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Peichun Han Date

Impact of non-pharmaceutical interventions for COVID-19 on norovirus outbreaks in the United States July 2012–December 2020

By

Peichun Han
Master of Science in Public Health

Gangarosa Department of Environmental Health

Benjamin Lopman, PhD
Committee Chair

Alicia Kraay, PhD
Field Advisor

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
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in Environmental Health and Epidemiology
2021

Abstract

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By Peichun Han

A drop in the total number of suspected and confirmed norovirus outbreaks starting from March 2020 was observed in the panel of Norovirus Sentinel Testing and Tracking (NoroSTAT) network of Centers for disease control and prevention (CDC). A previous analysis was performed to determine if the declining incidence of norovirus outbreaks (July 2012–July 2020) was attributable to reduced exposure due to non-pharmaceutical interventions (NPIs), underreporting, or seasonal trends. The authors found that the decline in norovirus incidence could not be explained by underreporting or seasonal trends. In this research, NoroSTAT data were revisited in December 2020 to see if there are still reduced norovirus outbreaks. Generalized additive models (GAMs) and generalized linear models (GLMs) are used to evaluate if the decreased incidence of norovirus outbreaks is explained by NPIs, underreporting, or seasonality. A decline of over 85% in norovirus outbreak incidence was reported to NoroSTAT during April–December 2020 compared to the monthly norovirus outbreak incidence during the same period 2013–2019, indicating that the implementation of non-pharmaceutical interventions for SARS-CoV-2 may help reduce the number of norovirus outbreaks. This pattern is consistent across all 9 NoroSTAT states and settings, and persisted after accounting for seasonality, suggesting that this decreased norovirus outbreaks could not be explained by seasonality and underreporting. Our analysis suggests NPIs may provide merits for prevention of other pathogens, such as norovirus. When NPIs are rolled back entirely, increase of norovirus outbreak incidence may occur, which may aggravate the burden to health systems.

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Introduction

Since February 2020, the United States has experienced an epidemic of coronavirus disease 2019 (COVID-19) (Jernigan & Team, 2020). In response, non-pharmaceutical interventions (NPIs) such as school and business closings, physical distancing, improved hand hygiene/surface decontamination, and public mask requirements were implemented to reduce the spread of SARS-CoV-2 beginning March 2020 (Pan et al., 2020), with many of these interventions still in place to varying degrees. Impacts of NPIs for COVID-19 on influenza have been observed in the United States (Zipfel & Bansal, 2020), and other countries (Karg et al., 2021; Miller et al., 2013; Sakamoto et al., 2020; Soo et al., 2020) and similar patterns were observed for other non-respiratory pathogens (Bruggink et al., 2021), including norovirus (Kraay et al., 2021).

Norovirus is the leading cause of gastroenteritis in all age groups (Glass et al., 2009), which transmission routes include person-to-person, foodborne, environmental contamination other than food/water and others. Non-pharmaceutical interventions, such as hand hygiene, surface cleaning (Fullman et al., 2020), are important measures to control the fomite transmission of norovirus.

In the panel of Norovirus Sentinel Testing and Tracking (NoroSTAT) network of Centers for disease control and prevention (CDC), there was a drop in the total number of suspected and confirmed norovirus outbreaks starting from March 2020 (National Center for Immunization and Respiratory Diseases). A previous analysis was performed to determine if the declining incidence of norovirus outbreaks (July 2012-July 2020) was attributable to reduced exposure due to NPIs, underreporting, or seasonal trends (Kraay et al., 2021). The authors found that the decline in norovirus incidence could not be explained by underreporting or seasonal trends. In this research, NoroSTAT data is revisited in December 2020 to see if there are still reduced norovirus outbreaks. In previous years, winter seasonality of norovirus was observed (Ahmed et al., 2013; Lopman et al., 2009). Since latest 2020 norovirus outbreak data can be accessed in this analysis, the initial wintertime seasonality of norovirus in the United States will be assessed as well.

Methods

Data Sources

We include disease and mobility data in our analysis. Norovirus Sentinel Testing and Tracking (NoroSTAT) network was established by CDC in August 2012, maintaining standard practices for norovirus outbreak reporting to CDC surveillance systems, with collaboration of twelve state health departments (CDC, 2019). Norovirus outbreak data, which consist of preliminary outbreak data entered into National Outbreak Reporting System (NORS) within 7 days of outbreak notification and genetic sequence data uploaded into CaliniNet within 7 days of receiving specimens, are summarized and published by NoroSTAT (CDC, 2019). These data include states where outbreak exposure occurred, estimated total numbers of primary cases (including lab-confirmed and probable cases), earliest date of reported illness onset, primary mode of transmission, NoroSTAT seasonal year and a calculated variable combining setting of exposure variables from each mode of transmission. We use detailed data for all reported norovirus outbreaks from nine states joined NoroSTAT before 2017: Minnesota, Ohio, Oregon, Tennessee, Wisconsin, Michigan, South Carolina, Massachusetts, and Virginia. All data began on the date each state began participating in NoroSTAT (**Table 1**) and continued through December 31, 2020. For Ohio, data were only available through July 31, 2020, as later outbreak reports had not yet been finalized at the time of analysis.

Google COVID-19 community mobility from workplaces, residential and other settings, were used to provide insights into the changed social distancing intensity in response to different NPI polices for COVID-19, including relaxation of initial declines in mobility later in the US COVID-19 epidemic. Mobility data (March–December 2020) quantify relative travel in categorized places (e.g. workplaces, parks, transition stations, retail and recreation) compared with baseline days (the median value from the 5-week period Jan 3 – Feb 6, 2020) (Google, 2021). These data are publicly available on GitHub (Google).

Data Analyses

To evaluate if the observed decline in number of norovirus outbreaks by NoroSTAT can be attributable to reduced exposure due to non-pharmaceutical interventions, or seasonal trends, cyclic cubic generalized additive models (GAMs) are used to compare the number of monthly outbreaks before and after NPI policies are implemented (COVID era vs. non-COVID era), adjusting for seasonal trends, stratified by both state and setting. For all incidence models, the March 2020 was excluded because it was a transition month, during which NPIs were gradually introduced in many states.

A regression equation for the overall GAM stratified by state level is shown below:

$$Count(Outbreaks_t) = \beta_1 COVID\ Era_t + \ spline(t)$$

Where *Count(Outbreaks$_t$)* is the number of norovirus outbreaks by month, *COVID Era* is the proxy predictor of non-pharmaceutical interventions, and *spline(t)* represents the smooth term for month, with a dimension of 12. Results were estimated separately for each of the 9 NoroSTAT states.

To explore how the impact of different NPI policies might vary by transmission venue and how relaxation of NPIs might also impact transmission differently (e.g., restaurants, schools/colleges/universities, hospitals, child daycares, long-term care facilities), we ran similar GAM models to the state-specific models for each transmission venue.

A regression equation for the overall GAM stratified by setting level is shown below:

$$Count(Outbreaks_t) = \beta_1 COVID\ Era_t + \ spline(t)$$

Results are stratified by different settings (restaurants, schools/colleges/universities, hospitals, child daycares, long-term care facilities, and others).

To assess if different states distort the association between COVID Era and number of norovirus outbreaks, reported states are controlled in GAM models to evaluate the potential confounding.

A regression equation for the GAM model adjusting for states, stratified by setting level:

$$Count(Outbreaks_t) = \beta_1 COVID\ Era_t + \beta_2 Reporting\ State + \ spline(t)$$

Where *Reporting State* represents the 9 states joining NoroSTAT before 2017 where outbreak exposure occurred, and spline(t) represents the smooth term for month with 12 knots.

Since different states enacted non-pharmaceutical interventions on different dates and the true effect estimate for setting-level NPIs might differ across states, an indicator variable for state is also included in our analysis to assess the potential effect modification between setting-level non-pharmaceutical interventions and states.

The regression equation for effect modification of` state and COVID Era GAM is shown below:

$$\begin{aligned} Count(Outbreaks_t) &\\ &= \beta_1 COVID\ Era_t + \beta_2 Reporting\ State \\ &+ \beta_3 (Reporting\ State \times COVID\ Era) + \ spline(t) \end{aligned}$$

Where $Reporting\ State \times COVID\ Era$ represents the potential effect modification between state-level non-pharmaceutical policies and states.

To evaluate if the observed decline in number of norovirus outbreaks is explained by underreporting, GAM models are used to compare the sizes of norovirus outbreaks reported to NoroSTAT during April–December before and after the beginning of SARS-CoV-2 pandemic when NPI policies started to implement, unadjusted and adjusted for state. To assess whether changes in outbreak sizes vary by different transmission venue, we compared outbreaks in restaurants, schools/colleges/universities, hospitals, child daycares, long-term care facilities, and other settings.

The equation for the overall GAM for norovirus outbreak sizes stratified by setting is shown below:

$$Count(Cases_t) = \beta_1 COVID\ Era_t + spline(t)$$

Where *Count(Cases$_t$)* is the estimated total number of primary cases by month, *COVID Era* is the proxy predictor for distancing intensity when non-pharmaceutical interventions were implemented, and *spline(t)* represents the smooth term for month with 9 knots. Results are stratified by 6 settings.

The equation for the overall GAM for norovirus outbreak sizes stratified by setting, adjusting for state is shown below:

$$Count(Cases_t) = \beta_1 COVID\ Era_t + \beta_2 Reporting\ State + spline(t)$$

Where *Reporting State* represents the 9 states joining NoroSTAT before 2017 where outbreak exposure occurred, and *spline(t)* represents the smooth term for month with 9 knots. Results are stratified by 6 settings.

Since non-pharmaceutical interventions with different levels of enforcement might lead true effect estimate for setting-level NPIs to differ across states, an indicator variable for setting is also included to consider the potential effect modification between state-level non-pharmaceutical interventions and settings.

The regression model for effect modification of Setting and Covid Era GAM, adjusting for state is shown below:

$$Count(Cases_t) = \beta_1 COVID\ Era_t + \beta_2 Reporting\ State + \beta_3 Setting + \beta_4 COVID\ Era * Setting + spline(t)$$

Where $Setting \times COVID\ Era$ represents the potential effect modification between state-level non-pharmaceutical policies and settings.

Sensitivity analysis of the relationship between COVID Era and Number of Norovirus Outbreaks is conducted by fitting generalized linear models (GLMs) testing the association between mobility, a proxy for social distancing behavior, and the number of norovirus outbreaks. For all mobility models, the March 2020 was included for higher statistical power.

The regression for the mobility GLM stratified by state level is shown below:

$$Count(Outbreaks_t) = \beta_1 Average\ Mobility_{t,k}$$

Where *Mobility* is the proxy predictor of non-pharmaceutical interventions at time *t*, and *k* represents different transmission venues (retails & groceries, and workplaces). Results are stratified by 9 NoroSTAT states.

To evaluate if the effect of monthly average mobility can be confounded by norovirus seasonality, a binary variable *NoroSeason* is included to assess the potential confounding effect. According to the time series plot by NoroSTAT entry date and for all 9 states (**Figure S2, 3**), 1 is used to represent norovirus season from October to March in the following year, and 0 is used to represent non-norovirus season (April–September).

The regression equation for the overall GLM for mobility adjusting for norovirus seasonality, stratified by states is shown below:

$$Count(Outbreaks) = \beta_1 Average\ Mobility_{t,k} + NoroSeason$$

Where *NoroSeason* is a binary variable indicating whether it is norovirus season or not (1: October–March, 0: April–September). Results are stratified by 9 NoroSTAT states.

Time-series plots are used to visualize the wintertime seasonality of norovirus overall, by different NoroSTAT entry date, and for the 9 NoroSTAT states (Minnesota, Ohio, Oregon, Tennessee, Wisconsin, Michigan, South Carolina, Massachusetts, and Virginia) in the United States.

Results

The monthly mean of reported outbreaks was 0.55 (range: 0, 4) in April–December during Covid Era across all 9 states, compared to 7.00 (range: 0, 71) during April–December during 2013–2019 (**Table 1**). In the overall GAM model, the incidence of norovirus outbreaks reported to NoroSTAT was decreased significantly for all 9 states April–December 2020 compared to the reference period (April–December 2013–2019) for each state (pooled monthly incidence rate ratio (IRR) = 0.076, 95% CI: 0.044, 0.130), accounting for seasonality. The point estimate for the model with states combined without adjusting for seasonality was slightly lower (IRR = 0.051, 95% CI: 0.020, 0.130); and the point estimate for the model only included April–December of each year (IRR = 0.080, 95% CI: 0.036, 0.077) was similar to that in the overall GAM model, suggesting that the decline in the number of norovirus outbreaks might not be explained by seasonality. Point estimates for all 9 states were strong, with IRR values ranging from 0 (95% CI: 0, Inf) for Tennessee to 0.141 (95% CI: 0.044, 0.449) for Wisconsin (**Figure 1A**). Combing norovirus outbreaks in all 9 states together, the reduction in the incidence of norovirus outbreaks was obvious among all settings, with the range of IRR values from 0 for restaurants (95% CI: 0, Inf) to 0.260 for hospitals and other healthcare facilities (95% CI: 0.107, 0.629) (**Table 2**, **Figure 1B**).

By using GAMs adjusting for seasonality, the overall size of outbreak numbers significantly decreased (IRR = 0.348, 95% CI: 0.182, 0.667, p-value = 0.001) across all settings. The size of corresponding outbreaks for long term care facilities was significantly decreased as well (IRR = 0.394, 95% CI: 0.253, 0.612, p-value < 0.001), indicating that the overall decline in norovirus outbreaks and the decreased norovirus outbreaks in long-term care facilities were not explained by underreporting. While the effect estimate outbreak sizes in other settings, such as child daycare and schools/colleges/universities, was not statistically significant (due to small numbers of outbreaks), these outbreaks tended to be, on average, much smaller than in prior years (**Figure 2**).

Generally, mobility declined in March and April and then rebounded during the summer months (**Appendix Figure S4**). However, when this variable was included as an independent variable in GLMs, reduction in norovirus incidence with adjusting for norovirus season cannot be explained by mobility in workplaces. And it was similar without adjusting for seasonality, except for Massachusetts (IRR: 1.35, 95%CI: 1.14, 1.58, p-value = 0.007). Mobility in retail and recreation cannot explain the reduction in norovirus incidence, and this was the case with or without accounting for seasonality. When accounting for the potential confounding by norovirus seasonality, the decrease in norovirus outbreak incidence in 8 of 9 NoroSTAT states cannot be explained by the monthly average mobility in workplaces; decrease in the norovirus outbreak incidence cannot be explained by mobility in retail and recreation in all 9 NoroSTAT states.

Discussion

We observed a decline of over 85% in norovirus outbreak incidence reported to NoroSTAT during April–December 2020 compared to the monthly norovirus outbreak incidence during the same period 2013–2019, indicating that the implementation of non-pharmaceutical interventions for SARS-CoV-2 helped to reduce the number of norovirus outbreaks. This pattern is consistent across all 9 NoroSTAT states and settings, and persisted after accounting for seasonality, suggesting that this decreased norovirus outbreaks could not be explained by seasonality and underreporting.

We assessed the potential confounding by reporting state. The difference of outbreak number incidence and considered the potential effect modification between reporting states, setting and COVID Era. Using Google mobility as independent variables in GLMs was performed in this analysis as well. Since reduction of norovirus incidence in most states and setting cannot be explained by mobility in workplace, retail and recreation, the increase in mobility observed during the fall prior to the start of the typical norovirus season did not trigger an increase in norovirus incidence, indicating changing behavior did not initially change norovirus incidence.

The overall size of outbreak numbers adjusting for seasonality is significantly decreased across all settings, as well as the sizes of outbreaks for long term care, indicating that the decreased norovirus outbreaks in this setting are not explained by reporting of only the most severe outbreaks. However, the outbreak sizes in other settings, such as child daycare and schools/colleges/universities, were similar to prior years. According to the continuing dialogue with CDC, all known norovirus outbreaks till December 31, 2020 in all 9 states joined

NoroSTAT before 2017 are reported to NORS, expect for Ohio with unfinalized data since August 1, 2020.

Despite these promising results, our work has a number of limitations. In the latest NoroSTAT panel, a small peak of norovirus outbreaks can be observed around March 2021. Since NoroSTAT data only through December 31, 2020 were included in this study, further analysis including new data through April 2021 is needed to assess the full wintertime season of norovirus in 2020–2021, as school gradually reopen in spring 2021. For the mobility regression, mobility data is the relative visitors (or time spent in) compared to the same baseline days (median value from the 5-week period Jan 3 – Feb 6, 2020). Since mobility may vary through the whole year, further analysis with mobility data comparing to the same period in each year is needed. In the outbreak size GAM models, obvious difference between COVID Era and reference period can be observed in all six settings (**Figure 2**). Because of the limited sample size, only the size of norovirus outbreaks in long-term care facilities was significant decreased. Although all known norovirus outbreak through December 2020 in 9 states except Ohio are reported to NORS, it remains possible that some of the decline is a result of underreporting rather than true decline in norovirus outbreak incidence.

NPIs are actions without receiving vaccination or medication or community mitigation strategies (CDC, 2020) which can help reduce respiratory diseases like influenza (Reiman et al., 2018; WHO, 2019), and other non-respiratory diseases. Norovirus is a contagious non-respiratory disease for which transmission can be reduced by NPIs, such as improved hand hygiene and surface decontamination (Kraay et al., 2018). Previous research suggests that the declining incidence of norovirus outbreak (July 2012–July 2020) early in the US epidemic was explained by reduced exposure due to NPIs (Kraay et al., 2021). In this analysis, NoroSTAT data were revisited in December 2020–April 2021 with consistent results. Our analysis suggests NPIs may provide merits for prevention of other pathogens, which may mitigate health system strain during the continued SARS-CoV-2 pandemic.

Conclusion and Recommendations

A decline of over 85% in norovirus outbreak incidence was reported to NoroSTAT during April–December 2020 compared to the monthly norovirus outbreak incidence during the same period 2013–2019, indicating that the implementation of non-pharmaceutical interventions for SARS-CoV-2 may help reduce the number of norovirus outbreaks. This pattern is consistent across all 9 NoroSTAT states and settings, and persisted after accounting for seasonality, suggesting that this decreased norovirus outbreaks could not be explained by seasonality and underreporting. Our analysis suggests NPIs may provide merits for prevention of other pathogens, such as norovirus. When NPIs are rolled back entirely, increase of norovirus outbreak incidence may occur, which may aggravate the burden to health systems.

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Tables & Figures

Table 1. Average monthly norovirus outbreaks before and during the SARS-CoV-2 pandemic by NoroSTAT state, adjusting for seasonality

		Pre-SARS-CoV-2		SARS-CoV-2	
Participating state	**Date state joined NoroSTAT**	**Reference Period (April–December of each year)**	**Monthly norovirus outbreaks during the reference period Average (Range)**	**Monthly norovirus outbreaks April–December of 2020 Average (Range)**	**Monthly norovirus outbreaks April–December 2020 vs. monthly outbreaks reference period Adjusted IRR[a] (95% CI)**
Minnesota	August 1, 2012	2013–2019	7.92 (0, 50)	0.33 (0, 2)	0.043 (0.005, 0.369)
Ohio*	August 1, 2012	2013–2019	7.85 (0, 31)	0.22 (0, 2)	0.027 (0.002, 0.382)
Oregon	August 1, 2012	2013–2019	7.71 (0, 37)	0.89 (0, 3)	0.118 (0.033, 0.421)
Tennessee	August 1, 2012	2013–2019	2.49 (0, 14)	0 (0, 0)	0 (0, Inf)
Wisconsin	August 1, 2012	2013–2019	10.1 (0, 71)	1.44 (0, 4)	0.141 (0.044, 0.449)
Michigan	August 1, 2015	2016–2019	6.8 (0, 27)	0.33 (0, 1)	0.045 (0.008, 0.252)
South Carolina	August 1, 2015	2016–2019	4.15 (0, 11)	0.22 (0, 2)	0.050 (0.009, 0.27)

Massachusetts	August 1, 2016	2017–2019	7.25 (1, 30)	0.56 (0, 3)	0.066 (0.014, 0.313)
Virginia	August 1, 2016	2017–2019	8.28 (0, 38)	0.67 (0, 2)	0.077 (0.028, 0.212)
Average	--	--	7.00 (0, 71)	0.55 (0, 4)	0.076 (0.044, 0.130)

Abbreviations: [a]IRR, incidence rate ratio.

*Results of Ohio are calculated using data –July 31, 2020.

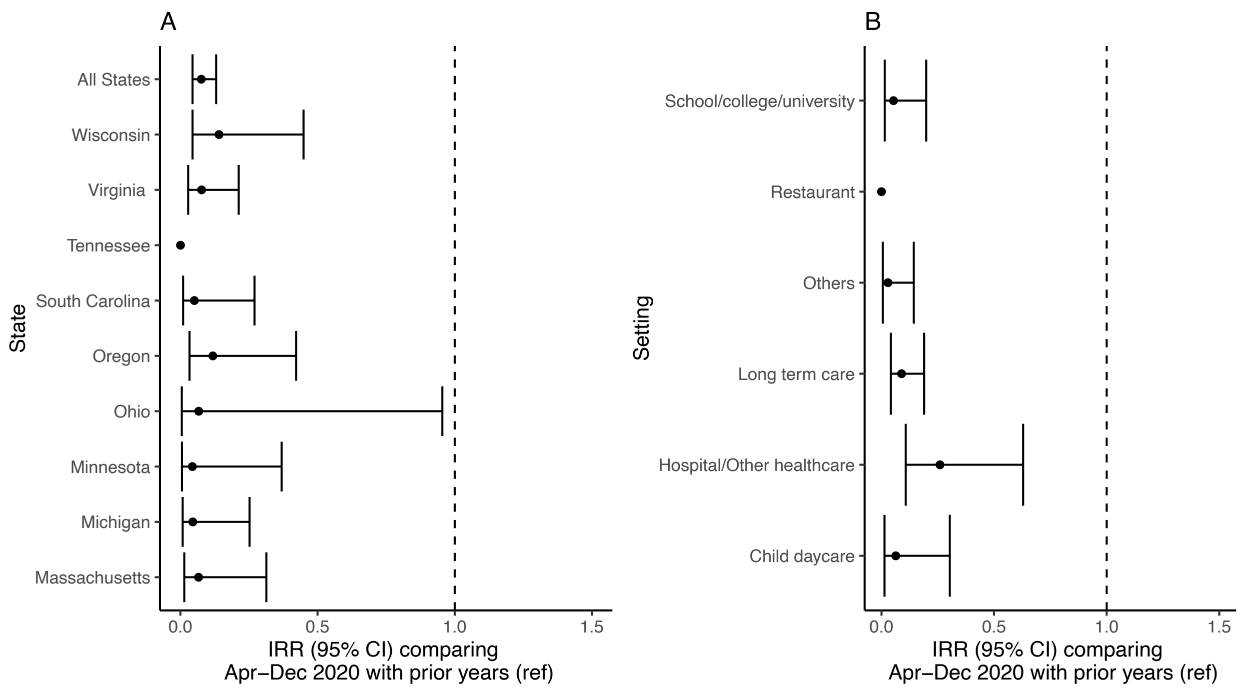
Table 2. Average monthly norovirus outbreaks before and during the SARS-CoV-2 pandemic by setting, adjusting for seasonality

	Pre-SARS-CoV-2		**SARS-CoV-2**	
Settings	**Reference Period (April–December of each year)**	**Monthly norovirus outbreaks during the reference period Average (Range)**	**Monthly norovirus outbreaks April –December of 2020 Average (Range)**	**Monthly norovirus outbreaks April–December 2020 vs. monthly outbreaks reference period Adjusted IRR[a] (95% CI)**
Long term care	2013–2019	32.46 (1, 167)	3.33 (0, 12)	0.089 (0.042, 0.19)
Hospital/Other healthcare	2013–2019	1.74 (0, 10)	0.44 (0, 1)	0.260 (0.107, 0.629)
Child daycare	2013–2019	2.91 (0, 11)	0.22 (0, 1)	0.064 (0.013, 0.303)
School/college/university	2013–2019	8.31 (0, 36)	0.44 (0, 1)	0.053 (0.014, 0.199)
Restaurant	2013–2019	7.79 (0, 19)	0 (0, 0)	0 (0, Inf)
Others	2013–2019	7.31 (1, 19)	0.22 (0, 1)	0.029 (0.006, 0.143)

Abbreviations: [a]IRR, incidence rate ratio.

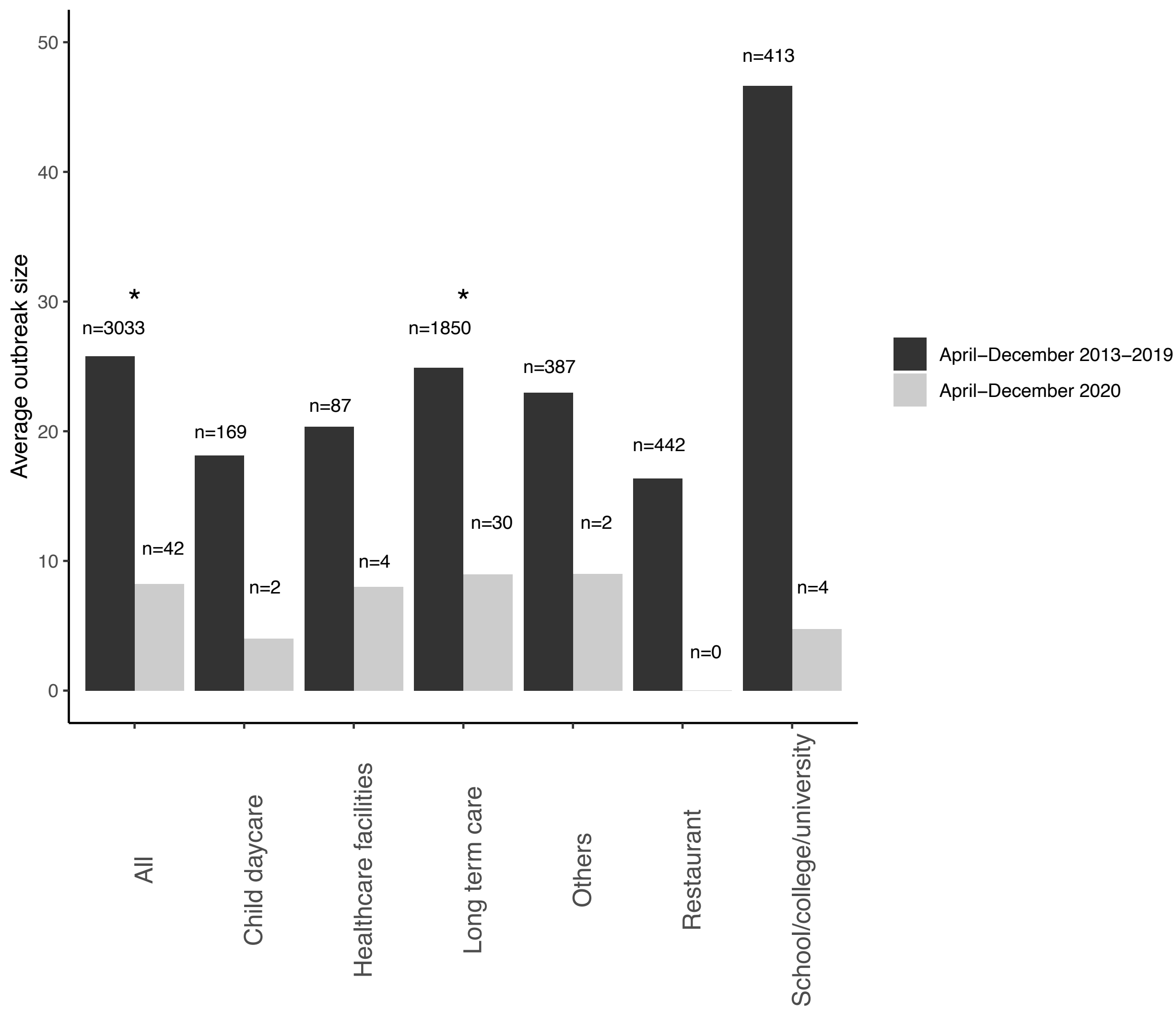
Note: Results are calculated for 9 NoroSTAT states (Minnesota, Ohio, Oregon, Tennessee, Wisconsin, Michigan, South Carolina, Massachusetts, and Virginia). We used data –July 31, 2020 for Ohio.

Figure 1. Incidence rate ratio and 95% confidence intervals of norovirus outbreaks for April–December 2020 compared with prior years (ref) by state (A) and setting (B). (exclude Ohio)



Note: there were no outbreaks reported in Tennessee in April–December 2020 (A), and no outbreaks in restaurants in April–December 2020 (B). We used data –July 31, 2020 for Ohio.

Figure 2. Average norovirus outbreak size by setting for April–December 2020 vs. April–December 2013–2019.

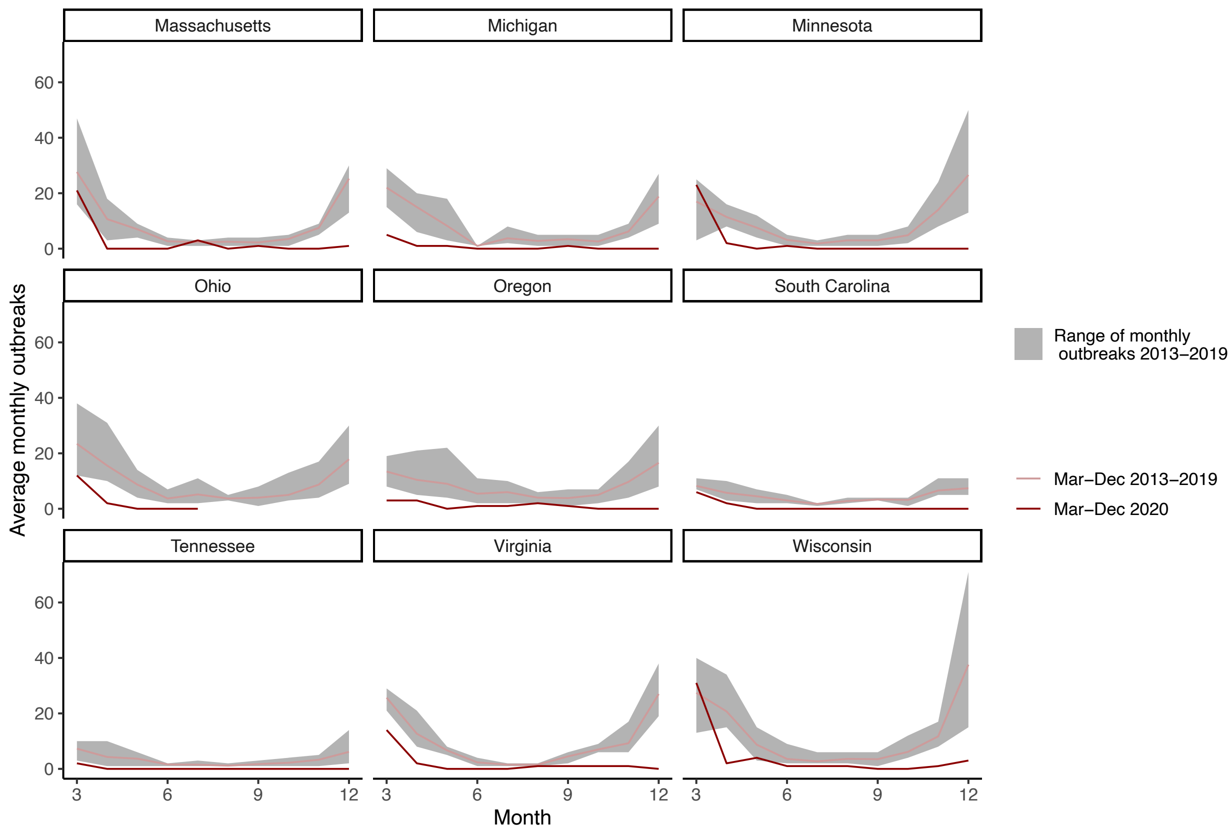


Note: *Significant difference between time periods using generalized additive models with quasi-Poisson distribution. The number of outbreaks (n) used to calculate the size for each period is shown above each bar.

Outbreak size regressions were conducted by using data for 9 NoroSTAT states (Minnesota, Ohio, Oregon, Tennessee, Wisconsin, Michigan, South Carolina, Massachusetts, and Virginia). We only used data –July 31, 2020 for Ohio.

Appendices

Figure S1. Time series plots of average monthly outbreaks by state, March–December 2020 vs. March–December 2013–2019



Note: We only used data –July 31, 2020 for Ohio.

Figure S2. Time series plot of average monthly outbreaks for all 9 states joined NoroSTAT before 2017, March–December 2020 vs. March–December 2013–2019

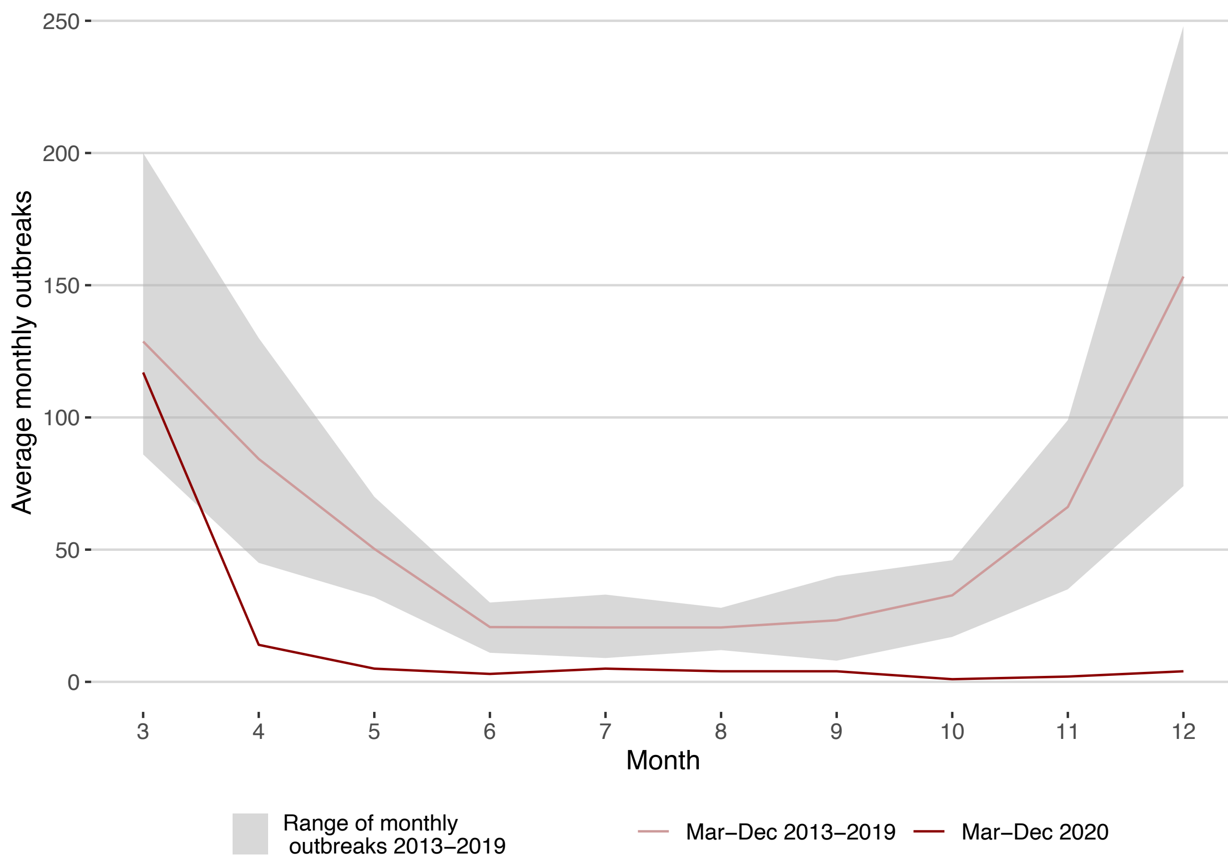
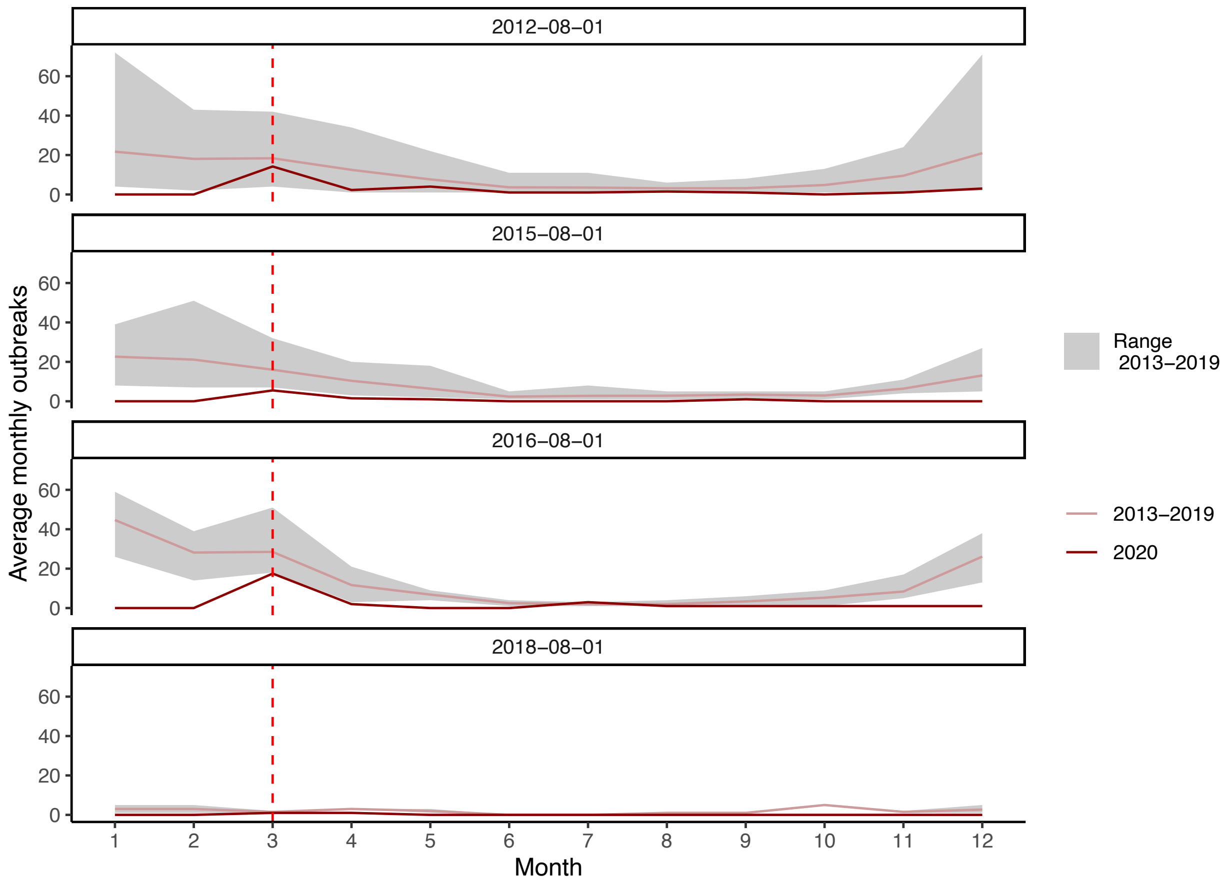


Figure S3. Time series plot of average monthly outbreaks by different NoroSTAT Entry Date, January–December 2020 vs. January–December 2013–2019



Red dashed line: March — Start of COVID Era

Figure S4. Weekly average mobility in workplace (A) and retail/recreation (B) for all 9 states joined NoroSTAT before 2017