the remaining three, although there was also subsequent person-to-person transmission in one foodborne outbreak.

Twenty-one (83.7%) outbreaks occurred in autumn and winter months and 9 (16.3%) in spring and summer months ($p = 0.0003$). Of the 27 outbreaks with person-to-person transmission, 14 (51.8%) occurred during the colder months (December to March) (Fig. 1).

A total of 4,631 people were exposed, with an attack rate of 25.9%: 3,034 were residents (attack rate 32.2%) and 1,597 staff (attack rate of 14.1%). The RR for resident vs staff was 2.28 (95% CI 2.0 to 2.60).

In outbreaks due to person-to-person transmission, the overall attack rate was 25.1%, and was higher in residents than in the staff (32.5% and 10.6%, respectively; RR 3.07 95% CI 2.60 to 3.59). In foodborne outbreaks the overall attack rate was 33.2%, and was 28.9% in residents and 39% in staff (RR 0.74; 95% CI 0.57 to 0.96)

Of the centres where outbreaks occurred, 13 had a capacity of ≥ 100 residents and the attack rate was 19.2%. The remaining 17 centres had a capacity of < 100 residents and the attack rate was 38.5%. The RR, both globally and for staff or residents, indicated an increased risk of being affected in smaller centres (Table 1).

Table 1
Attack Rates and Rate Ratio (RR) in staff and residents of LTCF according to the capacity of the residence

	Centers with < 100 residents			Centers with ≥ 100 residents			RR (95% CI)
	Affected	Unaffected	Attack rate	Affected	Unaffected	Attack rate	
Residents	508	616	45.2	468	1442	24.5	1.84 (1.67–2.04)
Staff	111	374	22.9	114	998	10.2	2.23 (1.76–2.83)
Total exposed	619	990	38.5	582	2440	19.2	2 (1.81–2.2)

A total of 495 exposed persons (365 residents and 130 staff) were interviewed, of whom 106 (21.4%) were male and 389 (78.6%) female. Of the total exposed persons, 371 were affected and 124 unaffected. The attack rate was 72.6% in males and 75.6% in females (p = 0.61).

Attack rate in person-to-person outbreaks was 76.55% and 69.16% in common vehicle outbreaks (RR 1.11; 95% CI 0.96–1.27).

Information on underlying diseases was obtained in 80.3% of residents and 83% of those affected. Heart disease was the most common recorded disease, both in all residents and in those affected (38.1% and 40.7% respectively, p = 0.04), followed by diabetes mellitus (20.8% in all residents and 21.3% in those affected, p = 0.74) and dementia (15.9% in all residents and 15.9% in those affected, p > 0.99). The degree of dependence (measured by the Barthel index) was obtained in 236 residents (188 affected and 48 unaffected). In residents with total or severe dependence the attack rate was 85.16% and in residents with moderate and low dependence or independent was 69.13% (RR 1.23, 95CI 1.05–1.45) (Table 2).

Table 2
Degree of dependency (Barthel index) in affected and unaffected residents

Degree of dependency	Affected residents	Unaffected residents	Attack rate	RR (95% CI)
Total dependency (0 to 20)	45	13	77.59%	
Severe dependency (21 to 60)	87	10	89.69%	
Moderate dependency (61 to 90)	48	22	68.57%	
Low dependency (91 to 99)	5	2	71.43%	
Independent (100)	3	1	75%	
Total + severe	132	23	85.16%	1.23 (1.05–1.45)
Moderate + low + independent	56	25	69.13%	1

Information on occupation was obtained in 123 staff members: 58 were service personnel or kitchen staff (of whom 26 were affected) and 65 were health staff or caregivers (of whom 49 were affected); in 7 staff members this information was not available.

Kitchen staff and service personnel had a lower risk of being affected than health staff and caregivers (RR 0.59; 95% CI 0.43 to 0.82) (Table 3).

Table 3
Attack Rates and Rate Ratio (RR) in LTCF staff according occupation.

Occupation	Affected	Unaffected	Attack rate	RR (95% CI)
Kitchen staff and service personnel	26	32	44.83%	0.59 (0.43–0.82)
Health staff and caregivers	49	16	75.38%	1
Total	75	48	60.98%	

Of the 30 outbreaks studied, 5 were due to genogroup I (16.7%), 21 to genogroup II (70%) and the remaining 4 (13.3%) were mixed genogroup I and genogroup II infections. We obtained 425 stool samples: norovirus was identified by RTqPCR in 256. Genogroup I was identified in 53 samples (20.7%) and genogroup II in 198 samples (77.3%). In 5 samples (1.9%) both GI and GII (2 symptomatic and 3 asymptomatic) were identified. The remaining 169 samples were negative for norovirus.

Of the 53 samples of infected persons in which GI was identified, 8 were asymptomatic and the other 45 were symptomatic. Of the 198 GII samples of infected persons, 29 were asymptomatic and 169 were symptomatic (Table 4). No association was found between the genogroup and presenting symptoms (OR

0.96; 95% CI 0.41 to 2.26), indicating that the percentage of asymptomatic infections was similar in both genogroups (Table 4)

Table 4
Norovirus genogroup in symptomatic and asymptomatic infected LTCF staff and residents

Genogroup	Symptomatic	Asymptomatic	Total	OR (95% CI)
GI	45	8	53	0.96 (0.41–2.26)
GII	169	29	198	1

With respect to the viral load in symptomatic and asymptomatic persons (Table 5), the difference between the means of the Cq was − 3.35 (95% CI -5.34 to -1.35), with a greater viral load found in symptomatic than in asymptomatic persons (p = 0.001).

Table 5
Cycle of quantification values in symptomatic and asymptomatic infected staff and residents of LTCF**

	Symptomatic	Mean (SD)	Positive samples*	Difference between means of Cq (95% CI)	*p* value
Staff	Yes	28.11 (5.54)	46	-1.85 (-4.87 to 1.17)	0.225
	No	29.96 (5.15)	18		
Residents	Yes	24.96 (5.87)	164	-3.19 (-5.82 to -0.56)	0.018
	No	28.15 (5.84)	22		
All persons	Yes	25.65 (5.93)	210	-3.35 (-5.34 to -1.35)	0.001
	No	29.00 (5.50)	40		
* In 6 samples positive for GII norovirus, the Cq value could not be determined					
**LTCF: Long-term care facilities					

Discussion

Our results show 18.8% of AGE outbreaks occurred in LTCF, similar to the results obtained by Torner et al. in a study carried out in Catalonia in 2010 and 2011[25].

In 75% of the 40 outbreaks in LTCF, norovirus was the causal agent identified, results similar to those of other studies. Inns et al. described 566 AGE outbreaks in LTCF in North East England between 2016 and 2018 and norovirus was detected in 64% of outbreaks with a pathogen identified[26]. Steele et al. studied 7,094 norovirus outbreaks between 2009 and 2017 in United States of which 5,335 (75%) occurred in LTCF[27] and Espenhain et al. found that 77% of norovirus outbreaks in Norway between 2005 and 2018 were in LTCF[28].

A seasonal distribution was observed, with most of outbreaks occurring in autumn and winter. Our results are consistent with previous findings by other authors indicating a seasonality of norovirus disease[4,28]. Of the outbreaks analysed, there was person-to-person transmission in 90% and foodborne transmission in 10%. Similar results were found by Kroneman et al. in a study of norovirus outbreaks in 13 European countries between July 2001 and June 2006 (person-to-person transmission in 88%, foodborne in 10% food and waterborne in 2%)[29]. We found no outbreaks due to waterborne transmission. Chen et al. in a review of norovirus outbreaks in LTCF found person-to-person transmission in > 90% of outbreaks and linked this to close contact with other residents, shared facilities and contact with visitors and staff[30].

Lian et al. in an analysis of norovirus outbreaks reported in China from 2014 to 2017 found that 77% were person-to-person transmission, 6% foodborne, 4% waterborne and 13% of multiple transmission[4].

Our results suggest that the closeness of contact between residents and staff probably plays an important role in the transmission, as staff who had greater contact with residents (health staff and caregivers) had an increased risk of being affected than those who did not. A 2014 meta-analysis by Petrignani et al.[31] including 40 outbreaks in LTCF also found that the closeness of contact between staff and residents was related to the risk of staff being affected. The authors found that residents with medium or high dependence had a higher attack rate than those with low dependence. Our results showing that 70.2% of affected residents had total or severe dependence (Barthel score between 0 and 60) agree with the results obtained by these authors suggesting that people with greater dependence require greater contact with caregivers.

RTqPCR identified norovirus in the faeces of 36.7% (40/109) of asymptomatic exposed persons which is similar to the values estimated by Miura et al. in foodborne outbreaks in Japan from 2005 to 2006 in which they identified norovirus in 32.1% of asymptomatic[32].

We found that symptomatic infected persons had a higher viral load, with a mean Cq of 25.65, compared with 29.00 in asymptomatic infected persons. These results are similar to those obtained by Shioda et al. who studied 12,910 samples from outbreaks and isolated cases in the United States and Latin America with a mean Cq of 25.3 for symptomatic affected persons and 28.5 for asymptomatic affected persons[18].

We have found that lower capacity centers have a higher attack rate than those with higher capacity. A possible explanation is that in smaller centres the cleaning and disinfection protocols in outbreaks may

be less developed than in large centres. Rosenthal et al. in a study conducted in Oregon between 2003 and 2006, found contrary results[27], with the differences possibly being due to the characteristics of the centres that were not studied.

A strength of the study is that all outbreaks reported in a region with the same surveillance system were included, and therefore the results should reflect the real situation.

Our study has some limitations. The mild severity of AGE outbreaks due to norovirus means underreporting may be greater in small centres than in large ones as, because there are fewer cases, contacts with the health services and notification of the outbreak may be less likely.

Another limitation is that the number of samples from infected asymptomatic persons was low which may result in no significant differences being found due to low statistical power.

Conclusions

Norovirus caused the vast majority of AGE outbreaks in LTCF, affecting residents more than staff, and especially residents with a high degree of dependence. Person-to-person transmission was the main mechanism. Genogroup II was more often the causal agent than genogroup I, and no outbreak due to genogroup IV was detected.

Mean viral loads were higher in infected symptomatic persons than in infected asymptomatic persons, both globally and in residents. Because norovirus was detected in asymptomatic persons, control measures should be applied not only to people with symptoms but to all persons in LTCF where norovirus outbreaks occur.

Declarations

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The Working Group for the Study of Outbreaks of Acute Gastroenteritis in Catalonia is composed of:

Miquel Alsedà, Josep Álvarez, Irene Barrabeig, Anna Isabel Belver, Neus Camps, Sofia Minguell, Monica Carol, Pere Godoy, Conchita Izquierdo, Mireia Jané, Ana Martínez, Ignacio Parrón, Cristina Pérez, Ariadna Rovira, Maria Sabaté, Maria Rosa Sala, Núria Torner, Rosa Maria Vileu (Agència de Salut Pública de

Catalunya); Anna de Andrés, Javier de Benito, Esteve Camprubí, Montse Cunillé, Maria Lluïsa Forns, Antonio Moreno-Martínez, Efrén Razquín, Cristina Rius, Sara Sabaté, Mercé de Simón (Agència Salut Pública de Barcelona; CIBERESP); Rosa Bartolomé, Thais Cornejo (Hospital Vall d'Hebron); Susana Guix (Laboratori de Virus Entèrics, Universitat de Barcelona); Lorena Coronas, Àngela Domínguez, Núria Soldevila (Departament de Medicina, Universitat de Barcelona; CIBERESP)

Conflict of Interest Statement: The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS STATEMENT

1. Parrón and A. Domínguez conceptualized and designed the study, carried out the initial analyses and interpretation of data and drafted the initial manuscript.

Miquel Alseda and Anna de Andres: designed the study and acquisition of data and revised critically the manuscript.

1. Cornejo-Sánchez carried out analyses and interpretation of data, performed the

laboratory analyses and drafted the initial manuscript.

1. Jané, C. Pérez, I. Barrabeig and S. Guix contribued to final analyses and interpretation of data and revised critically the final manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Figures

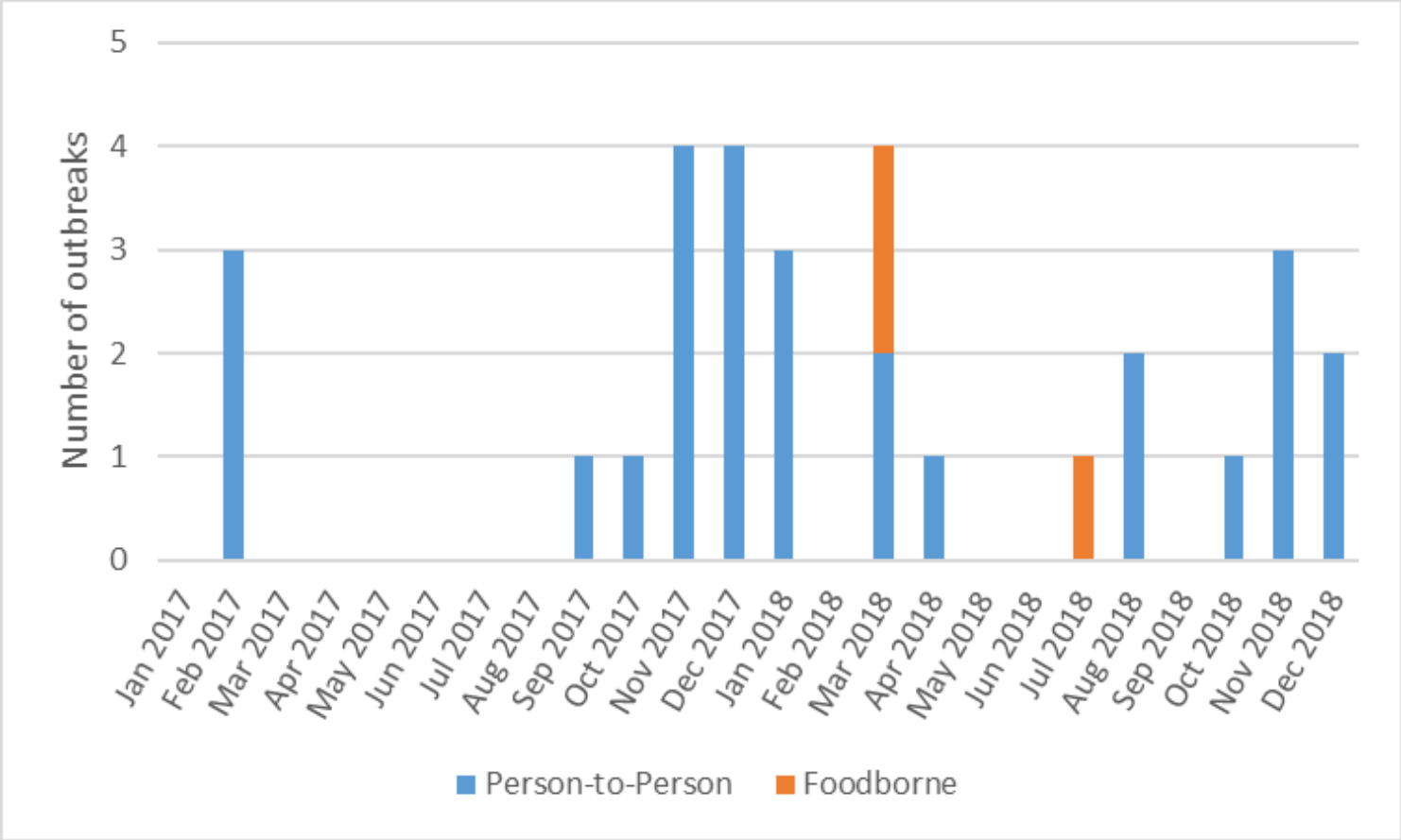

Figure 1

Number of AGE outbreaks due to norovirus in long-term care facilities according to the month of onset