MAJOR ARTICLE

The Roles of *Clostridium difficile* and Norovirus Among Gastroenteritis-Associated Deaths in the United States, 1999–2007

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Background. Globally, gastroenteritis is recognized as an important contributor to mortality among children, but population-based data on gastroenteritis deaths among adults and the contributions of specific pathogens are limited. We aimed to describe trends in gastroenteritis deaths across all ages in the United States and specifically estimate the contributions of *Clostridium difficile* and norovirus.

Methods. Gastroenteritis-associated deaths in the United States during 1999–2007 were identified from the National Center for Health Statistics multiple-cause-of-death mortality data. All deaths in which the underlying cause or any of the contributing causes listed gastroenteritis were included. Time-series regression models were used to identify cause-unspecified gastroenteritis deaths that were probably due to specific causes; seasonality of model residuals was analyzed to estimate norovirus-associated deaths.

Results. Gastroenteritis mortality averaged 39/1 000 000 person-years (11 255 deaths per year) during the study period, increasing from 25/1 000 000 person-years in 1999–2000 to 57/1 000 000 person-years in 2006–2007 ($P < .001$). Adults aged ≥65 years accounted for 83% of gastroenteritis deaths (258/1 000 000 person-years). *C. difficile* mortality increased 5-fold from 10/1 000 000 person-years in 1999–2000 to 48/1 000 000 person-years in 2006–2007 ($P < .001$). Norovirus contributed to an estimated 797 deaths annually (3/1 000 000 person-years), with surges by up to 50% during epidemic seasons associated with emergent viral strains.

Conclusions. Gastroenteritis-associated mortality has more than doubled during the past decade, primarily affecting the elderly. *C. difficile* is the main contributor to gastroenteritis-associated deaths, largely accounting for the increasing trend, and norovirus is probably the second leading infectious cause. These findings can help guide appropriate clinical management strategies and vaccine development.

Despite recent progress, gastroenteritis remains a major cause of mortality worldwide, particularly in developing countries among children aged <5 years [1]. In contrast, the elderly account for the majority of gastroenteritis hospitalizations and deaths in the United States [2, 3]. However, the specific causes of severe gastroenteritis in US adult and elderly populations have been poorly characterized. In the last published description of gastroenteritis deaths in the United States during 1979–1987, nearly 90% of deaths lacked indication of a specific cause [2]. The majority of these deaths were recorded as presumed noninfectious, although their distinct winter seasonality suggested an infectious etiology.

In recent years, 2 pathogens have emerged and gained recognition as important causes of infectious gastroenteritis in US adults. The emergence and continued rise of *Clostridium difficile* as a leading cause of gastroenteritis hospitalizations and deaths, particularly in the elderly, has been documented [4–6]. Although the cause of this increase may be multifactorial, it is probably in large part due to the emergence and

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spread of a hypervirulent strain known variously as BI (based on restriction enzyme analysis), North American Pulsed Field type 1 (NAP1), or 027 (based on polymerase chain reaction ribotyping) [7–9]. This strain first emerged in Pittsburgh in 2000 and quickly spread throughout North America and Europe; although the current prevalence has declined in many parts of Europe [10], it remains as the predominant strain in at least some parts of North America [11]. With better availability of molecular assays, noroviruses are now known to be the leading cause of gastroenteritis outbreaks in the United States [12, 13]. Norovirus outbreaks are particularly frequent in elderly populations in nursing homes, and deaths during these outbreaks have occasionally been reported [13, 14]. However, lack of clinical diagnostic assays for norovirus has limited population-based data on endemic disease [15, 16].

Accurate understanding of the specific causes of severe gastroenteritis is critical to guide appropriate treatment and prevention strategies. *C. difficile* mortality was last examined in 2004 [5], and national data on recent trends are lacking. In addition, candidate vaccines against both *C. difficile* and norovirus are currently under development [17, 18]; thus, establishing the burden and causes of severe gastroenteritis resulting in mortality is vital to understand the potential health value of these vaccines. Our objective was to describe recent trends in gastroenteritis-associated deaths in the United States and determine the relative contribution of specific infectious agents. Because the majority of gastroenteritis deaths lack indication of a specific etiology, we relied on indirect methods to estimate the fraction of these deaths likely to be due to specific pathogens based on seasonal patterns [19, 20]. In preliminary analysis, it was apparent that *C. difficile* and norovirus were leading infectious causes of gastroenteritis-associated mortality and had emerged during the study period. Thus, our secondary objective was to develop improved mortality estimates for these 2 pathogens.

METHODS

Data Source

Gastroenteritis-associated deaths across all ages in the United States were identified from the National Center for Health Statistics (NCHS) multiple-cause-of-death mortality data for the years 1999–2007. All deaths in which gastroenteritis was listed as either the underlying cause or any of the contributing causes were included in the study. The specific codes used for this extraction were based on the *International Classification of Disease, 10th Revision* (ICD-10) and included cause-specified infectious gastroenteritis codes (bacterial, viral, and parasitic) and cause-unspecified gastroenteritis codes (Table1).

Statistical Analysis

Data were grouped into seasonal years from July through June; thus, 8 seasonal years from July 1999 through June 2007 were included in the analysis. Frequencies of demographic characteristics and place of death (ie, in or out of hospital) were calculated for all-cause gastroenteritis deaths. Gastroenteritis-associated death rates were calculated using NCHS Bridged Race population estimates for 1999–2007 [21, 22] and expressed as the number of deaths per 1 000 000 population. Changes in mortality rates over time, as well as differences by sex and race-ethnicity groups were assessed by using Poisson

Table 1. Coded Causes of Gastroenteritis-Associated Deaths in the United States, July 1999 Through June 2007

Cause	ICD-10 Code(s)	Total No. of Deaths (%)	Mean Annual No. of Deaths	Rate per 1 000 000[a]
Cause unspecified[b]		44 444 (49.4)	5556	19.1
Presumed infectious	A09	1163 (1.3)	145	0.5
Presumed noninfective	K52.9	39 310 (43.7)	4914	16.9
Other or unspecified viral	A08.3-A08.5	1325 (1.5)	166	0.6
Acute or unspecified vascular[c]	K55.0, K55.9	2815 (3.1)	352	1.2
Cause specified[b]		45 596 (50.6)	5700	19.6
Viral	A08.0-A08.2	85 (0.1)	11	0.04
Clostridium difficile	A04.7	43 517 (48.3)	5440	18.7
Other bacterial	A00.0-A04.6, A04.8-A05.9	1665 (1.8)	208	0.7
Parasitic	A06.0-A07.9	348 (0.4)	44	0.1
Total		90 040 (100)	11 255	38.8

Abbreviation: ICD-10, *International Classification of Diseases, 10th Revision*.

[a] Average annual mortality rate based on census estimates [21, 22].

[b] Multiple codes may be assigned to a given death; thus, the sum of deaths for each specific cause exceeds the subtotals for "cause unspecified" and "cause specified." However, if any cause-specified code was included in the record, the death was categorized as such.

[c] Vascular codes were included only for children aged <5 years, owing to an ICD-10 coding error (see Supplementary Modeling Methods) [42].

regression analysis after adjusting for age. Monthly mortality rates were annualized for comparison with annual rates.

ICD diagnostic codes for specific pathogens are known to underestimate mortality because they are typically used only when there is laboratory confirmation of a specific etiology. For *C. difficile*, ICD-9 clinical modification codes as used for hospital discharges perform reasonably in gauging the overall burden of laboratory-confirmed infections [23]. However, the most commonly used diagnostic assays for *C. difficile* have sensitivities that range from only 75% to 95% [24]. For norovirus, clinical diagnostic assays for sporadic illnesses are not widely available in the United States, so the norovirus-specific ICD-10 code is very rarely used (~4 deaths per year). We therefore adapted a previously developed indirect method to identify the proportion of cause-unspecified gastroenteritis deaths probably due to specific causes [3, 25]. Specifically, time-series regression models were developed to predict the number of cause-unspecified gastroenteritis deaths in a given month that could be attributed to a specific pathogen or pathogen group based on the number of deaths in that month coded to the specific pathogen or pathogen group (ie, *C. difficile*, other bacteria [excluding *C. difficile*], rotavirus, and parasites). Seasonality of model residuals was then analyzed to estimate the number of norovirus-associated deaths (see Supplementary Modeling Methods). Model estimates were summed with coded deaths to yield total pathogen-specific estimates. All analyses were performed by using SAS software, version 9.2 (SAS Institute).

RESULTS

During the 8-year study period from July 1999 to June 2007, a total of 90 040 deaths (annual average, 11 255 deaths) were recorded in the United States with gastroenteritis as either the underlying or a contributing cause (Table 1); in 45 281 (50%), gastroenteritis was specifically indicated as the underlying cause. Approximately half of the gastroenteritis-associated deaths were classified as cause unspecified. The overwhelming majority of the average annual cause-unspecified gastroenteritis deaths (n = 5556) were coded as presumed noninfective (88%), with relatively minor contributions of unspecified vascular (6%), unspecified viral (3%), or unspecified presumed infectious causes (3%). Among the 5700 average annual cause-specified gastroenteritis deaths, *C. difficile* was specifically coded for 5440 deaths (95%).

All-cause gastroenteritis mortality averaged 39/1 000 000 person-years during the 8-year study period. However, mortality more than doubled from 25/1 000 000 person-years in 1999–2000 to 57/1 000 000 person-years in 2006–2007 ($P < .001$), driven primarily by a sharp rise in *C. difficile* coded deaths (Figure 1). Although most cause-unspecified

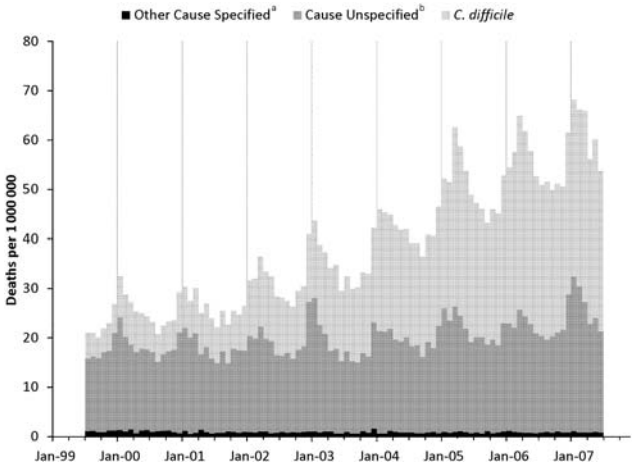

Figure 1. Cumulative annualized gastroenteritis mortality rates by *International Classification of Diseases, 10th Revision* (ICD-10) code and month, United States, July 1999–June 2007. *A,* Codes include specified viral (A08.0–A08.2), non–*Clostridium difficile* bacterial (A00.0–A04.6, A04.8–A05.9), and parasitic (A06.0–A07.9). *B,* Codes include presumed infectious (A09), presumed noninfective (K52.9), other or unspecified viral (A08.3–A08.5), and for children aged <5 years only, acute or unspecified vascular (K55.0, K55.9).

gastroenteritis deaths were coded as presumed noninfective, these deaths exhibited clear seasonality with consistent winter peaks.

Older adults (aged ≥65 years) accounted for 83% of gastroenteritis deaths, and rates increased with age from 86 to 295 to 832 per 1 000 000 person-years among those aged 65–74, 75–84, and ≥85 years, respectively. Most gastroenteritis deaths occurred in hospitals (73%); 14% occurred in long-term care facilities, 6% occurred in hospice, and 5% occurred at home. Significantly elevated gastroenteritis mortality rates were observed among women compared with men (46/1 000 000 person-years vs 32/1 000 000 person-years, respectively; $P < .001$) and among non-Hispanic whites compared with all other race-ethnicity groups combined (48/1 000 000 vs 19/1 000 000 person-years, respectively; $P < .001$).

On the basis of the final regression model (see Supplementary Modeling Results), *C. difficile* contributed to an estimated 7903 deaths per year (27/1 000 000 person-years), of which 5440 (69%) were specifically coded as such and an additional 2463 (31%) were estimated from deaths coded as cause unspecified (Table 2). During the 8-year study period, *C. difficile* mortality increased 5-fold from 10/1 000 000 person-years (2675 deaths per year) in 1999–2000 to 48/1 000 000 person-years (14 368 deaths per year) in 2006–2007 ($P < .001$). *C. difficile* mortality rates at the end of the study period were 0.2/1 000 000 person-years, 6/1 000 000 person-years, and 341/1 000 000 person-years for persons aged <5, 5–64, and ≥65 years, respectively.

Table 2. Estimated Annual Deaths and Mortality Rates Associated With Norovirus and *Clostridium Difficile* by Age Group, United States, July 1999 Through June 2007

	All-Cause Gastroenteritis		Norovirus			*Clostridium difficile*				
						No. of Deaths				
Age Group, y	No. of Deaths	Rate per 1 000 000[a]	No. of Deaths (95% CI)[b]	% of All-Cause Gastroenteritis	Rate per 1 000 000[a] (%)	Coded	Modeled (95% CI)[c]	Total	% of All-Cause Gastroenteritis	Rate per 1 000 000[a]
0–4	599	30	27 (19–35)	4.5	1.3	6	0 (NA)	6	1.0	0.30
5–64	1347	5.7	52 (41–66)	3.9	0.22	499	355 (232–478)	854	63.4	3.6
≥65	9310	258	718 (611–824)	7.7	20	4934	2108 (1818–2399)	7043	75.6	195
Overall	11 255	39	797 (671–924)	7.1	2.7	5440	2463 (2050–2876)	7903	70.2	27.2

Abbreviations:CI, confidence interval; NA, not applicable.

[a] Average annual mortality rate per 1 000 000 person-years based on census estimates [21, 22].

[b] Includes both coded (~4/y) and predicted deaths estimated through time series regression model; 95% CIs are based on uncertainty of overall model fit and applied to total norovirus death estimate because 99% of deaths were predicted (see Supplementary Materials).

[c] 95% CIs are based on uncertainty of model predicted *C. difficile* coefficient (β_1); β_1 was not significant in the 0–4-year age group, so only coded deaths were included for this group (see Supplementary Materials).

Analysis of model residuals yielded temporal patterns highly consistent with norovirus, both with respect to seasonality and annual variations (Supplementary Figure S1). A strong winter seasonality was observed among the norovirus-associated deaths, with nearly half (48%) occurring during December–February (Figure 2). Although less pronounced and distinct from that of norovirus, *C. difficile*–associated deaths also demonstrated seasonality, with slightly elevated rates during March–May (ie, 30% of annual deaths occur during these months). Long-term trends for norovirus-associated deaths, available only for persons aged ≥65 years, also revealed periodic increases in seasonal norovirus activity (Figure 3). Relative to the average norovirus mortality rate among persons aged ≥65 years during nonepidemic years (17/1 000 000 person-years), norovirus mortality rates surged during epidemic years by 55% in 2002–2003 (29/1 000 000 person-years; $P < .001$) and by 35% in 2006–2007 (26/1 000 000 person-years; $P < .001$).

Overall, norovirus was estimated to contribute to an average of 797 deaths per year (2.7/1 000 000 person-years), representing 7% of all-cause gastroenteritis deaths (Table 2). Norovirus was estimated to contribute to more deaths annually than the combined total of coded and modeled deaths attributed to all other pathogens, aside from *C. difficile*. Persons aged ≥65 years had the highest norovirus mortality rate (20/1 000 000 person-years)

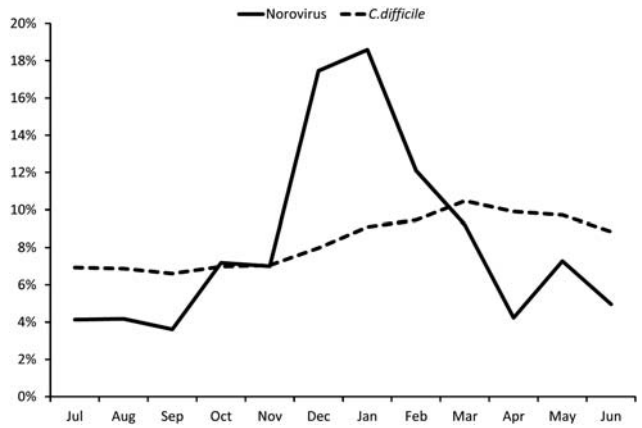

Figure 2. Percentage of average annual deaths associated with *Clostridium difficile* and norovirus by month, United States, July 1999 through June 2007.

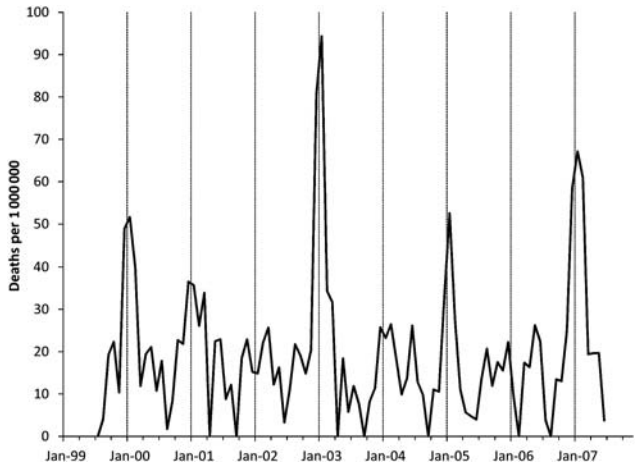

Figure 3. Annualized norovirus mortality rate by month among persons aged ≥65 years, United States, July 1999 through June 2007. Surges during 2002–2003 and 2006–2007 were contemporaneous with emergence of novel genogroup II type 4 (GII.4) norovirus strains [44].

and accounted for 90% of all norovirus deaths. Children aged 1–4 years had the next highest norovirus mortality rate (1.3/1 000 000), equating to an estimated 27 deaths per year.

DISCUSSION

Although most global attention to gastroenteritis deaths focuses on children, this study demonstrates that in the United States the overwhelming majority of deaths associated with gastroenteritis continue to occur in the elderly. Furthermore, a marked increase in all-cause gastroenteritis deaths has occurred during the last decade, owing largely to a rise in *C. difficile*–associated deaths [5, 6]. Although *C. difficile* is associated with nearly two-thirds of all gastroenteritis deaths, we demonstrate for the first time that norovirus is probably the second leading infectious cause of gastroenteritis deaths across all age groups. Deaths associated with these 2 pathogens exhibit distinct seasonal and long-term temporal patterns, with a consistent secular increase in *C. difficile*–associated deaths and periodic increases in norovirus-associated deaths during known norovirus epidemic years. These findings can help inform clinical management of severe acute gastroenteritis and guide the development of optimal prevention and control strategies.

C. difficile infection (CDI) was historically thought to be an uncommon cause of death with overall low rates of disease [4] and an attributable mortality ranging from as low as 0% to 1.5% [26, 27]. This epidemiology, however, has undergone marked change in the past 10 years with increasing overall rates of disease [4–6] and recent estimates of attributable mortality of 5% or more in nonoutbreak settings [23, 28] and ≥15% in some outbreaks [29]. It can be difficult to distinguish between patients who die with CDI (ie, death due to other causes) and those whose death is solely or largely attributable to *C. difficile*; comparison of death certificates to case review by senior clinicians suggests that death certificates generally overestimate the role of *C. difficile* in contributing to deaths [30]. However, another carefully controlled study found that excess mortality may extend out to 180 days after infection, suggesting that even expert reviewers may underestimate the role of CDI in patient deaths [31]. Regardless, the number of *C. difficile*–coded death certificates correlate with hospital discharges coded for *C. difficile* across states and over time (Centers for Disease Control and Prevention, unpublished data), further supporting *C. difficile*–coded death certificates as an important vital statistic of population health.

One possible explanation for the observed increase in both hospitalizations and deaths related to CDI is increased intensity of testing [32]. However, there were clear increases in both hospitalizations [4] and deaths related to CDI from 2000 to 2004 that preceded any general awareness of a new *C. difficile* strain or CDI as an emerging public health concern. Another possible cause could be a shift toward more sensitive diagnostics, such as nucleic acid amplification testing [33]; however, as of 2008, >90% of US hospital laboratories were still using toxin enzyme immunoassays [34].

The primary cause of both increased rates of CDI and the CDI-related deaths reflected here is more likely the emergence of the BI/NAP1/027 strain with increased virulence and resistance to the fluoroquinolone antibiotics [7–9]. Although the fluoroquinolone antibiotics are not used to treat CDI, they are widely used in healthcare facilities and in older patients who are at baseline increased CDI risk. It is likely that increased fluoroquinolone resistance has provided BI/NAP1/027 with a selective advantage over other competing strains that led to its initial rapid spread in North America and Europe [9, 11]. The precise cause of hypervirulence in this strain remains controversial but may include such factors as increased toxin A and/or B production [7], production of an additional toxin known as binary toxin [8, 35] or polymorphisms in the binding domain of toxin B [36]. Increased sporulation of BI/NAP1/027 has also been suggested as another possible cause for hypervirulence [37]; however, more in-depth analyses have called these findings into question [38]. Recent whole-genome comparative analysis has demonstrated a number of genetic rearrangements that BI/NAP1/027 has undergone during the past 20 years [39], offering further clues to this specific strain's hypervirulence and providing evidence that *C. difficile* has a fluid genome that can quickly adapt to new environmental changes and human interventions.

Previous descriptions of norovirus mortality in the United States have been primarily limited to outbreak investigations or case reports [14], and this study provides the first US population-based estimates of norovirus mortality. Prior estimates of norovirus-associated deaths in the United States were based on extrapolation from etiologic studies in other industrialized countries [40, 41]. The most recent of these studies reported a norovirus mortality rate of 1.7/1 000 000 population or 571 deaths annually [41], which is approximately 40% lower than the estimated norovirus mortality in our study (2.7/1 000 000 population or 797 deaths annually). An advantage of our approach is the capture of temporal variations over an extended time period and a breakdown into specific age groups. Although the majority of norovirus-associated deaths occur among the elderly, an estimated 27 norovirus-associated deaths occur each year in children aged <5 years, which is comparable to the estimated 20–40 annual rotavirus-associated deaths in this age group before the introduction of rotavirus vaccine in 2006 [42, 43]. Although our norovirus mortality estimates are based on indirect methods, we identified a strong seasonal pattern in norovirus-associated deaths, peaking during December–February, consistent with the seasonality of norovirus outbreaks and sporadic norovirus disease in the

United States reported previously [13, 16, 20]. We also noted a surge of up to 50% during 2002–2003 and 2006–2007, which have been documented as epidemic seasons associated with the emergence of new norovirus strains within genogroup II type 4 (GII.4) that were associated with increases in norovirus outbreaks and hospitalizations, particularly among the elderly [3, 14, 44].

Some limitations of our methods to estimate norovirus mortality should be considered. A key assumption is that any residual seasonality not otherwise accounted for by other pathogens included in the model is attributable to norovirus. This may overestimate norovirus mortality as other viral pathogens not included in the model, particularly astrovirus and sapovirus, have demonstrated winter seasonality in temperate climates and may indeed contribute to gastroenteritis-associated deaths [16, 45, 46]. However, as an added conservative measure among persons aged <65 years, only excess seasonality above the average monthly estimates during the 8-year period was attributed to norovirus. Thus, some residual seasonality in children and young adults, the age groups most affected by other viral gastroenteritis agents [47–49] remained unattributed to norovirus, although norovirus or other viruses with similar seasonality could have been associated with some of these deaths. Additionally, the seasonality observed among deaths in which gastroenteritis was simply contributory may be due, in part, to the overall seasonality of deaths in the United States or indirect causes of gastroenteritis that exhibit winter surges, such antibiotic use for respiratory infections. However, because a similar seasonal pattern was observed among deaths in which gastroenteritis was the underlying cause (Supplementary Figure S2E), this probably did not significantly bias our estimates.

On the other hand, the seasonal residual method may underestimate norovirus mortality because it captures only norovirus-associated deaths that are seasonal and further assumes that there are no norovirus-associated deaths in 1 month out of every seasonal year. Despite their winter seasonality, norovirus illness and outbreaks are known to occur year-round [13, 16]. Notably, approximately one-third of cause-unspecified gastroenteritis deaths were not attributed to any pathogen in our final model (Supplementary Figure S2*A*), some of which may well have been caused by norovirus. Modeling methods similar to ours have been used recently to estimate norovirus hospitalizations in the United States [3], as well as norovirus-associated mortality in the elderly in the United Kingdom [25] and the Netherlands [50]. Our reported US norovirus-associated mortality rate in the elderly (20/1 000 000 person-years) is on the same order of magnitude as that in the United Kingdom (9/1 000 000 person-years) and the Netherlands (4/1 000 000 person-years) [25, 50]. Consistent with these European studies and prior estimates of norovirus-associated deaths in the United States [25, 41, 50], both contributory and underlying gastroenteritis deaths were included in our analyses to account for variability in death certificate coding practices and to capture the full range of gastroenteritis-associated mortality.

Although *C. difficile* has become recognized as a leading cause of gastroenteritis hospitalizations and deaths, norovirus remains a largely underappreciated cause of such severe disease outcomes. Although such outcomes of norovirus infection are indeed relatively rare [47, 51], the high incidence of norovirus disease in the community [15, 16] still yields a significant burden of severe disease and death attributable to norovirus. The mortality estimates highlighted by this study underscore the need for effective measures to prevent, accurately diagnose, and appropriately manage gastroenteritis associated with these 2 pathogens, especially in the elderly. Although judicious use of antibiotics is one key to the prevention of *C. difficile*–associated disease, perhaps equally as important and effective against a wide range of gastroenteritis pathogens are proper infection control measures, such as appropriate hand hygiene, environmental disinfection, and isolation of ill patients. Nonetheless, targeted interventions may ultimately be necessary to make significant progress in reducing the burden of severe gastroenteritis and death. To that end, these data identify important target populations for future vaccines and establish a baseline burden estimate with which the impact of future vaccine interventions may be compared.

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

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