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## Brief report

## Clinical characteristics of norovirus-associated deaths: A systematic literature review

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## Key Words:

Norovirus  
Death  
Mortality

Although deaths are often reported in the context of norovirus outbreaks, clinical and epidemiologic characteristics of the decedents prior to death are not well established. Through a literature review of published reports of deaths associated with norovirus infection, we identified and summarized 158 norovirus-associated deaths in 12 countries from 1988 to 2011.

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Noroviruses cause an estimated 21 million gastrointestinal illnesses annually and are the most common cause of gastroenteritis outbreaks in the United States.<sup>1</sup> Although norovirus gastroenteritis typically causes a mild self-resolving illness, it can lead to severe dehydration, hospitalization, and potentially death in vulnerable populations including children and in the elderly population in health care facilities.<sup>2</sup> Risk factors have not been well established, although advanced age with prolonged symptoms of diarrhea, cardiovascular disease, renal transplant/failure, and immunosuppression have been associated with severe disease or death.<sup>3</sup> A comprehensive description of the underlying conditions of decedents, immediate causes of death, or settings of deaths associated with norovirus infection may help assess the etiologic role of norovirus in these deaths and identify groups at greater risk of severe disease outcomes who may be targets for interventions.

## METHODS

We performed a systematic literature review to identify publications reporting deaths associated with norovirus infection according to PRISMA guidelines. Searches for variations of the terms "norovirus" and "death," limited to humans, were performed in MEDLINE (US National Library of Medicine, Bethesda, MD) (see

Fig 1). We supplemented our search with articles from a previously published literature review on norovirus outbreaks.<sup>4</sup>

A reviewer screened all articles for deaths reported among symptomatic norovirus cases. All such deaths were included for abstraction, unless the article specifically stated that the death was due to an unrelated cause and norovirus did not contribute. A norovirus case was defined as an individual with diarrhea and/or vomiting whose stool either tested positive using reverse-transcription polymerase chain reaction, electron microscopy, or enzyme immunoassay or who was symptomatic in the context of a laboratory-confirmed norovirus outbreak ( $\geq 2$  positives).<sup>1</sup> For each norovirus death identified, we recorded demographic, clinical, and epidemiologic features. We calculated frequency distributions of these variables where possible.

## RESULTS

We identified 159 articles, of which 25 met study inclusion criteria (Fig 1) plus an additional 3 from the outbreak database,<sup>4</sup> yielding a total of 28 articles (Table 1). These articles included a total of 158 norovirus-associated deaths between 1988 and 2011 from 12 countries. Norovirus infection was established by epidemiologic linkage to a laboratory-confirmed outbreak in 149 cases (95%); virus was detected directly in 9 (5%) cases, and 56% and 32% of infections were acquired in long-term care facilities and from hospitals (80 and 45 of 142), respectively. Other locations included the individual's home (1), a retirement facility (1), and psychiatric institutions (4).

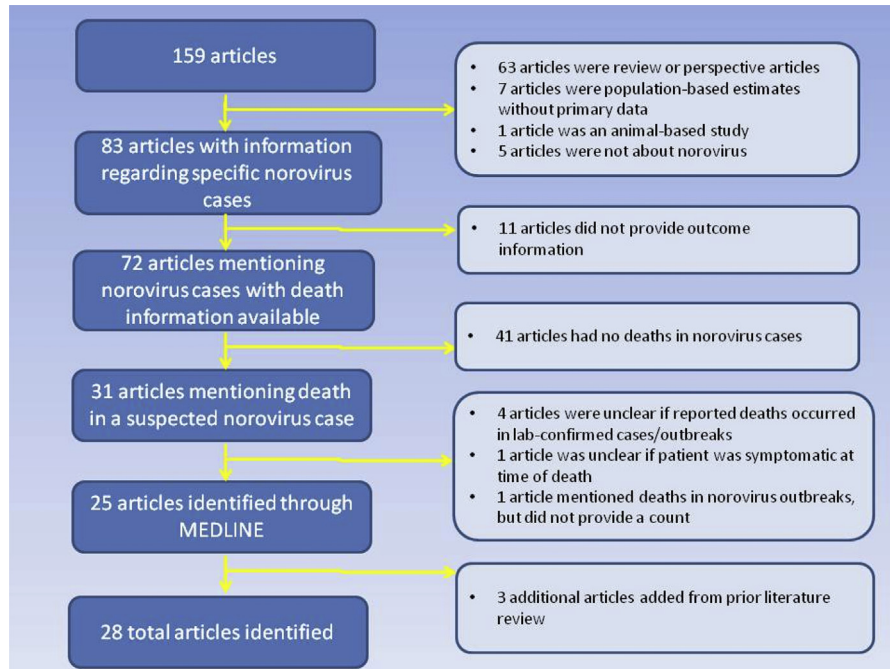
Twenty percent (31/158) of reports had individual-level clinical information (Table 2), with the rest only reporting outbreak-level data including setting, geographic location, and year (Table 3). Age at death

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Conflicts of interest: None to report.



**Fig 1.** Search results of systematic review: flow of included studies. MeSH terms were expanded, and Boolean operators were used to include all forms of “norovirus” and “death.” The following search string was used to generate the 159 articles screened in this study: “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 (deaths or death or mortality or died or fatal or fatality) NOT (animals or rabbits or cats).” Of the 159 articles, the language breakdown was as follows: English (141), French (4), Spanish (5), German (4), Polish (2), Dutch (1), Norwegian (1), and Mandarin (1).

was reported in 18 case-patients, with 4 deaths among children (<34 weeks to 2 years) and 14 deaths among adults (49 to 95 years), with most deaths among those 67 years or older (11/18, 61%).

Among the 31 norovirus deaths with individual-level data, the most commonly reported coprevalent conditions listed as the immediate cause of death were aspiration or pneumonia (n = 10,

**Table 1**  
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Table 2

Norovirus-associated deaths, 1988-2011: Immediate causes, settings, and underlying conditions

Immediate cause of death	Age	Location	Setting	Year of death	Underlying condition(s)	Ref*
Sepsis (n = 6)						
Sepsis	80	The Netherlands	Psychiatric institution	2008		1
Pneumococcal sepsis	85	The Netherlands	Psychiatric institution	2008		1
Septicemia	95	Japan	Long-term care facility	2005		2
<i>E coli</i> sepsis		Germany	Oncology unit: hospital	2010/2011	Acute myelogenous leukemia with treatment-induced neutropenia	3
<i>E coli</i> sepsis		Germany	Oncology unit: hospital	2010/2011	Allogeneic hematopoietic stem cell transplant	3
Septic shock	64	USA		2009	Hypogammaglobulinemia and chronic lymphocytic leukemia, treated with rituximab, vincristine, cyclophosphamide, and prednisone	4
Aspiration/pneumonia (n = 10)						
Aspiration pneumonia		Israel	Long-term care facility	2002		5
Aspiration pneumonia		Israel	Long-term care facility	2002		5
Aspiration pneumonia		Israel	Long-term care facility	2002		5
Aspiration pneumonia		Israel	Long-term care facility	2002		5
Aspiration pneumonia		Israel	Long-term care facility	2002		5
Severe aspiration w/ hypoxic brain damage		Germany	Oncology unit: hospital	2010/2011	BEAM chemotherapy before autologous hematopoietic stem cell transplant	3
Pneumonia	91	The Netherlands	Psychiatric institution	2008	Illeus, parastomal hernia	1
Suffocation from vomiting	82	Japan	Long-term care facility	2005		2
Aspiration of gastric content	1	Germany	Home	2004		6
Bilobar pneumonia	59	USA		2010	Hypogammaglobulinemia and chronic lymphocytic leukemia, treated with rituximab and corticosteroids	4
Gastrointestinal bleeding (n = 1)						
Acute GI bleed	90	Japan	Long-term care facility	2005		2
Cardiac complications (n = 3)						
Cardiac complication	81	Switzerland	Geriatric ward: hospital	2003	Unstable angina	7
Ischemic heart disease		Scotland, UK	Hotel	1993		8
Sinus bradycardia w/ severe hypotension	49	CA, USA	Hospital	1988/1989	Obesity, hypertension	9
Necrotizing enterocolitis (n = 2)						
Necrotizing enterocolitis	<34 wk <sup>†</sup>	PA, USA	Neonatal ICU: hospital	1998	Birth prematurity	10
Necrotizing enterocolitis	<34 wk <sup>†</sup>	PA, USA	Neonatal ICU: hospital	1998	Birth prematurity	10
Malnutrition (n = 2)						
Cachexia	93	The Netherlands	Psychiatric institution	2008	Acute diverticulitis, stroke	1
Malnutrition		England, UK	Hospital	2006	High-grade non-Hodgkin lymphoma treated with cyclosporine and prednisolone	11
Perforated colon (n = 1)						
Peritonitis/perforated colon		Finland	Hospital	2006/2007		12
Gastroenteritis (n = 6)						
	90	NC, USA	Long-term care facility	2006		13
Severe gastroenteritis	67	The Netherlands	Hospital	2005/2006	Churg-Strauss syndrome treated with dexamethasone and Mycophenolate Mofetil	14
"Poor health complicated by gastroenteritis"	2	The Netherlands	Hospital	2005/2006	Wiskott-Aldrich syndrome with allogeneic hematopoietic stem cell transplant	14
	84	Ireland	Geriatric ward: hospital	1993	Underlying carcinoma	15
		Australia	Long-term care facility	2002	"Chronic neurological condition"	16
		Switzerland	Long-term care facility	2002	"Severe underlying condition"	17

*E coli*, *Escherichia coli*; GI, gastrointestinal; ICU, intensive care unit.

\*References are listed in Table 1.

<sup>†</sup>Exact ages were not reported in the article.

**Table 3**  
Norovirus-associated deaths: Location, setting, and year

Number of deaths (n = 127)	State	Setting	Year of death	Reference
2	WI, USA	Long-term care facility	2006	13
9	Japan		2005	2
1	New Zealand	Rehabilitation: hospital	2000	18
5	MD, USA	Long-term care facility	1994	19
3	WA, USA	Long-term care facility	1996	20
12	USA	Long-term care facility	2002	21
8	Finland	Hospital	2006/2007	12
8	CA, USA	Long-term care facility	1988/1989	9
2	CA, USA	Retirement facility	1988	22
2	USA		2007	23*
1	USA		1999	24*
24	England/Wales	Hospital	1992–2000	25*
19	England/Wales	Long-term care facility	1992–2000	25*
20	OR, USA	Long-term care facility	1998–2002	26*
1	USA		2008	27*
10	England/Wales		1995/1996	28*

\*Six additional articles (references 23–28) reported surveillance data noting 64 additional norovirus-associated deaths with data presented in aggregate only.

32%), followed by gastroenteritis (n = 6, 19%), sepsis (n = 6, 19%), cardiac complications (n = 3, 10%), necrotizing enterocolitis (n = 2, 6%), malnutrition (n = 2, 6%), acute gastrointestinal bleeding (n = 1, 3%), and colon perforation (n = 1, 3%). Seventeen reported deaths specified an underlying condition among decedents, with chemotherapy (n = 7) and allogeneic hematopoietic stem cell transplantation (n = 3) the most common.

One previously healthy child, aged 1 year, was reported to have suddenly died from aspiration of gastric contents. Three other children (aged <34 weeks and 2 years, respectively) had an underlying condition: genetic disease causing immunodeficiency (1) or birth prematurity (2). The 2 premature infants died in the neonatal intensive care unit and were part of a larger cluster of 8 cases of necrotizing enterocolitis, all of whom had norovirus identified in stool samples.

## DISCUSSION

Norovirus infections associated with deaths were most commonly described among the elderly population and were acquired in health care facilities, and immunosuppression was frequently reported. Previous studies have also suggested norovirus as a potential cause of death in vulnerable populations. A review of nursing home outbreaks identified 16 norovirus-associated deaths between 1997 and 2007.<sup>5</sup> In our review of norovirus in all settings, many of the patients with a norovirus-related death had varying degrees of immunosuppression, which has been identified as a risk factor for chronic and severe infection.<sup>6</sup> Our review offers insights regarding patient-level information on causes and contributing factors, which cannot be gleaned from population-level estimates. For example, the age profile of severe disease contrasts with age-specific incidence in the community, where the elderly individuals have lower rates.<sup>7</sup>

Certain limitations must be considered. All of the published reports of deaths were in developed countries. Deaths in norovirus outbreaks occurring in these countries, specifically in health care settings, are more often investigated, laboratory confirmed, and reported than those in other settings. The profile of deaths in developing countries could be very different, mainly affecting infants through dehydration, for example. Additionally, the deaths in this study were norovirus-associated based on a report that the

symptoms of gastroenteritis were present at the time of death and may have contributed to this outcome. This does not demonstrate a causal link. The 158 norovirus-associated deaths reported over 23 years in this literature review are likely only a small fraction of the total number of norovirus-associated deaths. Indeed, an estimated 800 norovirus-associated deaths occur annually in the United States.<sup>8</sup> Diagnostic testing for norovirus has only recently become widely available, so it is not surprising that the data are limited.

This study offers a comprehensive description of the underlying conditions of decedents, immediate causes of death, or settings of deaths associated with norovirus infection, from what can be gleaned from the limited reports in the literature. Furthermore, immediate causes of death were plausible consequences of norovirus disease, and future studies could quantify the rates of these causes. Prospective studies gathering patient-level data are needed to demonstrate that norovirus infections are indeed causal—and not just incidental—to deaths. Future research should establish whether there is excess mortality in nursing homes or hospitals during outbreaks and directly estimate the overall mortality burden because of norovirus disease.

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