Hospitalizations and Mortality Associated With Norovirus Outbreaks in Nursing Homes, 2009-2010

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IN THE UNITED STATES, NURSING homes annually provide care to approximately 3.3 million residents1 and 22% of all deaths occur in these settings.2 Gastroenteritis outbreaks are common in nursing homes in high-income countries.3-5 Annually, more than 1000 outbreaks of acute gastroenteritis are reported by nursing homes to US public health agencies,6 and this likely represents only a fraction of the actual number due to underreporting. Although nearly half of all reported nursing home gastroenteritis outbreaks are never etiologically confirmed because of challenges in performing diagnostic testing, norovirus is implicated in 86% of etiologically confirmed outbreaks.7

Of the estimated 800 annual norovirus-associated deaths in the United States, 90% occur in persons aged 65 years and older.8 Both ecological stud-

Context Norovirus outbreaks are common among vulnerable, elderly populations in US nursing homes.

Objectives To assess whether all-cause hospitalization and mortality rates are increased during norovirus outbreak vs nonoutbreak periods in nursing homes, and to identify factors associated with increased risk.

Design, Setting, and Participants A retrospective cohort study of Medicare-certified nursing homes in Oregon, Wisconsin, and Pennsylvania that reported at least 1 confirmed or suspected norovirus outbreak to the Centers for Disease Control and Prevention’s National Outbreak Reporting System (NORS), January 2009 to December 2010. Deaths and hospitalizations occurring among residents of these nursing homes were identified through the Medicare Minimum Data Set (MDS).

Main Outcome Measures Rates of all-cause hospitalization and mortality during outbreak compared with nonoutbreak periods were estimated using a random-effects Poisson regression model controlling for background seasonality in both outcomes.

Results The cohort consisted of 308 nursing homes that reported 407 norovirus outbreaks to NORS. Per MDS, 67 730 hospitalizations and 26 055 deaths occurred in these homes during the 2-year study. Hospitalization rates were 124.0 (95% CI, 119.4-129.1) vs 109.5 (95% CI, 108.6-110.3) hospitalizations per nursing home−year during outbreak vs nonoutbreak periods, yielding a seasonally adjusted rate ratio (RR) of 1.09 (95% CI, 1.05-1.14). Similarly, mortality rates were 53.7 (95% CI, 50.6-57.0) vs 41.9 (95% CI, 41.4-42.4) deaths per nursing home−year in outbreak vs nonoutbreak periods (seasonally adjusted RR, 1.11; 95% CI, 1.05-1.18). The increases in hospitalizations and mortality were concentrated in the first 2 weeks (week 0 and 1) and the initial week (week 0) of the outbreak, respectively. Homes with lower daily registered nurse (RN) hours per resident (<0.75) had increased mortality rates during norovirus outbreaks compared with baseline (RR, 1.26; 95% CI, 1.14-1.40), while no increased risk (RR, 1.03; 95% CI, 0.96-1.12) was observed in homes with higher daily RN hours per resident (P = .007 by likelihood ratio test); the increase in hospitalization rates did not show a similar pattern.

Conclusion Norovirus outbreaks were associated with significant concurrent increases in all-cause hospitalization and mortality in nursing homes.

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ies of mortality patterns and outbreak reports have suggested that norovirus outbreaks may lead to hospitalization or death, particularly among elderly individuals, with reported case-fatality during outbreaks ranging from 0.01% to 0.5%. However, because hospitalizations and deaths are common among the vulnerable, elderly population in nursing homes, it is difficult to ascertain if there is actually an excess of these events during outbreaks.

To directly assess the association between norovirus outbreaks and excess all-cause hospitalization and mortality in nursing homes, rates of these outcomes during outbreak periods were compared with rates during nonoutbreak periods, after adjusting for seasonality. Setting for this study was Medicare-certified nursing homes in 3 states from 2009 to 2010.

METHODS
Data Sources
A retrospective cohort of nursing homes with reported norovirus outbreaks was constructed using data from the US Centers for Disease Control and Prevention (CDC) National Outbreak Reporting System (NORS). All hospitalizations and deaths occurring in residents in these homes were extracted from the Medicare Minimum Data Set (MDS). Nursing homes included institutions providing skilled nursing care or rehabilitation services for residents, as defined by Medicaid and Medicare. Nursing home characteristics were further examined using data from the Centers for Medicare and Medicaid Services (CMS). The CDC Human Subjects office reviewed the study protocol and determined that it was exempt from institutional review board review.

Outbreak Data From NORS
NORS is a dynamic web-based platform used by state health departments for reporting enteric disease outbreaks to the CDC. Nursing homes report gastroenteritis outbreaks to state and local health departments, which investigate outbreaks and analyze stool samples for diagnostics. Norovirus outbreaks are confirmed when stool samples from at least 2 symptomatic patients show positive results by reverse transcription-polymerase chain reaction. Suspected norovirus outbreaks are reported on the basis of compatible clinical and epidemiologic characteristics in the absence of laboratory confirmation. State and local health departments collect information on each outbreak including the onset dates for the first and last case, number of cases, number of outbreak-associated deaths and hospitalizations, and facility location. The information transmitted to NORS does not specifically identify individual nursing homes; however, this information was amended directly from state health departments collaborating on this study for the purpose of linking with other data sources.

We queried NORS to identify nursing homes from Oregon, Wisconsin, and Pennsylvania that reported at least 1 confirmed or suspected norovirus outbreak between January 1, 2009, and December 31, 2010, as of April 5, 2012. These 3 states were selected for the study because they had the greatest number of norovirus outbreaks reported to NORS; thus, misclassification of time resulting from underreporting of outbreaks could be minimized.

Hospitalizations and Deaths From MDS
Using the MDS, we obtained individual-level information of all deaths and hospitalizations that occurred among residents of the nursing homes in our study. All Medicare-certified nursing homes are required to report any significant change in resident status, such as hospitalization or death (including deaths that occur after hospitalization). The validity of MDS data has been demonstrated by comparison with the Medicare enrollment files, which are considered to be the criterion standard and highly accurate.

Nursing Home Characteristics From CMS
Nursing home characteristics were obtained from the Nursing Home Compare Data set, a publicly available resource provided by CMS. This study included the following variables for each nursing home: (1) number of certified beds; (2) whether the home is located in a hospital; (3) type of ownership; (4) number of daily registered nurse (RN) hours per resident; and (5) 5-star quality ratings for health inspection, RN staffing adequacy, quality measures, and overall performance.

Data Analysis
The primary outcomes for this analysis were all-cause mortality and hospitalization rates in nursing home residents during the outbreak period compared with the nonoutbreak period. The outbreak period was defined as beginning 2 days before the date of symptom onset of the first recognized case of a confirmed or suspected norovirus outbreak and ending on the day of symptom onset in the last case, inclusive. Inclusion of the 2 days of exposure prior to the reported outbreak onset accounts for the challenges in identifying the sentinel case in an outbreak without active disease surveillance. This study explored whether overall rate ratios for hospitalization and mortality were sensitive to the definition of the first day of exposure. Additionally, this study assessed whether the risk of death and hospitalization remained stable throughout an outbreak by defining the exposure period in terms of 7-day periods relative to outbreak onset, and again beginning 2 days before the date of symptom onset of the first case.

Statistical Analysis
Hospitalization and mortality rates were calculated for outbreak and nonoutbreak periods. Using STATA 11.0, Poisson regression models with a random effect were fitted using the glm suite of commands to assess the association between norovirus outbreak period and mortality and hospitalization rates. A variable for nursing home (nh1..308) was included in the model as a random effect to account for the variation in these rates between nursing homes. Since death and hospitalization rates were
higher during winter, which coincided with the norovirus season, we adjusted for seasonal variation by including an indicator variable for calendar month in all models. Additionally, we explored if the main results were sensitive to the manner in which we controlled for seasonality by substituting a calendar week indicator variable rather than calendar month. Lastly, we used weekly regional data from the study period to determine if influenza may have confounded our norovirus effect estimate by separately including 2 indicators: (1) the proportion of reported outpatient visits due to influenza-like illness from the US Outpatient Influenza-like Illness Surveillance Network; and (2) and proportion of all influenza tests that were positive as tested by the US World Health Organization and National Respiratory and Enteric Virus Surveillance System collaborating laboratories.

We then examined if the effects of norovirus outbreaks on hospitalization rates and mortality were modified by certain characteristics of nursing homes, outbreaks, and residents (eAppendix available at http://www.jama.com). Stratified, seasonally adjusted rate ratios (RRs) were compared by likelihood ratio tests to determine if a given variable modified the effect of the norovirus outbreak exposure.

Statistical tests for all analyses were 2-sided and statistical significance was considered at a P value of less than .05.

Associated Mortality and Hospitalizations

We estimated the annual number of hospitalizations and deaths associated with norovirus outbreaks for all nursing homes in the 3 states in our study. Using a conservative approach, we assumed that there was no underreporting of outbreaks. This assumption allowed a full 2-year follow-up for all 1257 nursing homes in the 3 states. We multiplied the nonoutbreak hospitalizations and death rates from all nursing homes, including those that did not report outbreaks, by the proportion of total time that nursing homes were exposed (reported having an outbreak). Next, we multiplied this value by minus the seasonally adjusted RR, which represents the excess risk associated with outbreaks. This yielded a number of outbreak-associated hospitalizations and deaths per nursing home; we scaled this value up by multiplying by the total number of nursing homes in the 3 states (n=1257).

RESULTS

Of 1257 Medicare-certified nursing homes in Oregon, Pennsylvania, and Wisconsin from 2009 to 2010, 308 (24%) reported at least 1 suspected or confirmed norovirus outbreak during the 2-year study period, yielding a total of 616 nursing home–years of follow-up (Figure 1, Table 1). These nursing homes reported a total of 407 outbreaks, with 230 reporting 1 outbreak, 60 reporting 2 outbreaks, 15 reporting 3 outbreaks, and 3 reporting 4 outbreaks. The outbreaks exhibited strong winter time seasonality (Figure 2).

Nursing homes that reported outbreaks had more certified beds, more daily RN hours per bed, a higher nursing staff adequacy rating, and were more likely to be located outside of a hospital compared with homes that did not report an outbreak (Table 1).

Of the 407 norovirus outbreaks reported to NORS (Table 2), 293 (72%) were laboratory confirmed. The median duration of outbreaks was 13 days (range, 1-108), and the median number of cases per outbreak was 26 (range, 4-352). Hospitalizations and deaths were reported in 119 (29%) and 30 (7%) outbreaks, respectively, as determined in the outbreak investigation.

Hospitalization and Mortality Rates

A total of 67 730 hospitalizations and 26 055 deaths were reported in the nursing home cohort during the 616 nursing home–years of follow-up. Hospitalizations and deaths exhibited mild winter time seasonality (Figure 2). Nursing homes experienced 2533 hospitalizations (124.0/home-year; 95% CI, 119.4-129.1) and 1097 deaths (53.7/home-year; 95% CI, 50.6-57.0) during outbreak periods compared with 65 197 hospitalizations (109.5/home-year; 95% CI, 108.6-110.3) and 24 958 deaths (41.9/home-year; 95% CI, 41.4-
42.4) during nonoutbreak periods. After adjusting for seasonality by month, the rates of hospitalization (seasonally adjusted RR, 1.09; 95% CI, 1.05-1.14; \( P < .001 \)) and death (seasonally adjusted RR, 1.11; 95% CI, 1.05-1.18; \( P = .001 \)) were significantly elevated during outbreak periods (Table 3). A consistent but not necessarily statistically significant effect was observed in each individual state.

Adjusting for background seasonality using a weekly (rather than monthly) variable, weekly influenza-like illness activity or weekly laboratory-based influenza prevalence did not alter the association of norovirus outbreaks with hospitalization or mortality (eTable). Similarly, defining the start of the exposure period as the day of symptom onset of the first reported case yielded similar effect estimates (eTable).

The increase in hospitalizations was concentrated in the initial week 0 (RR, 1.12; 95% CI, 1.01-1.23; \( P < .001 \)) and the subsequent week 1 (RR, 1.11; 95% CI, 1.04-1.18; \( P = .001 \)), and the increased mortality rate was concentrated in the initial week 0 (RR, 1.12; 95% CI, 1.01-1.23; \( P = .02 \)), relative to outbreak onset. In subsequent weeks, the rates of hospitalizations and deaths returned to the levels observed in nonoutbreak periods (Figure 3).

### Nursing Home Characteristics

A significant effect modification was observed by the adequacy of RN staffing in nursing homes on the risk of increased mortality rate but not hospitalization rate. Nursing homes with lower daily RN hours per resident (<0.75) had a significantly increased rate of mortality during norovirus outbreaks compared with baseline (RR, 1.26; 95% CI, 1.14-1.40; \( P < .001 \)), while no increased risk was observed in homes with higher daily RN hours per resident (≥0.75; \( P = .007 \) by likelihood ratio test; Table 3). A similar pattern was noted when homes were stratified by RN adequacy ratings, which is a related indicator (Table 3). The risk of hospitalization or mortality during a norovirus outbreak did not differ when we stratified by other nursing home characteristics, including the number of certified beds, ownership status, location within a hospital, or overall 5-star quality rating.

### Outbreak and Local Health Department Investigation Characteristics

During outbreaks with investigation-reported hospitalizations, nursing homes experienced an actual elevation in hospitalization rate from baseline (RR, 1.23; 95% CI, 1.16-1.32; \( P < .001 \)), yet there was no significant increase in hospitalization rate during outbreaks with no investigation-reported hospitalizations (\( P < .001 \) by likelihood ratio test; Table 3). For mortality, we found a significant elevation in actual rates from baseline in both outbreaks with and without investigation-reported deaths, although outbreaks with investigation-reported deaths had a somewhat higher elevation in mortality (\( P = .06 \) by likelihood ratio test; RR, 1.31; 95% CI, 1.09-1.57; \( P = .003 \) than those from which deaths were not reported (RR, 1.09; 95% CI, 1.02-1.17; \( P = .01 \)). A laboratory-confirmed status of an outbreak or the ratio of total number ill to number of beds (an indicator of outbreak intensity) did not significantly modify the RRs for mortality or hospitalization during norovirus outbreaks.

### Resident Characteristics

During norovirus outbreaks, residents aged 90 years or older experienced a highly pronounced increase in hospitalization (RR, 1.24; 95% CI, 1.13-1.37; \( P < .001 \)) and mortality rates (RR, 1.28; 95% CI, 1.15-1.42; \( P < .001 \)). Hospitalization and mortality rates for both men and women were similarly affected by norovirus outbreaks.

### Estimates of Excess Hospitalization and Mortality

We estimated that norovirus outbreaks were associated with 101 excess hospitalizations (93% CI, 53-150) and 45 excess deaths (95% CI, 18-73) annually in the 1257 nursing homes from...
the 3 states in our study during 2009 and 2010. Applying this estimate to the reported 407 outbreaks, we calculated 1 excess hospitalization for every 4 outbreaks (25%) and 1 excess death for every 9 outbreaks (11%).

**COMMENT**

In this large cohort, we identified substantially elevated hospitalization and mortality rates in nursing homes during outbreaks of norovirus gastroenteritis vs nonoutbreak periods, and several lines of evidence support a causal association. First, the findings persisted after controlling for the seasonality of outbreaks at the level of the month and week, arguing against the possibility that the effect was confounded by some other underlying cause of increased wintertime mortality or hospitalization.

Second, examining the effect of outbreaks in each state individually showed similar directionality of association between outbreaks and rates of hospitalization and mortality. This is particularly compelling given the potential for variation in outbreak data ascertainment and transmission due to differences in organizational structures of public health agencies in these 3 states.

Third, the marked elevation in hospitalization and mortality rates is highly focused in time and synchronous with the first 2 weeks of the outbreak (Figure 3), when the majority of cases tend to occur; this finding strongly argues for a causal role of the outbreak. Overall, we estimated 101 excess hospitalizations and 45 excess deaths during norovirus outbreaks annually in these 3 states, which account for only 8% of the 15,884 homes nationwide.

Our findings are also consistent with a few limited studies suggesting that the risk of death and hospitalization from all causes increases in the context of a norovirus outbreak. In ecological studies, norovirus outbreak activity temporally coincides with seasonality in unspecified gastroenteritis morbidity, hospitalizations, and deaths. It should be noted that recognition of deaths within outbreaks may be subject to ascertainment or observer bias, reporting bias and ultimately publication bias. However, our study was largely unaffected by these biases in that exposure data (outbreaks) were ascertained independently from outcome data (deaths and hospitalizations) among nursing homes reporting outbreaks.

Our findings have important implications for clinicians, nursing home administrators, and public health professionals. First, our findings challenge the
notion that norovirus causes only a benign self-limiting illness; the 20% to 30% increase in risk of death and hospitalization during outbreaks among individuals who are older than 90 years suggests that this is a particularly high-risk population that warrants closer attention during outbreaks, possibly requiring earlier transport to the hospital. Vulnerable groups could also be a target population for future vaccines.27 Moreover, norovirus is highly infectious and hospitalizations present a

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<th>Table 3. Outbreak and Nonoutbreak Hospitalizations, Deaths, and Rate Ratios by Characteristics of Nursing Homes, Outbreaks, and Residents</th>
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<td><strong>No. of Hospitals</strong></td>
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Abbreviations: RN, registered nurse; RR, rate ratio.  
\(^a\)Rate ratios are seasonally adjusted.  
\(^b\)Overall model does not incorporate characteristics of homes, outbreaks, or residents shown in this table. The model does include each nursing home as a random effect, which takes into account variation in baseline mortality and hospitalization between nursing homes.  
\(^c\)P values of less than .05 were determined using the likelihood ratio test.  
\(^d\)All nursing homes in this study (N=308) contribute to these subanalyses since outbreak time is compared with nonoutbreak time from all nursing homes. Because all homes included in the study (by definition) had an outbreak, they are all included, but time is stratified as either being exposed (having an outbreak) or not exposed (nonoutbreak period).  
\(^e\)P values equal to .06 were determined using the likelihood ratio test.  
\(^f\)Likelihood ratio tests could not be conducted due to constraints in data.
break-associated deaths, as demonstrated by the 9% elevation in mortality rate even in outbreaks that were reported to have no associated deaths. Increased recognition for the potential of norovirus-associated deaths during outbreaks may help clinicians and public health investigators more appropriately identify norovirus gastroenteritis as a contributory factor to a patient’s death.

Several limitations should be considered. First, we included 115 outbreaks (28%) that were suspected to be due to norovirus, but without laboratory confirmation. Although clinical and epidemiological characteristics are highly specific for norovirus outbreaks, there remains a possibility that some of these outbreaks may be due to other etiologies. Reassuringly, the increased hospitalization and mortality risk persisted even when we included only the nursing home time during confirmed norovirus outbreaks in the analysis.

Second, we relied on voluntary reporting of norovirus outbreaks by nursing homes and found that more daily nursing hours and resident and location outside of a hospital were associated with greater reporting. This could bias our results toward an effect if homes selectively reported outbreaks associated with severe disease outcomes. However, given that a majority of outbreak investigations reported no associated hospitalizations or deaths, and that many nursing homes reported multiple outbreaks, this was likely not a major bias. Conversely, underreporting of outbreaks would likely result in a bias toward the null since true outbreak-associated hospitalizations and deaths would have been incorrectly classified.

Third, use of all-cause mortality and hospitalization data also limits the specificity of the association. Norovirus outbreaks may disrupt the daily routine in nursing homes due to high attack rates in residents who may require more care, while ill staff members are encouraged to stay home for 48 to 72 hours after the resolution of their symptoms. Hence, we were unable to assess whether increases in deaths and hospitalizations were due directly to norovirus infection or from an indirect effect such as altered delivery of care.

Fourth, norovirus outbreaks occur during winter and possibly overlap with outbreaks of other infectious diseases. However, we carefully controlled for seasonality in our analysis using monthly and weekly adjustments, as well as adjustments for influenza activity using weekly, regional indicators. Given the consistency of the association, it is unlikely that substantial residual confounding exists, especially considering the strong temporal association during the first week of the outbreak.

In conclusion, we detected a consistently increased risk of hospitalization and death from all causes during norovirus outbreaks among residents in nursing homes from 3 US states. As a next step, research should be directed to determine if this increase is directly attributable to norovirus infection and subsequent disease resulting from gastro-

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**Figure 3.** Seasonally Adjusted Rate Ratios for Hospitalizations and Deaths, and Counts of Hospitalizations and Deaths By Week Relative to Outbreak Onset

Error bars indicate 95% CIs for rate ratios. Rate ratios of hospitalizations and death rates in a specific week (relative to the outbreak start) over hospitalization and death rates during all other weeks.

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The challenge in prevention of nosocomial transmission.28 Nursing homes with fewer than 0.75 daily RN hours per resident and lower RN staff adequacy ratings were at an increased risk of mortality during outbreak periods. This is consistent with findings for other outcomes25,30 and supports the recommendations of a 2001 report to Congress on the appropriateness of minimum RN staffing to patient ratios.31 Lastly, we found that outbreak investigations conducted by public health agencies identify norovirus outbreak-associated hospitalizations with reasonable accuracy; in nursing homes that did not report hospitalizations to NORS during outbreaks, the actual rate of hospitalization in MDS during an outbreak did not differ from baseline. However, these investigations may underestimate outbreak-associated deaths, as demonstrated by the 9% elevation in mortality rate even in outbreaks that were reported to have no associated deaths. Increased recognition for the potential of norovirus-associated deaths during outbreaks may help clinicians and public health investigators more appropriately identify norovirus gastroenteritis as a contributory factor to a patient’s death.

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enteritis. Additionally, more detailed information is necessary to understand the specific contributory causes and co-morbidities of norovirus-associated deaths. Given the lack of diagnostic testing in sporadic illness, outbreaks may provide the best opportunities for identifying such associations between norovirus disease and deaths. At present, strategies for averting these severe outcomes include general treatment for dehydration and infection control to prevent and control outbreaks. More targeted interventions would be welcome and in light of recent progress with a norovirus vaccine, these results highlight a set-terventions would be welcome and in light of recent progress with a norovirus vaccine, these results highlight a set-terventions would be welcome and in light of recent progress with a norovirus vaccine, these results highlight a set-terventions would be welcome and in light of recent progress with a norovirus vaccine, these results highlight a set-terventions would be welcome and in light of recent progress with a norovirus vaccine, these results highlight a set-terventions would be welcome and in light of recent progress with a norovirus vaccine, these results highlight a set-tering such associations between norovirus disease and deaths. At present, strategies for averting these severe outcomes include general treatment for dehydration and infection control to prevent and control outbreaks. More targeted interventions would be welcome and in light of recent progress with a norovirus vaccine, these results highlight a setting and population that may benefit if efficacy and safety of immunization can be demonstrated.

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