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Factors driving transmission of norovirus outbreaks in LTCFs: a case-level analysis of 107 outbreaks

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Bachelor of Medicine
Southern Medical University
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Abstract

Factors driving transmission of norovirus outbreaks in LTCFs: a case-level analysis of 107 outbreaks

By Yangping Chen

Background Norovirus is the most common cause of gastroenteritis outbreaks in long-term care facilities (LTCFs) in the United States, causing high disease burdens in both residents and staff. Understanding how individual case symptoms and characteristics contribute to norovirus transmission can lead to more informed control measures in LTCFs.

Methods We examined line lists for 107 norovirus outbreaks that took place in US LTCFs in six states from 2015 to 2019. We estimated the individual effective reproduction number, R_{Ei}, to quantify individual case infectiousness and examined the contribution of vomiting, diarrhea, and residents (vs. staff) to case infectiousness. Individual estimations of R_{Ei} were calculated by a maximum likelihood procedure that uses information on symptom onset dates and the serial interval distribution of norovirus to infer who infected whom. The associations between case characteristics and R_{Ei} were estimated using a multivariate, mixed log-linear model with inverse variance weighting.

Results Vomiters infected 1.28 (95% CI: 1.11, 1.48) times the number of secondary cases compared to non-vomiters and LTCF residents infected 1.31 (95% CI: 1.15, 1.50) times the number of secondary cases compared to staff. There was no difference in infectiousness between cases with and without diarrhea (1.07 (95% CI: 0.90, 1.29)).

Conclusion Individuals who vomit, particularly LTCF residents, are more infectious than those who do not vomit and tend to drive norovirus transmission in US LTCF outbreaks.

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Background

Norovirus is the most common cause of acute gastroenteritis globally. In the United States, there are approximately 19-21 million norovirus cases across all age groups reported each year[1]. While the highest incidence of norovirus gastroenteritis is among children <5 years of age, older individuals (≥65 years) have the greatest risk for norovirus-associated severe illness and death, accounting for 90% of all norovirus-associated deaths in the United States [2].

In the United States and other high-income countries, the majority of norovirus outbreaks occur in LTCFs [3], accounting for >60% of all reported norovirus outbreaks [4]. The majority of these outbreaks are caused by the GII genotype 4 (GII.4) strain [5]. Norovirus is highly infectious and can be transmitted through direct contact with an infectious person or through contaminated food, water and surfaces. Both stool and vomit are infectious, with aerosol dispersal of vomiting spray often leading to a wide radius of surrounding environmental contamination [6]. Norovirus typically presents with a sudden onset of vomiting and/or diarrhea that lasts for approximately 24 to 72 hours[1]. While asymptomatic infections can also occur and contribute to transmission, symptomatic patients are assumed to be the main drivers of transmission in LTCF and other healthcare facility outbreaks [7]. For most individuals with symptomatic infection, norovirus is self-limiting and can be resolved without medical attention. However, due to underlying conditions such as immune-deficiencies, chronic inflammation, and microbiome alterations [8], older adults aged ≥65 years are at increased risk of severe disease that could result in hospitalization and even death [9]. Moreover, for older residents of LTCFs, the congregate living and high dependency on staff increases their risk of norovirus infection [10].

Not only are norovirus outbreaks common in US LTCFs, but they often have high attack rates and long durations. The median attack rate in US nursing home outbreaks is a staggering 50%, with outbreaks typically lasting more than two weeks [11]. The majority of these outbreaks occur during winter months, with more than 80% occurring from November to April. Because other infections, such as influenza, are also common during these months, outbreaks of norovirus further increase the medical burden placed on LTCFs [8,12]. Currently, there is no licensed vaccine or specific anti-virus therapy for norovirus gastroenteritis. Treatment is mainly supportive, with the goal of preventing dehydration and electrolyte abnormalities [8,13].

Because norovirus outbreaks are common in LTCFs, where older residents experience an increased risk of severe illness and mortality, effective prevention and control measures are urgently needed in LTCF settings. Current control measures are based on general infection control principles, including enhanced environmental cleaning, enhanced hand hygiene and case isolation, however the efficacy of these measures in controlling norovirus is not well quantified [8]. By examining transmission patterns and factors associated with increased transmissibility, we can facilitate progress on interventions aimed at reducing the burden of norovirus diseases in LTCFs.

We aim to quantify the infectiousness of individuals involved in US LTCF norovirus outbreaks and identify risk factors for increased infectiousness. Control measures that target individuals with increased infectiousness (e.g., vomiters) could lead to reduced transmission of norovirus in LTCFs. In a previous study, authors found that vomiting was the leading risk factor for infectiousness in six US LTCF norovirus outbreaks. Diarrhea (compared to no diarrhea) was also

associated with increased infectiousness, although to a lesser extent, as was being a LTCF resident (compared to staff) [14]. In our study, we will use a much larger dataset that includes information on 107 US LTCF norovirus outbreaks to further examine and quantify risk factors for norovirus infectiousness, with the ultimate goal of informing more evidence-based control measures in this setting.

Methods

Data Source

We requested data on individual norovirus outbreaks occurring in LTCFs (nursing homes, skilled nursing facilities and assisted living facilities) between December 1, 2012 and May 1, 2019 from state health departments participating in Norovirus Sentinel Testing and Tracking (NoroSTAT), a collaborative network of 12 selected state health departments and CDC created to improve completeness of norovirus outbreak reporting [15]. We asked that data be in the form of de-identified line lists, or tables with each row representing a case and each column representing case-specific information, such as demographic and clinical information. Line lists included the following information: 1) dates of symptom onset of gastroenteritis, 2) the presence/absence of individual symptoms, including vomiting and diarrhea, 3) if the case was a resident or staff, and 4) demographic information (e.g., gender and age). We requested that line lists be complete, such that all cases, including both resident and staff cases, throughout the entirety of the outbreak were included. Furthermore, we requested line lists from confirmed (i.e. two or

more laboratory-confirmed case) and probable (i.e., one laboratory-confirmed case) outbreaks only. If available, we also requested that the following information also be included in line lists: 1) specific intervention methods used by the facility and when each method was implemented, 2) information on the physical layout of the facility (e.g., number of beds and units/wings in the facility), and 3) case-level information on duration of illness, hospitalization, emergency department visits and lab results. Five state health departments (Minnesota, New Mexico, Ohio, South Carolina and Wisconsin) responded to our data request, providing a total of 108 line lists. One line list from Minnesota was excluded from all analyses due to substantial missingness of symptom onset dates (45% of cases). The remaining 107 line lists, with a total 3,363 cases, were included in the analyses.

Estimation of Individual Effective Reproduction Numbers, R_{Ei}

Infectiousness of a pathogen can be quantified by its basic reproduction number, R_0, which is defined as the average number of secondary cases infected by a single infectious case in a population with no immunity. However, when examining the course of disease spread during an outbreak, in which some individuals may already be, or will become, immune to disease, the effective reproduction number, R_E, is often more useful, as it is the average number of secondary cases infected by a single infectious case in a population with some immunity. The value of R_E is always less than or equal to R_0, as R_E is equal to R_0 multiplied by the proportion susceptible in the population. We expect an outbreak to go to extinction when R_E consistently drops to a level below 1, meaning that each infectious individual, on average, infects less than one other individual.

In this analysis, our primary outcome of interest is individual case infectiousness, which we quantified by the individual effective reproduction number, R_{Ei}, or the expected number of secondary cases that an individual, i, generates in an outbreak. We estimated R_{Ei} using the Wallinga-Teunis (WT) method, which uses a maximum likelihood algorithm based on transmission links between any pair of two cases in an outbreak. This method is described in detail elsewhere [1617] . Briefly, it uses the difference in symptom onset dates between cases and the probability distribution of the serial interval, or the time between symptom onset in primary cases and the secondary cases they generate [18], to calculate the relative likelihood that cases with earlier onset dates infected cases with later onset dates. The relative likelihoods that case i infected any other case j are summed to estimate R_{Ei}, while the corresponding 95% confidence interval is generated by Markov chain Monte Carlo (MCMC) methods. Cases cannot infect other cases with the same or earlier symptom onset dates, and cases with the same symptom onset date will have the same R_{Ei} and corresponding 95% confidence intervals. R_{Ei} from cases with symptom onset dates on the last day of an outbreak will always equal 0, as these cases did not produce any known secondary cases. We used a gamma probability distribution for the serial interval with a mean of 3.6 days and standard deviation of 2.0 days, which was derived from a previous study on several large norovirus outbreaks in child daycare centers in Sweden [19]. Considering the uncertainty of the true probability distribution of the norovirus serial interval in US LTCF outbreaks, we also conducted a sensitivity analysis with the mean serial intervals varying between 1.5 and 4.0 days in half day increments.

Analysis of Risk Factors for Transmission by Modeling

Considering the correlation and clustering effect between R_{Ei}s within each outbreak, we used a linear mixed model to investigate the association between individual case characteristics and R_{Ei}. Because the distribution of R_{Ei} was right-skewed, we used the natural log of R_{Ei} as the dependent variable. To include cases with $R_{Ei} = 0$ in the regression analysis, we added a small value (0.01) to these cases' R_{Ei} to let them be eligible for log transformation. As a sensitivity analysis, we also examined all associations with cases with $R_{Ei} = 0$ excluded. We selected vomiting (yes or no), diarrhea (yes or no) and being a resident or staff as our main exposure variables to examine their associations with norovirus infectiousness. We also examined evidence for an interaction between vomit and diarrhea. While additional variables were included in the line lists, including age, sex, hospitalization, illness duration, and presence of fever, headache, nausea, chills and muscle ache, these variables were missing for a large percentage of cases, with disproportionate missingness for residents and staff (resident cases tended to have more comprehensive records than staff cases), and were therefore excluded from our model.

The mixed linear model included a random intercept for outbreak, accounting for clustering induced by correlation of R_{Ei} within the 107 outbreaks. To incorporate the uncertainty of each R_{Ei} estimate, we used inverse variance weighting, with the weight of each R_{Ei} equal to the inverse of the sum of its three variance components: 1. the individual variance of the estimated R_{Ei}, 2. the within outbreak variance (unique to each outbreak), and 3. The between outbreak

variance (the same for all R_{Ei} estimates). The formula for the inverse variance weighting can be found below:

$$Inverse\ Variance\ Weighting = \frac{1}{Var(R_{Ei}) + Var(R_{Ei})_{Within-Outbreak} + Var(R_{Ei})_{Between-Outbreak}}$$

The final linear mixed model can be found below:

$$logR_{Eij} = \beta_0 + b_{0i} + \beta_1 Diarrhea_{ij} + \beta_2 Vomiting_{ij} + \beta_3 Resident_{ij} + e_{ij}$$

where log R_{Eij} represents the estimated log R_E of the j^{th} case from the i^{th} outbreak, b_{0i} represents the random slope for the i^{th} outbreak, and e_{ij} represents residual heterogeneity of the j^{th} case from the i^{th} outbreak not explained by the model. The residual heterogeneity, e_{ij}, and random slope, b_{0i}, are assumed to be independent and identically distributed with mean zero and their respective variances. Cases from the same outbreak were assigned the same random effect, whereas cases from different outbreaks were assumed to be independent. Final coefficient estimates and 95% confidence intervals were exponentiated to show the relationships between average R_{Ei} (rather than log R_{Ei}) and the variables in the model. All statistical analyses were performed using the EpiEstim [20] and metafor [21] packages in R software version 4.0.3. This model was adapted from a previous study [14].

For our secondary analysis, we used a logistic regression model to examine the association between being an index case (i.e., cases with illness onset on day 1 of an outbreak) and vomit, diarrhea and resident vs. staff. We also tested the relative infectiousness of index cases to non-index cases by fitting a bivariable mixed linear model and comparing index cases to cases with illness onset on days 2-4. We only incorporated cases from the first four outbreak days in this

model in order to diminish the impact of subsequent control measures and accumulation of acquired immunity on R_{Ei}. Lastly, to examine whether cases with specific symptoms/characteristics occur earlier in outbreaks, we used a linear, mixed multivariable model to examine the associations between outbreak day and vomit, diarrhea and resident vs. staff..

Results

Outbreak Characteristics

Of the 107 line lists and 3,363 cases , the median number of cases per outbreak was 27 (IQR: 18.5, 37) and the median length of outbreaks was 13 days (IQR: 8.5, 18.5) (**Table 1**). The majority of cases were female (71.3%) and over 65 years old (81.3%), with an average age of 76.6 years. Of all cases, 66.4% reported vomiting, 77.9%reported diarrhea, and 62.6% were LTCF residents. The vast majority of outbreaks occurred from 2017 to 2019 (94.4%) and occurred during winter (December-February) and spring (March-May) months (94.4%). Furthermore, of outbreaks with genotype and/or genogroup information, 56 (56.6%) were caused by norovirus GII.4. However, because an additional 6 outbreaks were caused by GII noroviruses but were not genotyped, this percentage is likely higher.

Outbreak Transmission Patterns

All outbreaks began with one or more index cases, defined here as cases with illness onset on day 1 of an outbreak, with a R_{Ei} greater than 1. After day 1, outbreaks either continuously declined to a R_{Ei} below 1 or increased again before declining to a R_{Ei} below 1 and eventually

going to extinction. In examining epidemic curves and R_{Ei} values, we found strong heterogeneity in the temporal patterns of R_{Ei} between outbreaks. Considering these temporal trends, we broadly categorized outbreaks into the following four transmission patterns (**Figure 1**):

1. **Continual decrease:** R_{Ei} started with a value greater than 1, and then continually declined to 0.

2. **Several small peaks:** R_{Ei} oscillated between values slightly below and slightly greater than 1 before declining to 0.

3. **One initial peak:** R_{Ei} started with a value around 1, increased to a peak greater than 2, and then continually declining to 0.

4. **M-shaped curve:** R_{Ei} declined initially, increased to create two separate peaks with values larger than 2, and then declined to 0.

Of the 107 outbreaks, we classified 74 (69%) as continual decrease, 14 (13%) as several small peaks, 14 (13%) as one initial peak, and 5 (5%) as m-shaped curve.

In comparing index cases to non-index cases, we found that R_{Ei} estimates for index cases were substantially larger (median R_{Ei} = 2.16 [IQR: 1.13, 4.57]) than those for non-index cases (median R_{Ei} = 0.59 [IQR: 0.35, 1.02]). Of cases who were highly infectious (i.e., $R_{Ei} > 4$), 70.2% were index cases. Furthermore, in examining the proportion of cases that were index cases by R_{Ei} values, with R_{Ei} categorized into 5 groups, we found that the proportion of cases that were index cases

(as opposed to non-index cases) increased with each increase in R_{Ei} category (**Figure 2**).. Similarly, as R_{Ei} values increased, the proportion of cases who vomited generally increased. This same pattern was less pronounced for residents vs. staff, however the proportion of cases who were residents increased or remained about the same as R_{Ei} values increased to 4, after which the proportion slightly decreased again. Lastly, the proportion of cases with diarrhea was consistent across all 5 categories of R_{Ei} magnitude.

Risk Factors for Norovirus Transmission in LTCFs

In our regression analysis, 167 (5%) of the total 3,363 cases were excluded due to missing outcome and/or exposure information. A total of 3,196 cases were included in the analysis.

Using a multivariable log-linear mixed model, we found that cases who vomited were more infectious than cases who did not vomit, with vomiters infecting 1.28 (95% CI: 1.11, 1.48) times the number of secondary cases compared to non-vomiters. Additionally, we found that LTCF residents were more infectious than staff, infecting 1.31 (95% CI: 1.15, 1.50) times the number of secondary cases compared to staff. However, cases with diarrhea had the similar infectiousness (1.07 (95% CI: 0.90, 1.29)) as cases without diarrhea (**Table 3**). In sensitivity analyses where cases with $R_{Ei} = 0$ were excluded, results were similar for the associations between infectiousness and vomiting (1.28 (95% CI: 1.14, 1.43)) and infectiousness and diarrhea (1.00 (95% CI: 0.87, 1.16)), and slightly attenuated for the association between infectiousness and resident/staff status (1.16 (95% CI: 1.04, 1.29)). Lastly, we examined an interaction between vomit and diarrhea and found no evidence of an interaction.

We found that these results were robust to assumptions about the serial interval length used in R_{Ei} calculations (**Figure 3**). The associations between vomit and residency status and increased R_{Ei} were existent for all serial interval lengths, with increasing magnitude as the serial interval length increased. The association between diarrhea and R_{Ei} remained approximately null for all serial interval lengths.

In a secondary analysis examining characteristics of index cases, we used multivariable logistic regression and found that index cases were more likely to be vomiters (OR = 1.65 [95% CI: 1.18, 2.35]) and residents (OR = 1.54 [95% CI: 1.13, 2.14]) compared to non-index cases. Conversely, there was no association between being an index case and having diarrhea (OR = 1.07 [95% CI: 0.76, 1.54). When examining the relative infectiousness of index cases to non-index cases, we found that index cases infected 2.23 (95% CI: 1.77, 2.79) times the number of secondary cases compared to cases with illness onset on days 2-4, indicating that index cases may be considerably more infectiousness than non-index cases.

Lastly, we examined the associations between outbreak day and vomit, diarrhea, and resident vs. staff using a multivariable linear mixed model. We found that cases who vomited occurred 1.01 (95% CI: 0.65, 1.37) days earlier in the outbreak than cases who did not vomit, resident cases occurred 1.13 (95% CI: 0.78, 1.47) days earlier in the outbreak than staff cases, and cases with diarrhea occurred (0.46, 95% CI: 0.05, 0.87) days earlier in the outbreak than cases without diarrhea.

Discussion

We quantified individual case infectiousness for norovirus outbreaks by inferring who infected whom from symptom onset dates and the norovirus serial interval distribution, and then examined individual risk factors for infectiousness and temporal changes in infectiousness. We found the following: 1) vomiting plays an important role in norovirus transmission in US LTCFs; 2) residents are more infectious than staff; and 3) outbreaks tend to start with one or more index cases who are considerably more infectious than subsequent, non-index cases. These results are based on a large dataset with information on 107 LTCF norovirus outbreaks and more than 3,000 cases.

This study supports results from a previous study [14] in which authors found that vomiters and residents are more infectious than non-vomiters and staff, respectively, and tend to drive norovirus transmission in US LTCFs. However, while the previous study also found that cases with diarrhea were slightly more infectious than cases without diarrhea, we found no association between diarrhea and increased infectiousness. This discrepancy may be due to the difference in sample size, with the previous study including information on only 6 norovirus outbreaks and 208 cases. With our much larger dataset, we found that diarrhea does not appear to play an important role in transmission.

Exposure to vomit has been identified as a risk factor for norovirus infection and transmission in LTCFs[10]. By testing norovirus particles from air samples close to infected hospitalized patients, a recent study found that recent vomiting (within 3 hours since the last vomiting episode) was

the major source of airborne norovirus, and implied a connection between airborne norovirus and outbreaks in hospitals [22]. The study also found that there was no association between positive air samples and time since the last instance of diarrhea, indicating that diarrhea may play less of a role in transmission than vomiting due to lack of aerosolization.

We also found that residents are more infectious than staff in LTCF norovirus outbreaks. A previous study found that initial fecal viral loads in affected residents were higher than in affected staff during a nursing home norovirus outbreak [23], indicating that the increased resident infectiousness may be due to increased amount of viral shedding. Furthermore, when staff develop symptoms, current infection control guidelines recommend they be excluded from work for a minimum of 48 hours after the resolution of symptoms, during which time they can no longer infect others in the LTCF [24]. Residents, on the other hand, require continued, and possibly even more, care after developing symptoms, allowing them to continue to transmit infection throughout the duration of their illness.

Lastly, we found that index cases are more infectious than non-index cases. There are several potential explanations for this, which were noted in the previous study [14]. First, a high level of infectiousness may be required for index cases to initiate and maintain an outbreak; second, there is a natural decrease in the reproduction number R_{Ei} as the outbreak progresses and more individuals become ill and later immune, which may result in index cases having inflated R_{Ei}'s compared to subsequent cases in the same outbreak; third, the implementation of control measures after the occurrence of an index case could result in reduced R_{Ei}'s in cases later in the outbreak; and fourth, index cases may have intrinsic case characteristics, like vomiting and

being residents, that increases their infectiousness. Most likely, the increased infectiousness in index cases is due to some combination of all four explanations.

We note a number of limitations in our study. First, we assumed that line lists were complete (i.e., no missing cases) and that asymptomatic cases did not contribute to transmission. However, it's possible that cases were missing from line lists, particularly if they occurred earlier in the outbreak, which could result in an inflated estimate of index case infectiousness. It is also possible for asymptomatic cases to contribute to norovirus transmission [25], however symptomatic cases are estimated to be the main drivers of transmission in healthcare settings such as LTCFs [7]. Second, we did not consider the heterogeneity of LTCF settings (e.g., skilled nursing facilities, assisted living, etc.), which may impact transmission patterns of norovirus due to different infrastructures and staff-resident contact intensities. We attempted to gather more specific setting information using data from The National Outbreak Reporting System (NORS)[26], however few outbreak reports contained this information and we were unable to examine it further. Third, we used a serial interval derived from several large norovirus outbreaks in child daycare centers in Sweden, which may not be generalizable to norovirus outbreaks in US LTCFs. However, results were generally robust in sensitivity analyses in which shorter and longer serial intervals were used to estimate R_{Ei}. Fourth, we did not consider heterogeneities in staff job roles when examining case infectiousness, and staff who provide direct care to residents (e.g., certified nursing assistants and nurses) may be more infectious than staff who provide little or no direct patient care (e.g., administrative staff) 25. However, we did not have information on staff job role and were therefore unable to examine this further. Lastly, we assumed that cases

could not infect cases with the same or earlier symptom onset dates. Because norovirus has a short incubation period[27], and because incubation periods can vary, it is possible, although unlikely, for the serial interval to be non-positive.

Because there is currently no publicly available vaccine or specific antiviral treatment, general infection control measures are the mainstay for curtailing norovirus transmission in LTCFs. Our study provides support for measures that target cases who vomit, particularly resident cases who vomit, and that limit exposure to infectious vomitus. Rapid response to vomiting events, including disinfecting contaminated environments with a chlorine-based disinfectant and isolating vomiters, may help to reduce the size and duration of norovirus outbreaks in US LTCFs. Additionally, quickly identifying and isolating early symptomatic cases, including index cases, may substantially reduce transmission. Future studies should focus on collecting detailed data on LTCF norovirus outbreak control measures, including which control measures are implemented and when, to evaluate the effectiveness of specific control measures on reducing norovirus transmission.

Conclusions

Vomiting, particularly by LTCF residents, appears to drive norovirus transmission in US LTCF outbreaks. Furthermore, index cases are substantially more infectiousness than non-index cases. These results support control measures that limit exposure to vomitus during norovirus outbreaks in LTCFs.

Tables & Figures

Table 1. Case characteristics and line list information of analyzed LTCF norovirus outbreaks

Variable	All Outbreaks (N = 107)
Total Cases (No.)	3363
(Median (IQR))[a]	27 (18.5, 37)
(Mean (SD))[a]	31.43 (21.9)
Outbreak Length (days) (Median (IQR))[a]	13 (8.5, 18.5)
(Mean (SD))[a]	14.50 (8.5)
Resident (No. (%))[b]	2,061 (62.6)
Diarrhea Cases (No. (%))[b]	2,578 (77.9)
Vomit Cases (No. (%))[b]	2,198 (66.4)
Female (No. (%))[b]	1,637 (71.3)
Age in Years (Mean (SD))[b]	76.6 (18.1)
State (No. (%))[b]	
Wisconsin	72 (67.3)
Minnesota	11 (10.3)
New Mexico	17 (15.9)
South Carolina	6 (5.6)
Ohio	1 (0.9)
Year (No. (%))[b]	
2015	4 (3.7)
2016	2 (1.9)
2017	20 (18.7)
2018	45 (42.1)
2019	36 (33.6)
Outbreak Season (No. (%))[b]	
Spring (March to May)	38 (35.5)
Summer (June to August)	2 (1.9)
Fall (September to November)	4 (3.7)
Winter (December to February)	63 (58.9)
Norovirus Genotype (No. (%))[b,c]	
GII.4	56 (56.6)
Non-GII.4	18 (18.2)
GII with unknown genotype	6 (6.0)
Genotypes in GI group	19 (19.2)

Abbreviations: long-term care facility, LTCF; number, N and No.; interquartile range, IQR; standard deviation, SD

[a] Median (IQR) and mean (SD) per outbreak.

[b] Number (%) and mean (SD) across all outbreaks. Percentages were calculated excluding cases with missing information.

[c] Percentages were calculated excluding outbreaks with missing genogroup information.

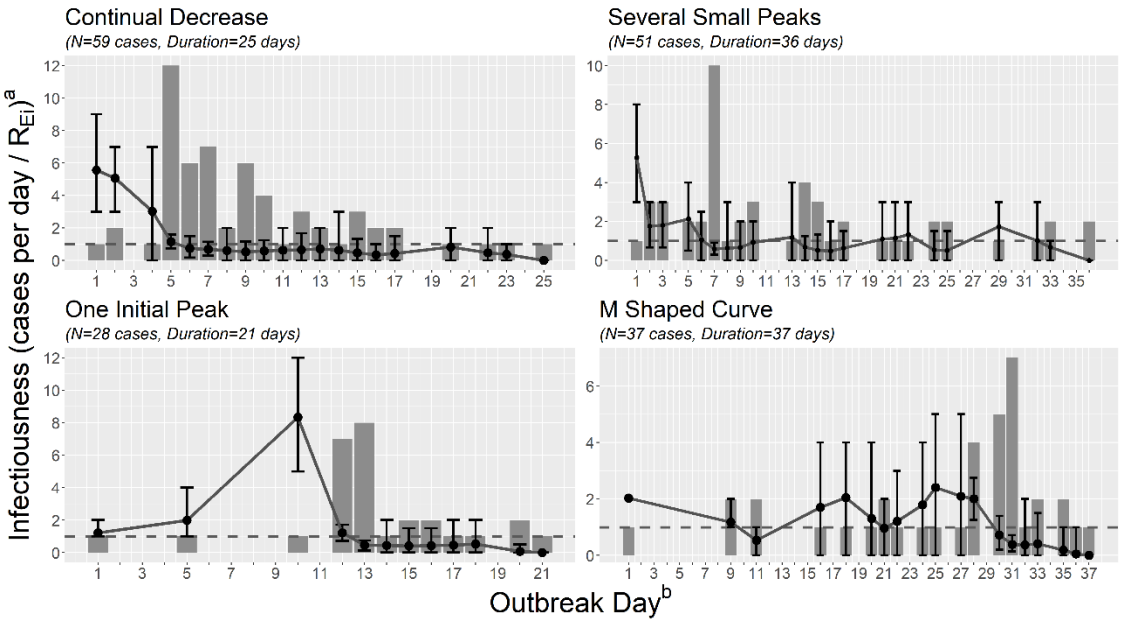

Figure 1: Epidemic curves and estimated individual reproduction numbers, R_{Ei}, by illness onset day for four outbreaks to demonstrate transmission pattern classifications.

[a]Infectiousness describes the number of cases per day (gray bars) and R_{Ei} (point estimates); dashed horizontal lines signify a REi of 1, below which an outbreak, on average, cannot be maintained; note the change in scale for different outbreaks.

[b]Outbreak day represents the day into the outbreak, with day 1 corresponding to the first illness onset date.

Figure 2. Percentages of cases with sympto/characteristics by categorized R_{Ei} value

[a]Cases with missing symptoms/characteristics information were excluded.

Table 2. Adjusted associations between norovirus case symptoms/characteristics and the individual effective reproduction number, REi

Variable[a]	Exponentiated coefficient (95% CI)[b]	P value
Vomit	1.28 (1.11, 1.48)	0.0006
Diarrhea	1.07 (0.90, 1.29)	0.4372
Resident	1.31 (1.15, 1.50)	<0.0001

[a]All variables are dichotomous: vomit vs. no vomit, diarrhea vs. no diarrhea, and resident vs. staff

[b]Multivariable log-linear mixed regression, with a random intercept for outbreak, was used; all variables included in the model are shown in the table;;results were exponentiated to show associations between R_{Ei}, rather than log(R_{Ei}), and exposure variables and all associations are on the multiplicative scale

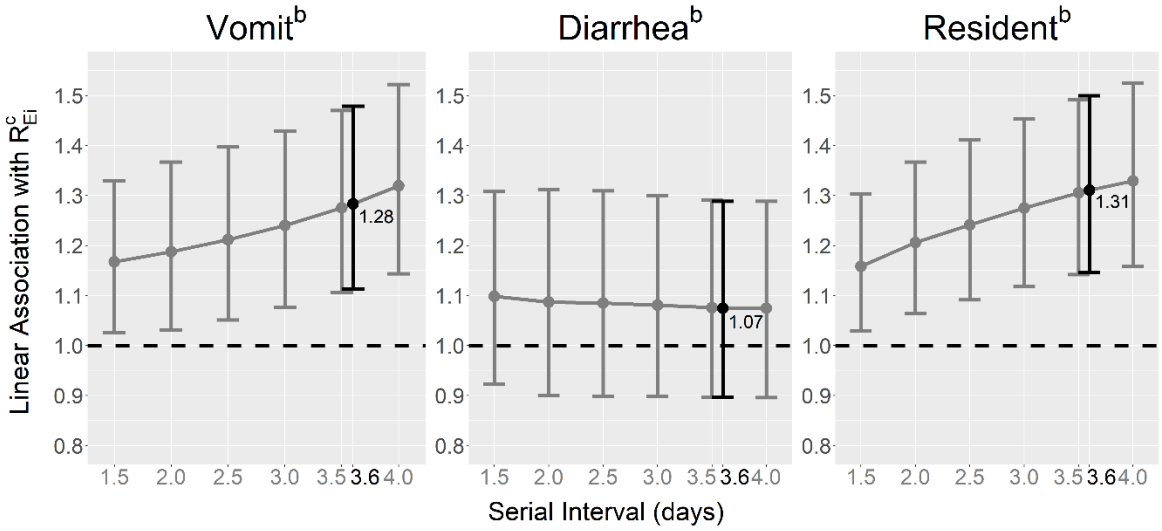

Figure 3. Associations between individual reproduction numbers, R_{Ei}, and symptoms/characteristics of norovirus cases by serial interval length[a].

[a]The serial interval length used in the final regression analysis is shown in black.

[b]Associations were estimated using a multivariable mixed linear regression model with a log-transformed outcome variable (R_{Ei}), inverse-variance weighting, a random slope for outbreak number, and the following dichotomous predictor variables: vomiting (vs. no vomiting), diarrhea (vs. no diarrhea), and resident (vs. staff).

[c]Estimates from the model were exponentiated.

Reference

1. Hall, A. J. *et al.* Norovirus disease in the united states. *Emerg. Infect. Dis.* **19**, (2013).
2. Hall, A. J., Curns, A. T., Clifford Mcdonald, L., Parashar, U. D. & Lopman, B. A. The roles of clostridium difficile and norovirus among gastroenteritis- associated deaths in the United States, 1999-2007. *Clin. Infect. Dis.* **55**, (2012).
3. Kambhampati, A., Koopmans, M. & Lopman, B. A. Burden of norovirus in healthcare facilities and strategies for outbreak control. *Journal of Hospital Infection* vol. 89 (2015).
4. Hall, A. J. *et al.* Acute gastroenteritis surveillance through the national outbreak reporting system, United States. *Emerg. Infect. Dis.* **19**, (2013).
5. Rosenthal, N. A. *et al.* Epidemiological and genetic characteristics of norovirus outbreaks in long-term care facilities, 2003-2006. *Epidemiol. Infect.* **139**, (2011).
6. Evans, M. R. *et al.* An outbreak of viral gastroenteritis following environmental contamination at a concert hall. *Epidemiol. Infect.* **129**, (2002).
7. Sukhrie, F. H. A. *et al.* Nosocomial transmission of norovirus is mainly caused by symptomatic cases. *Clin. Infect. Dis.* **54**, (2012).
8. Iturriza-Gómara, M. & Lopman, B. Norovirus in healthcare settings. *Current Opinion in Infectious Diseases* vol. 27 (2014).
9. Mattner, F. *et al.* Risk groups for clinical complications of norovirus infections: An outbreak investigation. *Clin. Microbiol. Infect.* **12**, (2006).
10. Petrignani, M., van Beek, J., Borsboom, G., Richardus, J. H. & Koopmans, M. Norovirus introduction routes into nursing homes and risk factors for spread: A systematic review and meta-analysis of observational studies. *Journal of Hospital Infection* vol. 89 (2015).

11. Harris, J. P., Lopman, B. A. & O'Brien, S. J. Infection control measures for norovirus: a systematic review of outbreaks in semi-enclosed settings. *Journal of Hospital Infection* vol. 74 (2010).

12. Ahmed, S. M., Lopman, B. A. & Levy, K. A Systematic Review and Meta-Analysis of the Global Seasonality of Norovirus. *PLoS One* **8**, (2013).

13. Shah, M. P. & Hall, A. J. Norovirus Illnesses in Children and Adolescents. *Infectious Disease Clinics of North America* vol. 32 (2018).

14. Adams, C. *et al.* Quantifying the roles of vomiting, diarrhea, and residents vs. staff in norovirus transmission in U.S. nursing home outbreaks. *PLoS Comput. Biol.* **16**, (2020).

15. Shah, M. P. *et al.* Near Real-Time Surveillance of U.S. Norovirus Outbreaks by the Norovirus Sentinel Testing and Tracking Network — United States, August 2009–July 2015. *MMWR. Morb. Mortal. Wkly. Rep.* **66**, (2017).

16. Wallinga, J. & Teunis, P. Different epidemic curves for severe acute respiratory syndrome reveal similar impacts of control measures. *Am. J. Epidemiol.* **160**, (2004).

17. Teunis, P. *et al.* Infectious disease transmission as a forensic problem: Who infected whom? *J. R. Soc. Interface* **10**, (2013).

18. Fine, P. E. M. The Interval between Successive Cases of an Infectious Disease. *American Journal of Epidemiology* vol. 158 (2003).

19. Heijne, J. C. M. *et al.* Enhanced hygiene measures and norovirus transmission during an outbreak. *Emerg. Infect. Dis.* **15**, (2009).

20. Cori, A., Ferguson, N. M., Fraser, C. & Cauchemez, S. A new framework and software to estimate time-varying reproduction numbers during epidemics. *Am. J. Epidemiol.* **178**,

(2013).

21. Viechtbauer, W. Viechtbauer, W. (2010). Conducting meta-analyses in R with the metafor package. Journal of Statistical Software , 36 (3), 1–48. *J. Stat. Softw.* **36**, (2010).

22. Alsved, M. *et al.* Sources of airborne norovirus in hospital outbreaks. *Clin. Infect. Dis.* **70**, (2020).

23. Lai, C. C. *et al.* A norovirus outbreak in a nursing home: Norovirus shedding time associated with age. *J. Clin. Virol.* **56**, (2013).

24. Norovirus Guidelines for Healthcare Settings. https://www.cdc.gov/infectioncontrol/guidelines/norovirus/index.html.

25. Teunis, P. F. M. *et al.* Shedding of norovirus in symptomatic and asymptomatic infections. *Epidemiol. Infect.* **143**, (2015).

26. National Outbreak Reporting System (NORS). https://www.cdc.gov/nors/index.html.

27. Devasia, T., Lopman, B., Leon, J. & Handel, A. Association of host, agent and environment characteristics and the duration of incubation and symptomatic periods of norovirus gastroenteritis. *Epidemiol. Infect.* **143**, 2308–2314 (2015).