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Quantifying the roles of vomiting, diarrhea, and residents vs. staff in norovirus transmission in U.S. nursing home outbreaks

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BAL conceptualized this study with input from CA. DY provided all outbreak data. CA led the main study analysis with support from BAL. PAG, PP, ZM, and AJH provided subject matter expertise and advice regarding epidemiologic methods and data analysis. CA drafted the manuscript with supervisory input from BAL. All authors reviewed, edited, and approved the manuscript.

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Abstract

The role of individual case characteristics, such as symptoms or demographics, in norovirus transmissibility is poorly understood. Six nursing home norovirus outbreaks occurring in South Carolina, U.S. from 2014 to 2016 were examined. We aimed to quantify the contribution of symptoms and other case characteristics in norovirus transmission using the reproduction number (R_{Ei}) as an estimate of individual case infectivity and to examine how transmission changes over the course of an outbreak. Individual estimates of R_{Ei} were calculated using a maximum likelihood procedure to infer the average number of secondary cases generated by each case. The associations between case characteristics and R_{Ei} were estimated using a multivariate mixed linear model. Outbreaks began with one to three index case(s) with large estimated R_{Ei}'s (range: 1.48 to 8.70) relative to subsequent cases. Of the 209 cases, 155 (75%) vomited, 164 (79%) had diarrhea, and 158 (76%) were nursing home residents (vs. staff). Cases who vomited infected 2.74 (95% CI: 1.90, 3.94) more individuals than non-vomiters, cases with diarrhea infected 1.62 (95% CI: 1.09, 2.41) more individuals than cases without diarrhea, and resident-cases infected 1.69 (95% CI: 1.18, 2.42) more individuals than staff-cases. Index cases tended to be residents (vs. staff) who vomited and infected considerably more secondary cases compared to non-index cases. Results suggest that individuals, particularly residents, who vomit are more infectious and tend to drive norovirus transmission in U.S. nursing home norovirus outbreaks. While diarrhea also plays a role in norovirus transmission, it is to a lesser degree than vomiting in these settings. Results lend support for prevention and control measures that focus on cases who vomit, particularly if those cases are residents.

Author summary

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The majority of all norovirus outbreaks reported to the CDC occur in long-term care facilities (LTCFs), including nursing homes, where older residents are at risk for more severe or prolonged infection. Because there is currently no publicly available norovirus vaccine, sound control measures are key to controlling norovirus outbreaks, but there is little evidence that standard control measures are effective in reducing the size and/or duration of LTCF norovirus outbreaks. Hence, studies leading to a better understanding of disease spread and prevention of additional cases, and thus more effective control measures, are needed. To this end, we aimed to quantify factors associated with norovirus transmission and to examine how transmission changes over the course of an outbreak. We show that vomiting and, to a lesser extent, diarrhea are critical in initiating and sustaining norovirus transmission in U.S. nursing home norovirus outbreaks. We also show that nursing home residents, rather than staff, are the primary drivers of transmission. Results suggest that control measures focusing on cases who vomit, particularly if those cases are residents, would be most effective at curtailing norovirus transmission in these settings.

Introduction

There are 49.2 million individuals over 65 in the U.S. population (15.2%) and this population is growing [1]. With nearly half of this age group spending some part of their lives in nursing homes [2], the number of older adults using paid long-term care services is expected to grow substantially over the coming decade [3]. In the U.S. and other high-income countries, gastroenteritis outbreaks are common in long-term care facilities (LTCFs), including nursing homes [4-7]. Despite the perception that norovirus is a foodborne disease or the ‘cruise ship

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virus', the majority of all norovirus outbreaks reported to the CDC occur in LTCFs [6]. While norovirus gastroenteritis is generally mild and self-limiting, older nursing home residents are vulnerable to infection leading to hospitalization and death [8], with the vast majority of norovirus-associated deaths in the U.S. occurring among persons aged 65 years and older [9].

Norovirus is highly transmissible in nursing homes [10-12], but there is no vaccine or specific antiviral therapy available to prevent or treat norovirus infection. As a result, rapid implementation of standard control measures is the mainstay for curtailing transmission [13]. Identifying factors associated with norovirus transmission is critical to better understanding disease spread and preventing additional cases. Individual-level risk factors for susceptibility to norovirus infection or severe disease in nursing home outbreaks have been identified, including resident mobility, dependency on staff assistance [14], immunodeficiency [15], and statin use [16]. But because transmission of norovirus from one person to another cannot be directly observed (unlike symptoms and/or positive test results that follow transmission), it remains poorly understood and the evidence base for the value of specific prevention and control measures is lacking [10].

Statistical algorithms can be used to infer outbreak transmission trees (i.e., who infected whom) from case onset dates and independent estimates of the serial interval (i.e., the time between symptom onset in primary cases and the secondary cases they generate) between generations of case pairs [17]. Individual reproduction numbers (R_i), or the number of secondary cases an individual generates, can then be calculated for all cases. We quantified the contribution of specific symptoms and residents vs. staff in norovirus transmission by examining the associations between these variables and individual case infectivity, which was characterized by R_i. Additionally, we examined how transmission changes over the course of an outbreak. Our

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overall aim was to inform implementation of effective norovirus prevention and control measures to reduce the size and duration of norovirus outbreaks in nursing homes. We achieved this aim by characterizing norovirus transmission in these settings.

Methods

Outbreak data

De-identified data from six separate and unique nursing home outbreaks from two consecutive norovirus seasons (2014-2015 and 2015-2016) were provided by the South Carolina Department of Health and Environmental Control (SCDHEC). All outbreaks were confirmed, meaning they had at least two laboratory confirmed norovirus cases. Outbreak data were in the form of line lists and included individual-level information on symptom onset dates, reported symptoms (vomiting, diarrhea, and fever), age in years, sex, illness duration, hospitalization, emergency department visit, and whether the case was a resident or staff. Probable cases were defined as residents or staff who had at least one episode of vomiting and/or three or more loose stools within a 24-hour period. Confirmed cases were probable cases with a laboratory confirmed norovirus infection. As this was an analysis of anonymized data that had already been collected through routine public health response, the Emory University Institutional Review Board (IRB) determined that this study was exempt from IRB review.

Estimation of reproduction numbers

Transmissibility of a pathogen can be quantified by its basic reproduction number, R_0, defined as the average number of secondary cases generated by a single infectious individual in a

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126 population that is entirely susceptible, or its effective reproduction number, R_E, defined as the
127 average number of secondary cases generated by a single infectious individual in a population
128 that has some level of immunity. R_0 or R_E of 1 signifies the extinction threshold, below which
129 each infectious individual, on average, infects less than one other individual and the outbreak
130 cannot be maintained. R_E can be converted to R_0 by dividing R_E by the proportion susceptible in
131 the population. Estimates for the R_0 of norovirus vary widely, from 1.1 to 7.2, and depend on
132 differences in settings [18].

133 The primary outcome of interest in this study was individual case infectiousness, which
134 we measured by estimating the reproduction number, R_{Ei}, for each case. Here, R_{Ei} is defined as
135 the number of secondary cases generated by an individual case *i*. We estimated R_{Ei} using a
136 maximum likelihood procedure to infer the number of secondary cases generated by each case
137 [17]. This method, originally described by Wallinga and Teunis, requires only onset dates of all
138 cases in the outbreak and knowledge of the frequency distribution of the serial interval [17]. We
139 used a serial interval for norovirus derived from several large norovirus outbreaks in child
140 daycare centers in Sweden with a gamma probability distribution, mean of 3.6 days, and standard
141 deviation of 2.0 days [19]. We performed sensitivity analyses with mean serial intervals varying
142 between 1.5 and 4.0 days in half day increments. Details of the estimation procedure are
143 available elsewhere [17, 19, 20]. Briefly, this method calculates, in a statistically rigorous
144 manner, the probability that cases with earlier symptom onset dates infected cases with later
145 symptom onset dates, selects the probabilities that are greatest using the frequency distribution of
146 the serial interval, and then, using these probabilities, determines the number of secondary cases
147 produced by cases with each symptom onset date. Individual cases were assigned a R_{Ei} based on

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their symptom onset date, and those with the same onset date within an outbreak were assigned the same R_{Ei}.

In preliminary analysis, we observed much higher R_{Ei} for index cases compared to those on subsequent days. To investigate whether this could indicate heightened infectiousness of index cases or just the natural decline of the susceptible population, we also calculated R_{0i} by dividing R_{Ei} by the proportion of the population susceptible on day i (p_i) [21]. To calculate the proportion susceptible, we made the extreme assumptions that all cases were susceptible at the start of the outbreak and that the final cumulative attack rate was 100%, such that $p_i = \frac{1 - \sum_0^i C_i}{C}$ where C is the total number susceptible on day 1 and $\sum_0^i C_i$ is cumulative incidence to day i. Using this approach, we compared estimates of R_{0i} of index cases on day 1 to R_{0i} estimated from cases with onset on days 2 to 4 of the outbreak (excluding days with no reported cases).

Analyses of risk factors for transmission

We used a linear mixed model to estimate the association between each case characteristic and R_{Ei}, while accounting for correlation between R_{Ei}'s within each outbreak. The outcome variable was the natural log of R_{Ei}.

The following information was available for cases: symptom onset date, resident/staff status, age in years, sex, illness duration, hospitalization, emergency department visit, and presence of diarrhea, vomiting, and fever. Because information on fever, age, sex, emergency department visit and hospitalization were missing for large percentages of cases (20%, 23%, 26%, 40% and 55%, respectively), we were unable to consider these variables as potential exposure, confounder, or effect modifying variables in the regression model. Information on

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resident vs. staff, diarrhea (yes or no), and vomiting (yes or no) were rarely missing (1%, 1%, and 0%, respectively) and were considered explanatory variables in our model. To account for clustering induced by correlation of R_{Ei}'s within the six outbreaks, outbreak number was included in the model as a random intercept. The full model, with log R_{Ei} as the outcome, included the following explanatory variables: diarrhea, vomiting, resident. The model was assessed for collinearity and no issues were found. We considered including 'time' in the model and adjusting for it as a potential confounder, as R_{Ei} inevitably declines over time. However, we determined that time cannot be a confounder, since it cannot affect diarrhea, vomiting, or resident vs. staff, our explanatory variables of interest. The final model is shown below:

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

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_{0j}, are assumed to be independent and identically distributed (iid) 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.

In addition to regression analyses, we also used the Kruskal-Wallis test to compare R_{Ei}'s for cases with vomiting vs. no vomiting, diarrhea vs. no diarrhea, both vomiting and diarrhea vs. vomiting only, and both vomiting and diarrhea vs. diarrhea only. The Kruskal-Wallis test was

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also used to compare the proportions of vomiting vs. no vomiting, diarrhea vs. no diarrhea, and residents vs. staff for cases with $R_{Ei} \geq 1$ to cases with $R_{Ei} < 1$.

All statistical analyses were performed using SAS software version 9.4 and the *EpiEstim* [22] package in R software version 3.4.2.

Exclusion criteria

The original dataset consisted of 209 lab-confirmed and probable cases from six separate outbreaks. One case was excluded from the estimations of R_{Ei} and all further analyses because he/she was missing an illness onset date. After the estimations of R_{Ei}, four additional cases were excluded from the regression analyses because they were missing information on diarrhea, vomiting, and/or resident vs. staff. Lastly, 9 more cases (4.3% of all cases with onset date information) had symptom onset dates on the last day the outbreak and thus did not produce any reported secondary cases. Therefore, they had estimated R_{Ei}'s of zero. Because log R_{Ei} could not be taken for these cases, they were excluded from all regression analyses. Sensitivity analyses were performed by adding 0.01 to these R_{Ei} estimates to examine the influence of these cases on model estimates.

Results

Across the six outbreaks, the median number of cases was 36.5 (IQR: 28.3, 44.8) and the median outbreak length was 12 days (IQR: 12.0, 12.8) (Table 1). All cases involved in the outbreaks were either nursing home residents or staff. The majority of cases were over 80 years of age (62%), female (74%), nursing home residents (76%), and had diarrhea (with or without vomiting) (79%), vomiting (with or without diarrhea) (75%), or both diarrhea and vomiting

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(54%). Of the 9 cases excluded from regression analyses for having $R_{Ei} = 0$, 55% were residents, 55% reported vomiting, and 55% reported diarrhea. All six outbreaks were caused by norovirus genogroup II, two of which were confirmed as GII.4 Sydney and four of which were not genotyped.

Table 1. Characteristics of analyzed nursing home norovirus outbreaks; South Carolina, 2014-2016.

Outbreak No.	Total Cases No.	Lab-confirmed Cases No.	Outbreak Length (in days)[a]	Age (in y) Mean (SD)	Female, No. (%)[b]	Resident, No. (%)[b]	Diarrhea, No. (%)[b]	Vomit, No. (%)[b]
1	27	3	12	79 (17)	NA[c]	23 (85)	27 (100)	19 (70)
2	11	4	10	84 (10)	8 (73)	11 (100)	6 (55)	10 (91)
3	46	4	13	83 (9)	31 (67)	38 (83)	34 (76)	28 (61)
4	52	4	18	88 (6)	29 (74)	44 (85)	47 (92)	49 (96)
5	32	4	12	84 (16)	24 (75)	20 (67)	28 (88)	22 (69)
6	41	4	12	81 (14)	22 (85)	22 (54)	22 (54)	27 (66)
Total[d]	208	23	NA	83 (12)	114 (74)	158 (76)	164 (79)	155 (75)

[a]Outbreak length is the difference in days between first illness and last illness onset dates (including the first illness onset date).

[b]Percentages were calculated excluding cases with missing information.

[c]Information on case sex was not collected for outbreak 1.

Outbreaks began with one to three index case(s) (nine index cases in total), defined as cases with onset of symptoms on day one of an outbreak, that had large estimated R_{Ei}'s (range: 1.48 to 8.70) relative to other cases in the outbreak. After the index case(s), each outbreak either continuously declined to a R_{Ei} below 1 or increased again before declining to a R_{Ei} below 1 (Fig 1). Of these index cases, at least one from each outbreak reported vomiting (Fig 2). While most index cases also reported diarrhea, outbreak 6 began with a case that reported vomiting only.

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Fig 1. Case counts and individual reproduction numbers, R_{Ei}, by day in nursing home norovirus outbreaks. From left to right, outbreaks 1-3 and 4-6 are presented on top and bottom, respectively. Case counts are represented by the gray bars and R_{Ei} estimates are represented by the point estimates with corresponding 95% confidence intervals. The horizontal dashed line signifies a R_{Ei} of 1, below which each infectious individual, on average, infects less than one individual and the outbreak cannot be maintained. [a]Infectiousness describes the number of cases per day (for the gray bars) and R_{Ei} (for the point estimates); note the change in scale for different outbreaks. [b]Outbreak day represents the day into the outbreak, with day 1 corresponding to the first day cases were reported.

Fig 2. Distribution of individual reproduction number[a], R_{Ei}, frequencies by vomiting[b] with index cases outlined in black. [a]Reproduction number describes the number of secondary cases generated by an infectious case. [b]Dichotomous variable vomit vs. no vomit.

When examining R_{0i} values (calculated from R_{Ei} estimates), we found that outbreaks had considerably higher basic reproduction numbers based on the index case(s) ($R_{0,1}$ = 6.8, 1.5, 8.4, 7.3, 4.6, and 8.7 for outbreaks 1-6, respectively) compared to the median basic reproduction number calculated from cases on days 2 to 4 (median $R_{0,2\text{-}4}$ = 1.7; IQR: 1.6, 2.0).

Cases with vomiting (with or without diarrhea) had a greater median R_{Ei} (0.54; IQR: 0.21, 1.01) than those without vomiting (0.36; IQR: 0.20, 1.47; p-value = 0.0009). Cases with diarrhea (with or without vomiting) had a similar median R_{Ei} (0.45; IQR: 0.20, 1.01) to those without diarrhea (0.47; IQR: 0.27, 0.82; p-value = 0.88). Cases with both vomiting and diarrhea

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had a greater median R_{Ei} (0.78; IQR: 0.21, 1.03) than those with diarrhea alone (0.36; IQR: 0.20, 0.47; p-value = 0.002) or vomiting alone (0.47; IQR: 0.27, 0.97; p-value = 0.24). Similarly, residents had a slightly greater median R_{Ei} (0.47; IQR: 0.21, 1.01) than staff (0.40; IQR: 0.21, 0.97; p-value = 0.11). Because all outbreaks ended, the overall median R_{Ei} for all cases was less than 1 (0.47; IQR: 0.21, 1.01). Similarly, the median R_{Ei} values for each outbreak were also less than 1, ranging from 0.40 to 0.63.

A total of 63 cases (30% of all cases) had an estimated R_{Ei} greater than 1, of which 89% reported vomiting, 83% reported diarrhea, and 86% were residents. Among the remaining 145 cases (70% of all cases) with an estimated R_{Ei} of less than 1, 68% reported vomiting, 77% reported diarrhea, and 71% were residents. These differences were significant for vomiting (p-value = 0.001) but not diarrhea (p-value = 0.23) or resident/staff status (p-value = 0.06). All index cases had R_{Ei}'s greater than 1 (median: 4.60; IQR: 1.48, 7.13).

In the final multivariable model, cases who vomited infected 2.74 (95% CI: 1.90, 3.94) more individuals than non-vomiters, cases with diarrhea infected 1.62 (95% CI: 1.09, 2.41) more individuals than cases without diarrhea, and resident-cases infected 1.69 (95% CI: 1.18, 2.42) more individuals than staff-cases (Fig 3). In sensitivity analyses where cases with $R_{Ei} = 0$ were included in the regression analysis, stronger associations between infectiousness and vomiting, diarrhea, and resident/staff status were observed (2.96, 1.90, and 1.89, respectively). Adding a dichotomous variable (index vs. non-index case) to the model indicated that index cases infected 6.64 (95% CI: 3.49, 12.63) more individuals than non-index cases, holding resident vs. staff, diarrhea, and vomiting constant. Furthermore, we examined the associations between outbreak day, counting the first illness onset date as day one, and case characteristics and found cases who vomited occurred 2.7 (95% CI: 1.8, 3.6) days earlier in the outbreak than cases who did not

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vomit, cases with diarrhea occurred 2.2 (95% CI: 1.2, 3.2) days earlier in the outbreak than cases without diarrhea, and resident-cases occurred 1.6 (95% CI: 0.8, 2.5) days earlier in the outbreak compared to staff-cases.

In sensitivity analyses to examine the effect of using different norovirus serial intervals (serial intervals shorter and longer than 3.6 days) when calculating R_{Ei}, we found that associations between vomiting and R_{Ei} and, to a lesser degree, resident and R_{Ei} increased as the serial interval increased. The association between diarrhea and R_{Ei} did not appear to change when the assumption about serial interval length was changed (Fig 3).

Fig 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 linear mixed regression model with 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 and indicate the number of secondary cases produced by a single primary case comparing: cases with vomiting to cases with no vomiting, cases with diarrhea to cases with no diarrhea, and resident-cases to staff-cases. [d]Estimates using a serial interval of 1.0 with a standard deviation of 2.0 (or 1.0) were unstable and therefore not reported

Discussion

We inferred who infected whom from outbreak line lists and investigated risk factors for transmission of norovirus in nursing home outbreaks, leading to several important findings. First,

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303 vomiting and, to a lesser degree, diarrhea play a critical role in norovirus transmission in these
304 settings. Second, outbreaks tend to start with one or more cases who infect substantially more
305 individuals than later cases in the outbreak. Third, residents, rather than staff, are the primary
306 drivers of transmission. Our findings are based on data from multiple outbreaks affecting a
307 considerable number of cases. The novel application of our modeling methods to estimate
308 reproduction numbers required few assumptions regarding norovirus transmission. Additionally,
309 our findings were generally robust to assumptions about the serial interval and
310 inclusion/exclusion criteria for cases with missing data.

311 While previous studies have found that exposure to vomit is associated with an increased
312 risk of norovirus infection in nursing home residents and staff [14], and that proximity to a
313 vomiting event is correlated with higher attack rates [23, 24], this is the first study to find that
314 individuals, particularly residents, who vomit are more infectious and tend to drive norovirus
315 transmission in U.S. nursing home outbreaks. Human challenge studies have found that
316 vomiting, compared to diarrhea, is more likely to result in environmental contamination
317 potentially leading to transmission through fomites and airborne droplets [25]. In household
318 norovirus outbreaks, however, primary cases with diarrhea, but not vomiting, have been
319 associated with higher secondary attack rates [26]. This suggests that the relative importance of
320 specific symptoms in norovirus transmission may be dependent on the outbreak setting.

321 There is little systematic information available on norovirus introduction into nursing
322 homes [14]. Outbreak reports have shown that nursing home outbreaks often start with single
323 index cases [14], however the relative infectiousness of index cases (compared to non-index
324 cases) has not been examined in these settings. We found that outbreaks tend to start with one or
325 more cases who infect substantially more individuals compared to later cases. There are multiple

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possible explanations for this greater infectiousness of index cases. First, as an outbreak progresses and more individuals become ill and later immune, there is a natural decrease in the proportion susceptible. However, we found that index cases generally had substantially greater R_{Ei}'s compared to cases with onset dates only a few days after outbreak initiation, before a sufficient number of susceptibles could accumulate to explain this pattern. We also found that $R_{0,1}$ (the basic reproduction number for index cases) tended to be substantially larger than $R_{0,2\text{-}4}$ (the basic reproduction numbers for cases on days 2-4), even under the extreme assumptions that all individuals were initially susceptible and that the total population consisted only of reported cases in the outbreak. If the observed declines in R_{Ei} had been due to a natural decrease in susceptibles alone, we would expect the calculated R_{0i} values to remain relatively constant over time. Therefore, these results suggest that index cases are more infectious than subsequent cases for reasons other than the natural decreases in susceptibles alone. Second, index cases may have been more infectious than non-index cases due to intrinsic case characteristics (e.g., vomiting). Under this hypothesis, the median R_{Ei} may be ~1.0, meaning that most cases in the outbreak are only moderately infectious, but a highly infectious case is required to initiate an outbreak [27]. Third, rapid implementation of effective outbreak control measures could curtail transmission. Lacking data on the timing and type of control measures, we could not explicitly account for this in our calculations. Results may be due to any one of these explanations, or some combination thereof.

U.S. nursing home residents have an increased risk of norovirus gastroenteritis [8, 14], but evidence for their relative infectiousness compared to staff was lacking. While staff clearly can transmit norovirus [12, 14], studies of nosocomial outbreaks in the Netherlands have shown that symptomatic patients have the largest contribution to virus transmission in those settings

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[28]. The role of residents (vs. staff) in norovirus transmission in U.S. nursing homes may depend on the average level of mobility and dependency of residents. If nursing home residents are generally mobile, self-sufficient, and able to gather in communal rooms, they may be more likely than staff to contribute to norovirus transmission. We did not have information on residents' mobility or dependence on nursing care for this study, so were unable to include these variables in our analyses.

We note a number of limitations of our study. First, all analyzed outbreaks took place in South Carolina, so results may not be generalizable to norovirus outbreaks in nursing homes in other U.S. states or elsewhere. Nursing home staffing levels vary widely across states [29], as do infection control training resources and healthcare-associated infection reporting [30]. Second, the probability model used to estimate R_{Ei} is built on the following assumptions: transmission of infection occurs only among reported cases, asymptomatic cases do not play a role in transmission, and all reported cases are part of the same outbreak. However, for norovirus, symptomatic cases may go unreported and asymptomatic cases could contribute to transmission. In particular, underreporting of cases in the early stages of an outbreak could lead to an overestimate of the infectiousness of index cases. Additionally, some reported cases could be sporadic or caused by a different etiologic agent. Furthermore, only the date of symptom onset, not time, was considered when calculating R_{Ei}'s. Because norovirus has a relatively short incubation period, it is possible, although unlikely, for primary and secondary cases to have the same symptom onset date. The method we used to calculate R_{Ei} assumes that such cases cannot infect each other. Third, we excluded 9 cases with $R_{Ei} = 0$ from the regression analyses, however including them in the main regression analysis only strengthened the associations between all three predictor variables and infectiousness. The association between vomiting and increased

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infectiousness remained the strongest. Lastly, we used a serial interval distribution estimated from household transmission associated with norovirus outbreaks in child daycare centers in Sweden and assumed a similar serial interval in our U.S. nursing homes. Unlike transmission in the households, where it was clear that the child daycare center attendee/staff infected others in the home, identifying transmission pairs in nursing home outbreaks is difficult, precluding direct estimation of serial intervals in these settings. The true serial interval may be longer or shorter in nursing homes. Regardless, we found that our main finding of the importance of vomiting in transmission was robust when using different values of the serial interval.

Because there is currently no publicly available norovirus vaccine, sound prevention and control measures are key to controlling norovirus outbreaks, but the present body of published literature does not provide an evidence-base for the value of specific measures [10]. These study results lend support for measures that focus on cases who vomit, particularly if those cases are residents (vs. staff). Results indicate that rapid response to a vomiting event may be effective in reducing the size and duration of norovirus outbreaks in nursing home settings, and support measures that reduce exposure to vomit, such as thorough cleaning and disinfection with a chlorine-based disinfectant, isolation of the case, and implementing antiemetic treatment after the first vomiting episode [25]. Information on type and timing of control measures was not available for this study. Future studies should collect such data and evaluate the effects of specific control measures using similar analytical methods to the approach used here.

Conclusions

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393 Vomiting, particularly by residents, drives norovirus transmission in U.S. nursing home
394 outbreaks. This has implications for prevention and control measure recommendations for
395 outbreaks in these settings.
396

397 # Acknowledgements

398 Not applicable.

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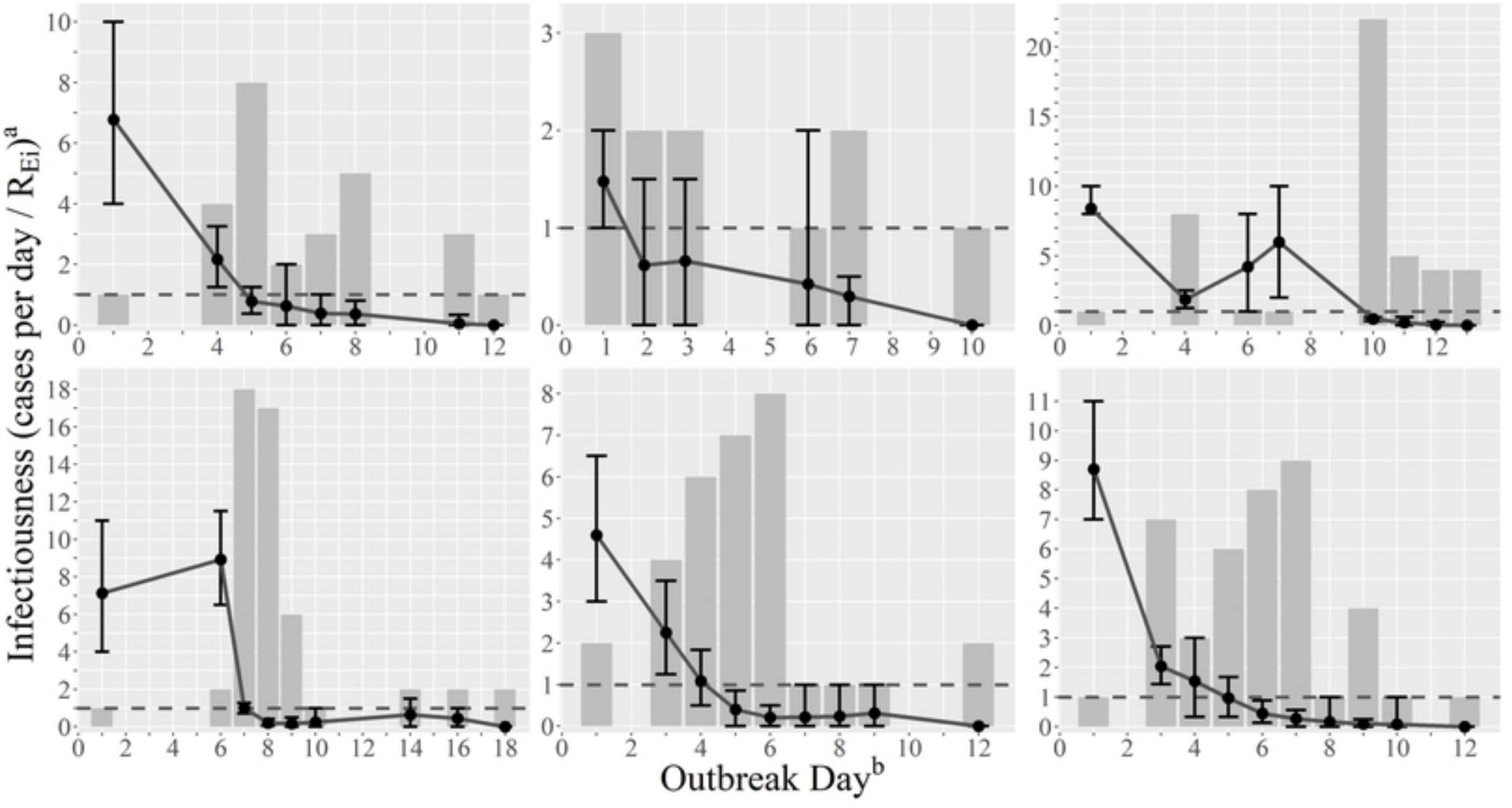

Figure 1

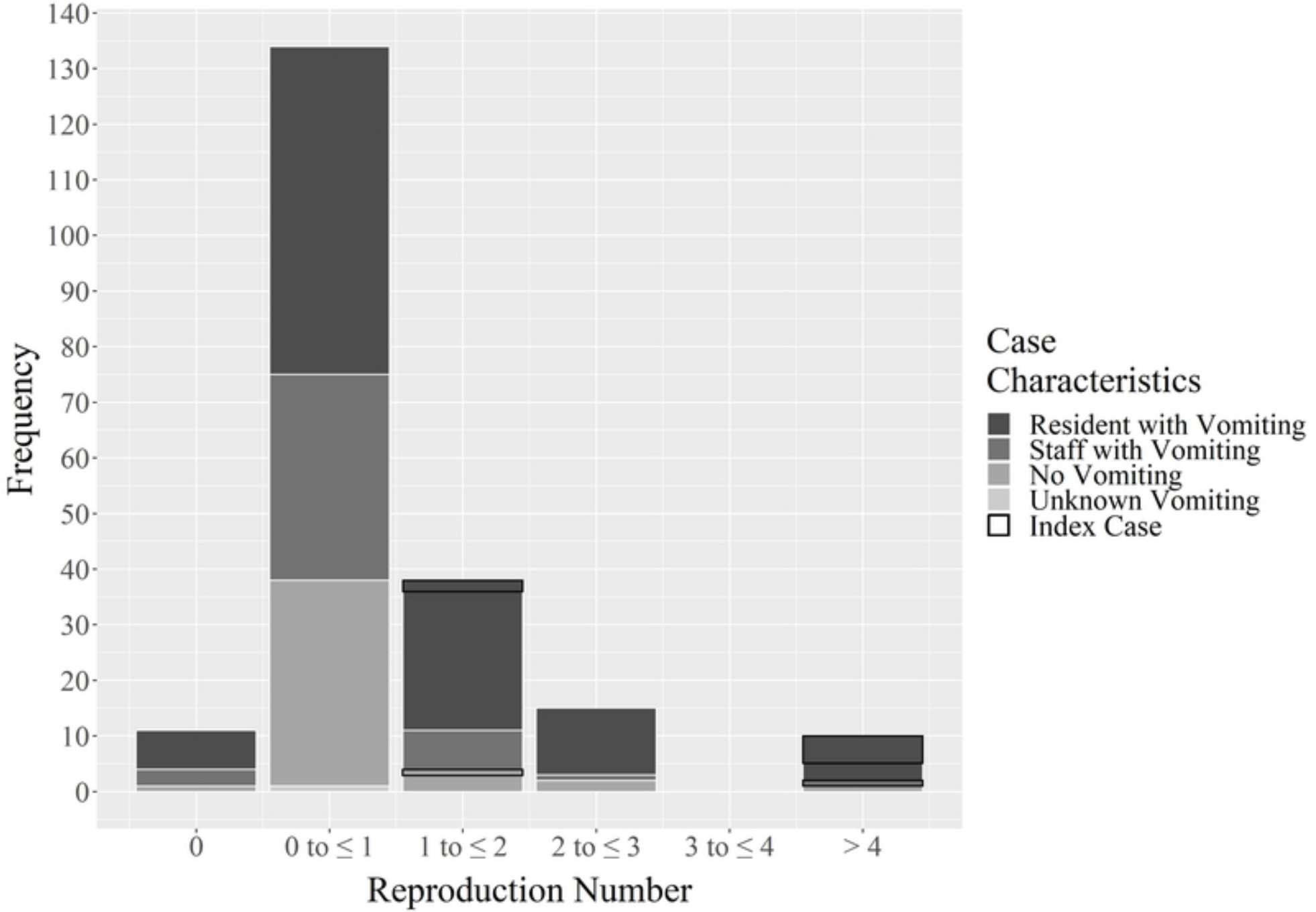
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Frequency
0
0 to ≤ 1
1 to ≤ 2
2 to ≤ 3
3 to ≤ 4
> 4
Reproduction Number
Case Characteristics
Resident with Vomiting
Staff with Vomiting
No Vomiting
Unknown Vomiting
Index Case

Figure 2

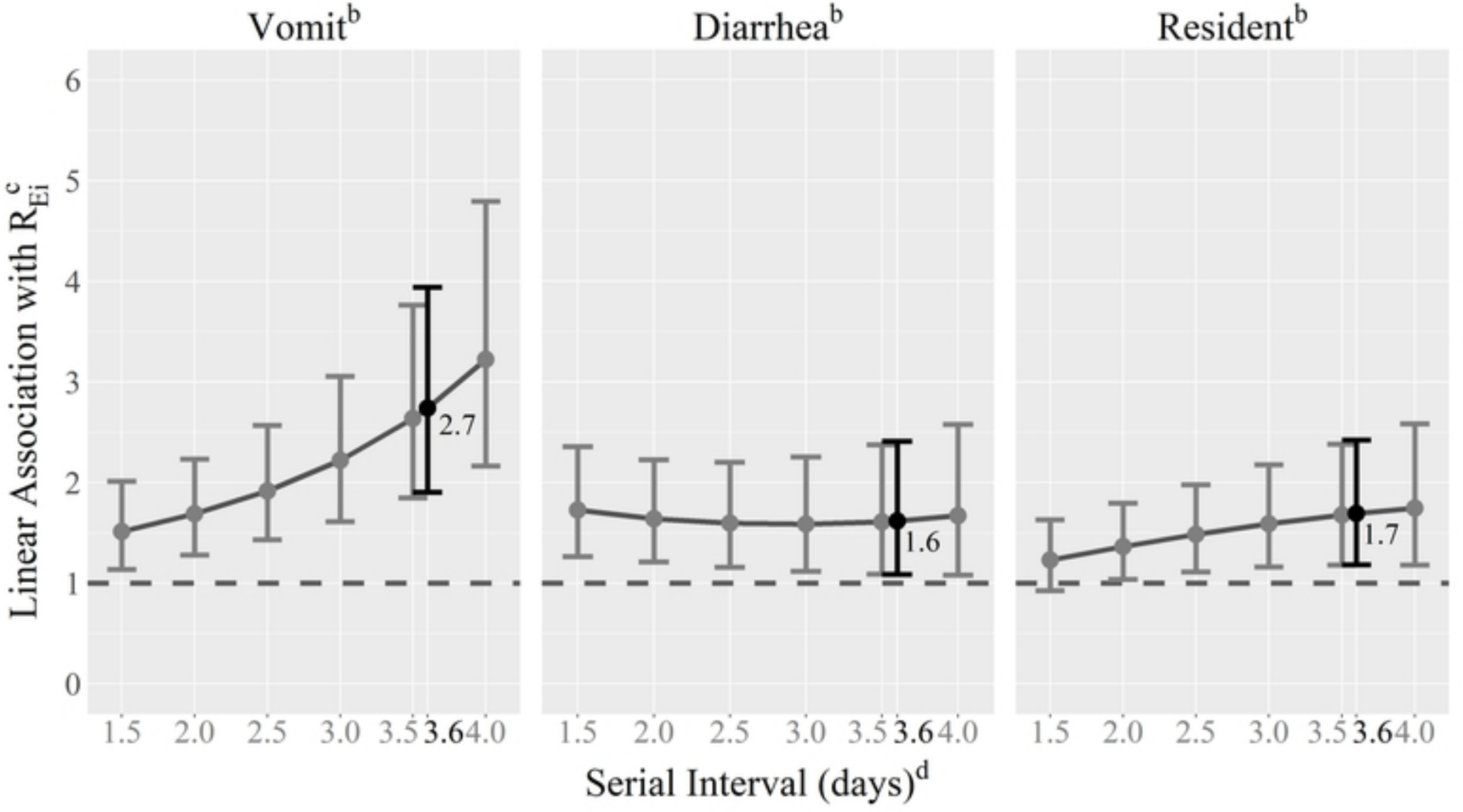
Vomit[b]
Diarrhea[b]
Resident[b]
Linear Association with R_{Ei}[c]
0
1
2
3
4
5
6
2.7
1.6
1.7
1.5
2.0
2.5
3.0
3.5
3.6
4.0
Serial Interval (days)[d]

Figure 3