Severe Outcomes Are Associated With Genogroup 2 Genotype 4 Norovirus Outbreaks: A Systematic Literature Review

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Background. Noroviruses (NoVs) are the most common cause of epidemic gastroenteritis; however, the relative impacts of individual factors underlying severe illness are poorly understood. This report reviews published NoV outbreak reports to quantify hospitalization and mortality rates and assess their relationship with outbreak setting, transmission route, and strain.

Methods. Using a string of terms related to "norovirus" and "outbreak," we 2435 nonduplicate articles identified in PubMed, EMBASE, and Web of Knowledge published between January 1993 and June 2011. Inclusion criteria included outbreaks with a minimum of 2 ill persons with a common exposure and at least 1 reverse-transcription polymerase chain reaction–confirmed case of NoV disease. Univariate analyses were performed, and multivariable models were fitted to estimate the independent effect of each factor.

Results. We analyzed 843 NoV outbreaks reported in 233 published articles from 45 countries. Based upon 71 724 illnesses, 501 hospitalizations, and 45 deaths, overall hospitalization and mortality rates were 0.54% and 0.06%, respectively. In multivariate analysis, genogroup 2 genotype 4 (GII.4) NoV strains were associated with higher hospitalization (incidence rate ratio [IRR], 9.4; 95% confidence interval [CI], 6.1–14.4; $P < .001$) and mortality rates (IRR, 3.1; 95% CI, 1.3–7.6; $P = .01$). Deaths were much more likely to occur in outbreaks occurring in healthcare facilities (IRR, 60; 95% CI, 6–109; $P = .01$).

Conclusions. Our review suggests that hospitalizations and deaths were more likely in outbreaks associated with GII.4 viruses, independent of other factors, and underscores the importance of developing vaccines against GII.4 viruses to prevent severe disease outcomes.

Noroviruses (NoVs) are the most common cause of epidemic gastroenteritis and a major cause of foodborne illness [1]. Noroviruses are responsible for approximately 50% of all reported gastroenteritis outbreaks in the United States and European countries (range, 36%–59%) [2]. In otherwise healthy adults, NoV gastroenteritis is typically mild and resolves without medical intervention. However, severe outcomes, including hospitalization and death, have been reported in more vulnerable populations, such as young children, immunocompromised persons, and the institutionalized elderly [3, 4]. The relative impact of individual factors underlying severe illness is poorly understood and difficult to tease apart in individual outbreaks or across a small number of outbreaks. For example, severe outcomes are more common among affected residents of long-term care facilities, but these outbreaks are also disproportionately caused by genogroup 2 genotype 4 (GII.4) viruses and transmitted from person to person. For this reason, it has been challenging to identify whether host characteristics, the source of infections (which may affect inoculum size), or

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characteristics of the virus predispose individuals affected by NoV disease to having more severe outcomes. This report reviews published reports of NoV outbreaks in order to quantify hospitalization and mortality rates in NoV outbreaks and assess their relationship with outbreak setting, transmission route, and strain.

METHODS

Article Identification

We performed a literature search for papers published between January 1993 and June 2011 for the terms "norovirus" and "outbreak" using PubMed, EMBASE, and Web of Knowledge. Medical Subject Heading terms were expanded in PubMed when available and Boolean operators were used to include all possible term forms, resulting in the final search string: (norovirus OR noroviruses OR calicivirus OR caliciviruses OR Caliciviridae OR Norwalk virus OR Norwalk viruses OR Norwalk-like virus OR Norwalk-like viruses OR Norwalk like virus OR Norwalk like viruses OR small round-structured virus OR small round-structured viruses OR small round structured virus OR small round structured viruses OR SRSV) AND (outbreak OR outbreaks OR pandemic OR pandemics OR epidemic OR epidemics OR infectious disease outbreak OR infectious disease outbreaks OR disease outbreak OR disease outbreaks).

Article Screening

The initial literature search identified 2435 nonduplicate articles. Two reviewers independently assessed each article for inclusion. Articles were required to meet the following five criteria: (1) be published in an article format (eg, citations of conference abstracts were excluded), (2) be published entirely in English, (3) describe human NoV outbreaks, (4) have a minimum of 2 cases of illness associated with a common exposure and have at least 1 case from each NoV outbreak confirmed by reverse-transcription polymerase chain reaction (RT-PCR), and (5) explicitly state the number of primary cases. Articles were ineligible if they were primarily reviews of NoV, experimental trials, case-control studies, documented sporadic cases of NoV, or were published prior to the development of RT-PCR methodology for NoV detection in 1992. Studies were only included if they reported data on individual outbreaks, not data in aggregate. Outbreaks of any duration were included in our analysis. Discrepancies between each pair of reviews were resolved by consensus or a third investigator. Rather than impose a uniform case definition on the articles, we adopted each author's case definition. Outbreaks reported in multiple publications were only recorded once. A range of data was extracted and is reported in full elsewhere [5]; here, we consider outbreak setting, route of transmission, and NoV strain.

Data Abstraction

Once eligibility was determined, 2 reviewers independently extracted data from selected articles using a standardized checklist, and discrepancies were corrected by consensus. The following information was retrieved: publication characteristics (year, title, country), outbreak characteristics (outbreak setting, route of transmission, and outbreak NoV strain), and reported outbreak-associated illnesses (hospitalizations and deaths) from each NoV outbreak report. When multiple publications reported on the same study population, we used the article that provided the most recent and most comprehensive data. Outbreaks where multiple pathogens were identified in >1 case patient were excluded from this analysis. If no hospitalizations or deaths were reported, we assumed that there were none caused by the outbreak.

Operational Definitions

Outbreak setting was defined as either healthcare facility (eg, hospital or long-term care facility) or community setting (eg, restaurants, schools, hotels, etc). For analysis of hospitalization rates, outbreaks in hospitals were excluded. *Mode of transmission* was defined as either foodborne/waterborne, person-to-person, or a combination of these routes. *Outbreak NoV strain* was defined as the predominant NoV strain(s) identified among affected individuals during the outbreak investigation and categorized as GII.4 strain(s), non-GII.4 strain(s), or mixed strains. If the outbreak was reported to be GII but no specific type was reported, we excluded that outbreak from analysis ($N = 97$) because it could not be determined if a GII.4 or another GII strain caused the outbreak.

Statistical Analysis

We used a zero-inflated Poisson regression model to generate pooled estimates of the proportion of cases that were hospitalized or died in an outbreak. Subsequently, separate Poisson regression models with a random-effect term (to account for interstudy variability) were fit to estimate the effect of setting, mode of transmission, and strain on hospitalizations and deaths, respectively. First, univariate analyses were performed by outbreak setting, transmission route, and outbreak strain; then multivariable models were fit to estimate the independent effect of each factor, controlling for the others. An indicator variable was created when data on setting, mode of transmission, or strain were missin, so that all data could be included in the multivariate models. Models were also fitted using only data from outbreaks where data were nonmissing ($n = 223$ outbreaks). Results were qualitatively similar to the presented models using data from all outbreaks, except that model convergence could not be achieved in the multivariable death model. All analyses were conducted using STATA version 11 (StataCorp. 2009).

RESULTS

We analyzed 843 NoV outbreaks reported in 233 published articles from 45 countries between January 1993 and June 2011. Among these outbreaks, 560 (66%) occurred in community settings and 219 (26%) occurred in healthcare settings, 370 (44%) had foodborne and/or waterborne transmission and 136 (16%) had only person-to-person transmission, and 293 (35%) were caused by non-GII.4 strains whereas 184 (22%) were caused by GII.4 strains. Of the 219 outbreaks in healthcare settings, 112 were in long-term care facilities and 107 were in hospitals. The number of hospitalizations and deaths were reported in 82 and 47 outbreaks, respectively. Based upon a total of 71 724 cases (69 857 from nonhospital settings), 501 hospitalizations, and 45 deaths, hospitalization and mortality rates were 54 per 10 000 cases (95% confidence interval [CI], 45–63) and 6 per 10 000 cases (95% CI, 0–39), respectively.

In univariate analysis, hospitalization rates were higher in healthcare facility outbreaks (including long-term care facility outbreaks but not hospital outbreaks) than in community settings (incidence rate ratio [IRR], 1.5; 95% CI, 1.2–1.9; $P < .001$), higher in outbreaks caused by GII.4 than by non-GII.4 NoV strains, excluding mixed GII infections (IRR, 10; 95% CI, 7–16; $P < .001$), and similar in person-to-person outbreaks compared with foodborne and waterborne outbreaks (IRR, 1.2; 95% CI, 1.0–1.4; $P = .08$). Very similar associations were found in multivariable analysis. Considering only healthcare facility settings, hospitalization rates were higher in outbreaks caused by GII.4 strains compared with outbreaks caused by non-GII.4 strains (IRR, 14; 95% CI, 5–42; $P < .001$). Mortality rates were dramatically higher in healthcare facility outbreaks than in community settings (IRR, 147; 95% CI, 20–1090; $P < .001$), person-to-person transmitted outbreaks than foodborne and waterborne outbreaks (IRR, 59; 95% CI, 8–444; $P < .001$), and in GII.4 outbreaks than in non-GII.4 outbreaks (IRR, 10; 95% CI, 4–25; $P < .001$). In multivariable analysis, the magnitude of association decreased with healthcare facility settings (IRR, 60; 95% CI, 6–609; $P = .001$), decreased with GII.4 outbreaks (IRR, 3.1; 95% CI, 1.3–7.6; $P = .01$), and became nonsignificant in person-to-person transmitted outbreaks (IRR, 2.8; 95% CI, .3–28; $P = .37$) (Table 1). Considering only healthcare facility settings, death rates were higher in outbreaks caused by GII.4 strains than in outbreaks caused by non-GII.4 strains (IRR, 6.1l; 95% CI, 2.0–18.3; $P = .001$).

DISCUSSION

Norovirus outbreaks in healthcare settings affect vulnerable populations (eg, elderly persons), but because these outbreaks are predominantly spread by person-to-person transmission and are caused by GII.4 viruses [1], it has not previously been possible to determine if the outbreak setting, transmission route, or virus strain was the cause of severe outcomes including hospitalization and death. Our review of over 800 outbreaks has highlighted that, indeed, hospitalizations and deaths were much more likely in healthcare outbreaks and, somewhat surprisingly, in GII.4 virus–associated outbreaks, independent of those factors for which we were able to control.

Among published NoV outbreak reports, we estimate an overall pooled NoV case hospitalization rate of 0.7% and mortality rate of 0.07%. However, these figures may overestimate the rate of severe outcomes because outbreaks with hospitalizations and/or deaths may also be more likely to be investigated and subsequently published in the peer-reviewed literature. Indeed, passive surveillance systems have estimated lower hospitalization and mortality rates [6]. Many NoV outbreaks likely go unrecognized, and among those that get reported to local public health authorities, the majority are not systematically investigated or well documented [7]. Additionally, the only outbreaks in this analysis that were reported from a low- (Afghanistan) or low-middle–income income (Iraq) setting occurred among US and UK military forces; however, it is thought that the burden of NoV disease is highest in developing regions [3]. Given that poorer outcomes are related to inadequate access to medical care, our figures may represent an underestimate of the true hospitalization and mortality rate attributable to NoV disease in some international settings.

The high hospitalization rates in long-term care facilities and mortality in all healthcare settings underscores the vulnerability of populations affected by outbreaks in these settings. Norovirus infection often causes prolonged symptoms in frail, elderly patients with limited mobility [8]. Due to limitations in the published outbreak data, it was not possible to assess whether healthcare settings may have been a proxy for intrinsic factors for patient vulnerability, such as age or comorbid conditions, which may have made residents and patients more likely to develop complications of NoV disease than staff or visitors. Unfortunately, only a minority of studies in our review discriminated between the NoV cases among staff and hospital patients/nursing home residents. If more studies had reported hospitalization and mortality rates separately for staff and patients/residents, we expect that estimates of severe disease frequency in these specific populations would have been even higher. Studies have demonstrated that rates of severe NoV disease are highest among the elderly [9], whereas overall NoV rates are highest in younger age groups [10], making advanced age a risk factor for higher NoV-associated hospitalization and fatality rates. Because age was not reported in the many outbreak reports, this unmeasured covariate could have confounded our results. However, because most patients

Table 1. Univariate and Multivariate Analysis of Hospitalization and Death Rates by Setting, Transmission Type, and Strain

		Univariate Analysis						Multivariate Analysis (N = 736)[a]	
Hospitalizations		Outbreaks	Cases	Hospitalizations	Crude Hospitalization Rate (per 1000 cases)	Hospitalization IRR (95% CI)	*P* Value	Hospitalization IRR (95% CI)	*P* Value
Setting	Community settings	560	52 548	391	7	1	…	1	…
	Healthcare facilities[b]	112	6784	100	15	1.5 (1.2–1.9)	<.001	1.4 (1.0–1.8)	.02
	Unknown	64	8053	10	1	0.08 (.04–.15)	<.001	0.6 (.2–1.3)	.16
Transmission	Food/water	370	33 424	284	9	1	…	1	…
	Person-to-person	109	13 999	192	14	1.2 (1.0–1.4)	.08	1.0 (.8–1.3)	.81
	Mixed/unknown	257	19 962	25	1	0.06 (.04–.11)	<.001	0.07 (.03–.14)	<.001
Strain[c]	Non-GII.4 infections	277	16 046	33	2	1	…	1	…
	GII.4 infections	135	17 654	99	6	10 (7–16)	<.001	9.4 (6.1–14.4)	<.001
	Mixed/unknown	324	33 685	369	11	5 (3–7)	<.001	7.6 (5.2–10.9)	<.001
Deaths		Univariate Analysis						Multivariate Analysis (N = 843)[a]	
		Outbreaks	Cases	Deaths	Crude Mortality Rate (per 100 000 cases)	Mortality IRR (95% CI)	*P* Value	Mortality IRR (95% CI)	*P* Value
Setting	Community settings	560	52 548	1	2	1	…	1	…
	Healthcare facilities	219	11 123	44	396	147 (20–1090)	<.001	60 (6–609)	.001
	Unknown	64	8053	0	…	…	…	…	…
Transmission	Food/water	370	32 633	1	3	1	…	1	…
	Person-to-person	136	16 234	44	271	59 (8–444)	<.001	2.8 (.3–28.0)	.37
	Mixed/unknown	337	22 857	0	…	…	…	…	…
Strain[c]	Non-GII.4 infections	293	16 594	6	36	1	…	1	…
	GII.4 infections	184	20 213	28	139	10 (4–25)	<.001	3.1 (1.3–7.6)	.01
	Mixed/unknown	366	34 917	11	32	0.7 (.3–1.9)	.51	1.3 (.47–3.64)	.60

Abbreviations: CI, confidence interval; GII.4, genogroup 2 genotype 4; IRR, incidence rate ratio.

[a] Models were also fitted using only data from outbreaks where data on setting, transmission route, and strain were nonmissing ($n = 223$ outbreaks). Results were qualitatively similar to the presented models using data from all outbreaks, except that model convergence could not be achieved in the multivariable death model.

[b] Hospital-based outbreaks were excluded from analysis of outbreak-associated hospitalizations.

[c] Out of 843 outbreaks, 696 (83%) reported the norovirus genogroup that was identified as the etiologic cause of the outbreak.

in hospital and long-term care facility settings are elderly, setting of outbreak is likely a very strong proxy for age.

Route of transmission was identified as being foodborne, waterborne, person-to-person, or a combination of these routes in 63% of the outbreaks. Prolonged outbreaks that occurred in long-term care facility or hospital settings—where large groups of individuals typically live in close proximity–were often categorized as person-to-person. Foodborne and waterborne transmission were the most frequent type of transmission identified in our data. However, broad-based surveillance studies as well as expert elicitation suggest that the majority of NoV outbreaks primarily involve person-to-person transmission [1, 11, 12], suggesting a publication bias favoring reports of foodborne and waterborne transmission. Fortunately, this bias would not affect our estimates of the association between mode of transmission and severe outcomes. In addition, this may be due to outbreak reports that concluded that outbreaks occurring over many days in community settings were the result of foodborne or waterborne transmission, even when a specific source was not identified. It is possible that transmission route may have been misclassified in some of these outbreaks.

Clinical and epidemiologic criteria can help attribute gastroenteritis outbreaks to NoV disease [13]. However, commercial NoV PCR testing has become more widely available in recent years [14], and there is now a Food and Drug

Administration–cleared enzyme immunoassay for outbreak investigation in the United States. All of the published outbreaks evaluated in this study used confirmatory laboratory testing. Comparing outbreaks known to be due to GII.4 with those known to be due to a strain other than GII.4, we found a striking difference in mortality rate and hospitalization rate, suggesting that this genotype may be responsible for severe disease. Previous observations that GII strains are shed at higher levels [15], are more likely to induce vomiting, and cause more severe disease in children [16, 17], when taken in the context of this study, demonstrate a consistent pattern. Noroviruses rapidly evolve and distinct strains have emerged every 2–4 years over the last decade [18–20]. At least 2 GII.4 variants have escaped population immunity and were associated with large global outbreaks of disease [19, 20].

Currently there is no licensed NoV vaccine. Efforts to reduce NoV disease burden have been focused on effective disease surveillance and limiting disease transmission. We have again highlighted the importance of outbreak prevention and control of outbreaks in healthcare settings, where hospitalization and death are more likely to occur. In addition, NoV vaccines are under development, and it has been demonstrated that, in principle at least, it is possible to immunize using a GI.1 vaccine against a homotypic challenge [21]. Our analysis highlights the importance of developing vaccines against GII.4 viruses that are safe and effective, particularly for vulnerable populations who suffer severe disease outcomes, including death.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention (CDC).

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