MAJOR ARTICLE

# Burden of Norovirus Gastroenteritis in the Ambulatory Setting—United States, 2001–2009

**Paul A. Gastañaduy,[1,2] Aron J. Hall,[2] Aaron T. Curns,[2] Umesh D. Parashar,[2] and Benjamin A. Lopman[2]**

[1]Epidemic Intelligence Service; and [2]Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

***Background.*** Gastroenteritis remains an important cause of morbidity in the United States. The burden of norovirus gastroenteritis in ambulatory US patients is not well understood.

***Methods.*** Cause-specified and cause-unspecified gastroenteritis emergency department (ED) and outpatient visits during July 2001–June 2009 were extracted from MarketScan insurance claim databases. By using cause-specified encounters, time-series regression models were fitted to predict the number of unspecified gastroenteritis visits due to specific pathogens other than norovirus. Model residuals were used to estimate norovirus visits. MarketScan rates were extrapolated to the US population to estimate national ambulatory visits.

***Results.*** During 2001–2009, the estimated annual mean rates of norovirus-associated ED and outpatient visits were 14 and 57 cases per 10 000 persons, respectively, across all ages. Rates for ages 0–4, 5–17, 18–64, and ≥65 years were 38, 10, 12, and 15 ED visits per 10 000 persons, respectively, and 233, 85, 35, and 54 outpatient visits per 10 000 persons, respectively. Norovirus was estimated to cause 13% of all gastroenteritis-associated ambulatory visits, with ~50% of such visits occurring during November–February. Nationally, norovirus contributed to approximately 400 000 ED visits and 1.7 million office visits annually, resulting in \$284 million in healthcare charges.

***Conclusions.*** Norovirus is a substantial cause of gastroenteritis in the ambulatory setting.

***Keywords.*** norovirus; gastroenteritis; ambulatory care; United States.

Noroviruses are the leading cause of acute gastroenteritis (ie, diarrhea or vomiting) worldwide. The advent of molecular assays have shown that noroviruses are the leading cause of foodborne disease [1], are responsible for approximately half of all gastroenteritis outbreaks [2], and are the leading cause of sporadic gastroenteritis across all ages [3, 4].

In the United States, noroviruses are estimated to cause 21 million episodes of gastroenteritis every year [1] and are increasingly recognized as a cause of severe disease, leading to an estimated 71 000 hospitalizations [5] and 800 deaths annually [6]. However, the absence of sensitive diagnostic tests in clinical settings has precluded a comprehensive description of the US norovirus disease burden. Notably, the contribution of norovirus to gastroenteritis in the ambulatory setting is sparsely characterized. The few studies estimating the incidence of norovirus-associated outpatient visits across all ages in Europe and the United States have yielded rates of 40–640 cases per 10 000 persons [3, 7–9].

An improved understanding of the role of norovirus among healthcare encounters for gastroenteritis has important implications for the practice and development of preventive strategies (eg, infection control measures and vaccines) and could help guide clinical management (eg, antibiotics vs rehydration therapy). Our objective was to assess the contribution of norovirus to gastroenteritis-associated ambulatory visits in the United States, including both ED and outpatient visits, across all ages and to provide estimates of the national burden.

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Correspondence: Paul A. Gastañaduy, MD, MPH, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, MS A-34, Atlanta, GA 30333 (pgastanaduy@cdc.gov)

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**Table 1. Pathogen Categories and Diagnostic Codes Used to Identify Gastroenteritis-Associated Ambulatory Visits, by Setting, MarketScan Commercial Claims and Encounters Database, United States, July 2001–June 2009**

| | | ED Visits | | Outpatient Visits | |
|---|---|---|---|---|---|
| Cause | ICD-9-CM Code(s) | Annual Mean No. (%) | Visits per 10 000 Persons | Annual Mean No. (%) | Visits per 10 000 Persons |
| Cause unspecified[a] | 009.0–009.3, 558.9, 787.91, 008.8 | 144 070 (94.6) | 65.5 | 988 302 (96.6) | 449.1 |
| Cause specified | | | | | |
| Rotavirus | 008.61 | 924 (0.6) | 0.4 | 1851 (0.2) | 0.8 |
| *C. difficile* | 008.45 | 4210 (2.8) | 1.9 | 19 652 (1.9) | 8.9 |
| Other bacterial[b] | 001.0–00.9, 002.0–002.9, 003.0–003.9, 004.0–004.9, 005.0–005.9, 008.0–008.5 | 2842 (1.9) | 1.3 | 11 155 (1.1) | 5.1 |
| Parasitic | 006.0–006.2, 006.8–006.9, 007.0–007.9 | 173 (0.1) | 0.1 | 2638 (0.3) | 1.2 |
| All-cause gastroenteritis | … | 152 219 | 69.2 | 1 023 597 | 465.1 |

Abbreviations: *C. difficile*, *Clostridium difficile*; ED, emergency department; ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*.

[a] Excluding records with a specific cause in a subsequent diagnostic position

[b] Excluding *C. difficile* (008.45).

## METHODS

### Data Source

The MarketScan Commercial Claims and Encounters database was used for this analysis. MarketScan data are derived from insurance claims, contain deidentified individual-level information from various public and private health plans, and, as of 2008, included approximately 30 million enrollees from all 50 US states [10]. Medicaid and uninsured populations are not included. No informed consent was required for our analysis. The database is coded on the basis of the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). By using ICD-9-CM codes, gastroenteritis-associated healthcare encounters from July 2001 through June 2009 were extracted and grouped into either cause-unspecified or cause-specified visits. Cause-unspecified visits included encounters coded as presumed infectious, presumed noninfectious, and unclassified viral diarrhea. Cause-specified visits were further grouped into 4 pathogen-based categories: rotavirus, *Clostridium difficile*, other bacterial, and parasitic coded visits (Table 1). We used records with codes in 1 of 2 diagnostic positions (primary or secondary). We defined an outpatient visit as an encounter with primary care providers and ambulatory care clinics within hospitals. An ED visit was defined as an encounter in which "urgent care facility" or "emergency room" was further specified in the record.

### Statistical Methods

Our main goal was to estimate the proportion of cause-unspecified gastroenteritis visits, that were due to norovirus. Because norovirus disease is rarely laboratory confirmed during ambulatory care and, consequently, because an ICD code for norovirus is rarely applied, we used a previously developed indirect statistical approach for this purpose [5, 6, 11–13]. First, we estimated the monthly number of unspecified visits due to pathogens other than norovirus. We assumed that, among the unspecified visits, the number due to a specified pathogen or pathogen group in a given month was proportional to and could be based on the number of visits actually coded as the specific pathogen for that month. By using time-series regression models that assumed a Poisson distribution, the monthly number of unspecified encounters was modeled as a function of cause-specified visits for the corresponding months and for each of the 4 pathogen categories simultaneously. Each age group (0–4, 5–17, 18–64, and ≥65 years) was modeled separately. To avoid attribution of background (aseasonal) or secular trends to norovirus, terms for these were included in the model. The model can be expressed by the following formula:

$$E(\mathrm{CU}_{x,y}) = \alpha + (\beta_1 \times \mathrm{Rota}_y) + (\beta_2 \times \mathrm{Bact}_{x,y}) + (\beta_3 \times \mathrm{CDiff}_{x,y}) + (\beta_4 \times \mathrm{Para}_{x,y}) + (\gamma \times \mathrm{Time}_y),$$

where CU, Rota, Bact, CDiff, and Para are the counts of cause-unspecified, rotavirus, bacterial, *C. difficile*, and parasite-associated visits, respectively, in age group $x$ and year-month $y$; α (or the intercept) represents the number of background visits that are not explained by an infection due to one of the specified pathogens categories; secular trends were controlled by including a sequential variable for month of study (Time); and β and $\gamma$ coefficients represent the relative contribution of each pathogen and of secular time trends to unspecified visits, respectively. Poisson models were fitted using Huber robust standard errors to account for overdispersion.

The number of ambulatory visits per month that were predicted to be due to a specific pathogen or pathogen group was estimated by multiplying the monthly number of visits coded as the specific pathogen by the corresponding coefficient from the regression model. Unspecified visits attributed to specific pathogens, background, and secular trends were then subtracted from the unspecified visits. What remained unexplained (ie, the model residuals) demonstrated wintertime seasonality and differing intensity from year to year, consistent with norovirus epidemiology. From the residuals, we estimated norovirus visits as the difference between the residual in a given month and the minimum residual for that seasonal year (from July through June). This estimate assumed that any remaining seasonality not explained by the model is due to norovirus and that there is 1 month each seasonal year with 0 norovirus-associated visits. Supplementary Figure S1 illustrates a deconstruction of cause-unspecified visits into pathogen groups on the basis of each age group-specific model. Model parameter estimates, by age group and setting, are shown in Supplementary Table S1.

Total rotavirus-associated visits were calculated by adding the number of cause-unspecified visits estimated from the model to be due to rotavirus to the encounters specifically coded as rotavirus for each corresponding month. This analysis was restricted to 2001–2006, to estimate the rotavirus disease burden in the prevaccine era. All analyses were performed using SAS, version 9.2.

### Population Data, Rate Calculations, and National Estimates

Rates of norovirus-associated ambulatory visits were expressed as the number of visits per 10 000 persons, using the age-specific populations enrolled per year in MarketScan insurance plans. Data were grouped by season, from 2001/2002 through 2008/2009, to reflect the winter seasonality of norovirus-associated ambulatory visits. By extrapolating rates of norovirus-associated ambulatory visits to the average US population during 2001–2009 [14], we estimated the national annual burden of norovirus gastroenteritis in both the ED and clinic settings for each age group. To estimate uncertainty around ambulatory visits associated with norovirus, we used the upper and lower bounds of the 95% confidence intervals (CIs) of the predictions of the fitted model. Our regression model assumed that testing and coding practices did not change over time. However, given the introduction of the rotavirus vaccine in 2006, it is possible that there was decreased testing for rotavirus over time, which could lead to an overestimate of norovirus-associated encounters. To investigate this association, we added an interaction term for rotavirus and time variables for children aged <5 years. This term was excluded from the final analysis because it was not found to be a significant predictor of unspecified visits for this age group.

### Economic Analysis

To estimate the total healthcare charges for norovirus-associated ambulatory visits, we calculated the annual median of total charges for all gastroenteritis encounters recorded in MarketScan databases and the average of these values over the 8-year study period. Charges for each age group and setting were calculated separately. National charges were obtained by multiplying the number of estimated norovirus-associated visits by the average charge of the visit. To estimate rotavirus-associated charges, only encounters in which rotavirus was specified as the cause were used. All charges were expressed in 2009 US dollars, using the Bureau of Labor Statistics Consumer Price Index for medical care to adjust for inflation [15].

## RESULTS

Among patients included in MarketScan over an 8-year period (seasonal years 2001/2002 through 2008/2009), all-cause gastroenteritis caused an average of 152 219 ED visits (69 per 10 000 persons) and 1 023 597 outpatient visits (465 per 10 000 persons) annually (Table 1). Of these, an annual mean of 144 070 ED visits (66 per 10 000 persons) and 988 302 outpatient visits (450 per 10 000 persons) were coded as cause unspecified, representing 95% and 97% of all-cause gastroenteritis visits, respectively. Cause-unspecified visits demonstrated clear seasonality across all age groups. A regular peak in March was evident each year for children aged <5 years, consistent with the seasonal pattern of rotavirus-associated visits; older age groups had earlier peaks, occurring in January in some years, but March peaks remained in all age groups (Supplementary Figure S1A–D).

In the regression models, both rotavirus and *C. difficile* were associated with cause-unspecified gastroenteritis in all age groups ($P < .001$, by the Wald test, for all results). In contrast, bacterial pathogens and parasites were associated with cause-unspecified gastroenteritis only for certain age groups and depending on the setting (Supplementary Figure S1A–D and Supplementary Table S1). Taken collectively, the predicted pathogens and pathogen groups did not account entirely for the early wintertime increase in healthcare encounters (Supplementary Figure S1A–D). Forty-nine percent of cause-unspecified gastroenteritis visits were attributed to a pathogen across all age groups, with 58%, 30%, 47%, and 67% of visits attributed to a pathogen among individuals aged 0–4, 5–17, 18–64, and ≥65 years, respectively.

Model residuals exhibited year-to-year variability and early wintertime seasonality consistent with norovirus epidemiology. In all age groups, norovirus-associated visits peaked in December or January in most years. Mean monthly rates reached 41 visits per 10 000 persons in December and 183 visits per 10 000 persons in January for the ED and outpatient settings, respectively (Figure 1*A* and 1*B*). On average, 58% of all ED

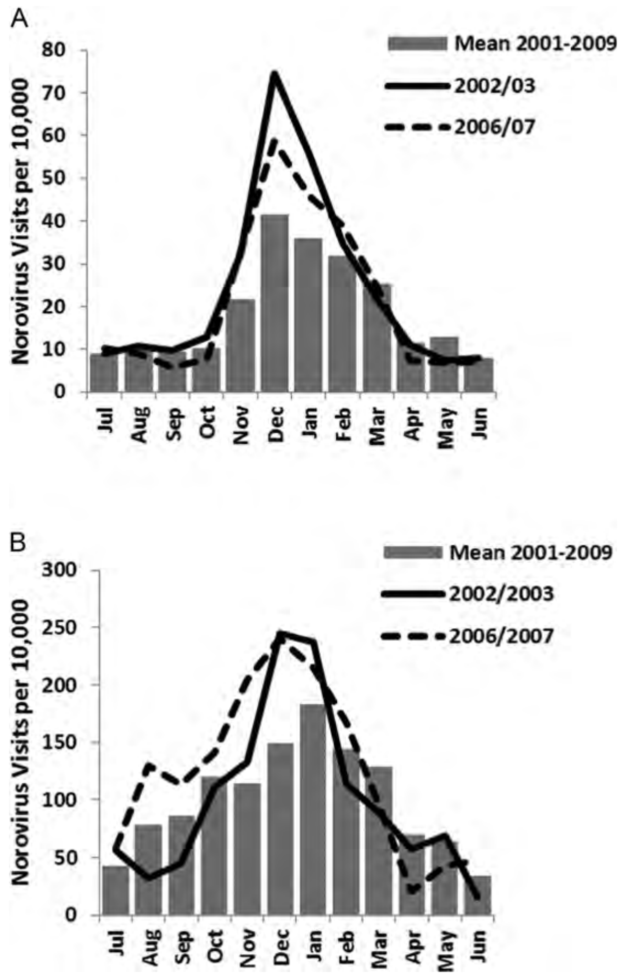


**Figure 1.** Mean monthly rate of norovirus-associated emergency department visits (*A*) and outpatient visits (*B*) across all ages, MarketScan Commercial Claims and Encounters Database, United States, July 2001–June 2009. On average, 58% of all emergency department visits and 49% of all outpatient visits attributed to norovirus occur from November to February. Rate peaks were 41 ED visits and 183 outpatient visits per 10 000 persons in December and January, respectively. Rates were higher for seasonal years 2002/2003 and 2006/2007, consistent with the emergence of new genogroup II type 4 strains, reaching 75 ED visits and 245 outpatient visits per 10 000 in 2002/2003.

visits and 49% of all outpatient visits attributed to norovirus throughout the year occurred from November to February.

The average annual rates of norovirus-associated ED and outpatient visits were 14 and 57 cases per 10 000 persons, respectively. In accordance with known norovirus epidemics associated with the emergence of new strains, annual rates were elevated during seasonal years 2002/2003 and 2006/2007, surging to 24 ED visits per 10 000 in 2002/2003 and increasing to 80 outpatient visits per 10 000 in 2006/2007 (Figure 2*A* and 2*B*).

By extrapolating MarketScan rates to the US population, we estimated that norovirus contributed to 400 000 ED visits and 1 700 000 outpatient visits per year in the United States, or approximately 2 100 000 total annual ambulatory visits (Table 2). These estimates represented 18% and 12% of all-cause gastroenteritis visits in the ED and outpatient settings, respectively. The highest rates of norovirus-associated ambulatory visits were observed among children aged <5 years, among whom an estimated 78 000 ED visits and 475 000 outpatient visits occurred annually.

From seasonal years 2001/2002 through 2005/2006, an estimated 211 000 ED visits and 1 078 000 outpatient visits associated with rotavirus occurred annually across all ages, including 122 000 ED visits and 540 000 outpatient visits among children aged <5 years (Supplementary Table S2). Across all age groups, rotavirus caused 12% and 9% of all-cause gastroenteritis visits in the ED and outpatient settings, respectively (Supplementary Table S2). Among all age groups other than children <5 years old, rates of ambulatory visits were higher for norovirus as compared to rotavirus.

On average, norovirus-associated ED and outpatient visits resulted in $140 and $144 million annually in healthcare charges, respectively. In comparison, corresponding ED and outpatient visits due to rotavirus resulted in $99 and $110 million annual healthcare charges (Table 2 and Supplementary Table S2).

## DISCUSSION

This analysis provides the first US estimates of ambulatory medical visits attributable to norovirus across all age groups, highlighting the substantial norovirus-associated burden in these settings. Nationally, we estimated that norovirus led to approximately 400 000 ED visits and 1.7 million office visits annually across all ages. These norovirus-associated visits exhibited winter seasonality, peaking in December and January, with >50% of all ED and outpatient visits attributed to norovirus occurring during November–February. Norovirus visits surged during epidemic years associated with the emergence of new strains; 2002/2003 was the peak year for ED visits, and 2006/2007 was the peak year for outpatient visits. Norovirus-associated encounters involved individuals of all ages; however, consistent with previous studies, the incidence of ambulatory healthcare encounters was substantially higher for children aged <5 years [8, 9]. The estimated burden of ambulatory visits due to norovirus exceeded that for rotavirus, which caused an estimated 211 000 ED and 1.1 million outpatient visits across all ages. These ambulatory disease burden estimates equate to $284 million per year in healthcare charges for norovirus, compared with nearly $209 million per year for rotavirus.

Our estimates are highly consistent with what is known about norovirus epidemiology, which provides reassurance about the validity of our indirect methods. First, model

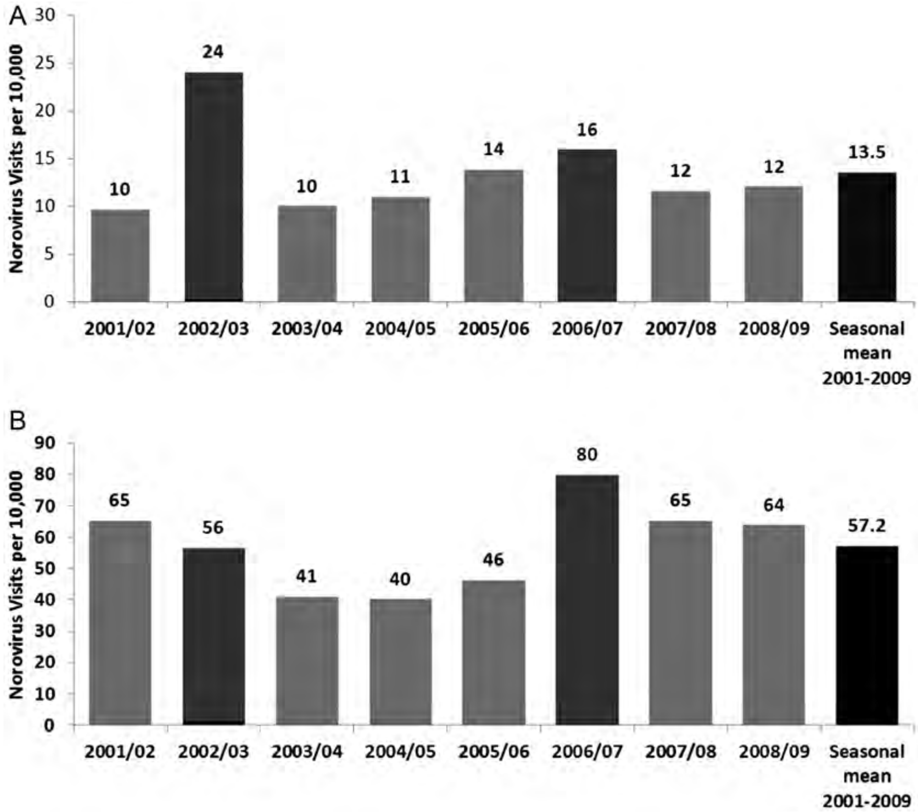


**Figure 2.** Mean annual rate of norovirus-associated emergency department visits (*A*) and outpatient visits (*B*) per 10 000 persons across all ages, MarketScan Commercial Claims and Encounters Database, United States, July 2001–June 2009. Rates were elevated during seasonal years 2002/2003 and 2006/2007, consistent with the emergence of new genogroup II type 4 strains.

residuals attributed to norovirus peaked in early winter, consistent with previously reported temporal patterns in the United States, including both norovirus outbreaks [16, 17] and endemic disease leading to ED visits [18] and outpatient visits [3]. Second, we noted heightened activity during known norovirus epidemic years of 2002/2003 and 2006/2007, which were associated with the emergence of new genogroup 2, type 4 (GII.4) variants. These epidemic seasons have been well documented both in the United States and internationally [18–23]. Third, the overall proportion of gastroenteritis visits that we attributed to norovirus was similar to that of previous studies. Although norovirus prevalence estimates in the United States are sparse, a recent study involving direct laboratory testing of outpatient visits in Georgia estimated that norovirus was responsible for 12% of outpatient visits, equal to our estimate of 12%. Similarly, a recent systematic review of 13 studies, most of which were conducted in industrialized countries, attributed a pooled proportion of 12% (95% CI, 9%–15%) of child and adult outpatient gastroenteritis visits to norovirus [24]. Finally, a prospective study of infectious intestinal disease–associated visits to general practitioners in England also showed a norovirus detection rate of 12% (95% CI, 10%–15%) [4]. Studies of the norovirus prevalence in EDs are scarcer. Our estimate of 17% among adults is lower than that from a recent US study, which reported a norovirus prevalence of 26% across multiple sites through direct laboratory testing [25]. Fourth, and perhaps most reassuring, is our outpatient incidence rate estimate of 57 visits per 10 000 persons, which is comparable to estimates from previous studies that used direct molecular testing for norovirus. These studies showed incidence rates of 64, 54, and 63 visits per 10 000 persons in Georgia, England, and Germany, respectively [3, 8, 9]. A similar study in the Netherlands noted a much lower incidence (4 visits per 10 000 persons) [26]; however, this may reflect health-seeking behavior practices particular to this country, where uncomplicated gastroenteritis is usually handled over telephone consultation [6, 8].

Our estimate of norovirus-associated ED visits among children aged <5 years (78 000 visits per year) is broadly similar to a previous estimate of 91 000 ED visits per year in the United States [24]. However, compared with the estimated >235 000 annual clinic visits and the incidence rate of 167 visits per 10 000 persons reported in that same systematic review, our estimates are considerably higher (475 000

**Table 2. Estimated Annual Mean All-Cause Gastroenteritis and Norovirus-Associated Ambulatory Visits, Rates, and Healthcare Charges, by Setting and Age Group, MarketScan Commercial Claims and Encounters Database, United States, July 2001–June 2009**

| | | All-Cause Gastroenteritis Visits | | Norovirus Visits | | | | |
|---|---|---|---|---|---|---|---|---|
| Setting | Age, Years | No. | No. per 10 000 Persons | No. | Percentage of All-Cause Visits[a] | No. per 10 000 Persons (95% CI[b]) | Annual US Estimates[c] (95% CI) | Charges, $[d] |
| ED | 0–4 | 22 078 | 187 | 4368 | 20 | 38.3 (24.2–52.4) | 78 000 (49 000–107 000) | 23 |
| | 5–17 | 16 032 | 45 | 3194 | 20 | 10 (5.8–14.3) | 54 000 (31 000–76 000) | 18 |
| | 18–64 | 87 417 | 64 | 15 013 | 17 | 12 (7.1–17) | 223 000 (131 000–315 000) | 90 |
| | ≥65 | 16 463 | 82 | 2827 | 17 | 14.5 (8.8–20.2) | 54 000 (33 000–75 000) | 9 |
| | All ages | 141 990 | 69 | 25 402 | 18 | 13.5 (8–18.9) | 399 000 (238 000–560 000) | 140 |
| Outpatient | 0–4 | 155 010 | 1340 | 27 912 | 18 | 232.7 (155.8–309.7) | 475 000 (318 000–632 000) | 34 |
| | 5–17 | 108 737 | 302 | 30 627 | 28 | 85 (60.2–109.8) | 453 000 (321 000–586 000) | 34 |
| | 18–64 | 533 224 | 398 | 43 709 | 8 | 34.7 (24.9–44.4) | 642 000 (462 000–822 000) | 60 |
| | ≥65 | 133 007 | 674 | 10 744 | 8 | 54 (36–72) | 200 000 (133 000–266 000) | 16 |
| | All ages | 929 978 | 459 | 112 992 | 12 | 57.2 (40–74.4) | 1 693 000 (1 185 000–2 200 000) | 144 |

Abbreviation: CI, confidence interval.

[a] Proportion of total visits.

[b] Based on uncertainty of the overall model fit.

[c] Based on annual rates in the MarketScan population and extrapolation to census estimates for the US population, by age group.

[d] Data are millions of 2009 US dollars.

outpatient visits annually, or 233 visits per 10 000 population) for this age group. The previous estimates, however, were based on extrapolations from a pooled detection rate among studies in other industrialized nations and applied to the US population. Our approach used age-specific data from a medical claims database that represented approximately 10% of the total US population, was derived from all 50 states, and was recorded consistently over an extended period. In addition, our denominators were the actual populations whose health-seeking behavior would be captured by the database. Thus, our approach should provide more accurate, complete (all ages), and generalizable estimates of the norovirus disease burden in US ambulatory settings.

By examining the association between unspecified and specified visits in the time-series regression analysis, we were also able to investigate the burden of rotavirus in the ambulatory setting before rotavirus vaccine introduction. Our annual rotavirus estimate of approximately 662 000 ED and office visits among children aged <5 years is similar to other prevaccine approximations of 615 000–682 000 visits [27], which further supports our methods. Importantly, we also showed a previously unrecognized and sizeable amount of rotavirus disease requiring ambulatory care among adults (approximately 500 000 visits/year).

Certain limitations of our study should be considered. The residual method used has the potential for both overestimation and underestimation biases. We assumed that all residual seasonality was due to norovirus, which may have overestimated the contribution of this pathogen to ambulatory visits, because other viral enteropathogens (eg, astrovirus and sapovirus) have also shown winter seasonality. However, as noted, the seasonality of visits ascribed to norovirus is highly characteristic. Additionally, studies using sensitive diagnostic tests for astrovirus and sapovirus have shown proportionally lower detection rates [3, 4, 25] and that symptomatic infections were mostly restricted to children [28, 29]. Another possible source of overestimation involved the assumption in our regression model that testing and coding practices did not change over time. In particular, given the availability of the rotavirus vaccine, starting in 2006, knowledge of a child's vaccination status could have decreased the likelihood that they would be tested for rotavirus, leading to an overestimate of norovirus-associated encounters. We investigated this possibility by adding an interaction term for the rotavirus and time variables among children aged <5 years and found that this interaction was not a significant predictor of unspecified visits in this age group. In addition, our methods may also have underestimated the norovirus disease burden. More than half of all unspecified visits were not attributed to a particular pathogen, and some could have been due to norovirus. For example, none of the aseasonal background visits were attributed to norovirus, and we assumed that, for 1 month each year, no norovirus visits occurred; however, norovirus is known to circulate year-round [3, 17]. Also, given the overlap in seasons among rotavirus, norovirus, and other viral enteric pathogens, some of the unspecified causes may have been erroneously attributed to rotavirus. Finally, the MarketScan databases we used did not include uninsured and Medicaid populations, which may have affected extrapolations to the general US population.

In conclusion, our results add to existing data on the significance of norovirus as a cause of gastroenteritis in the United States and on the large burden norovirus places on healthcare services. These findings support the development of rapid and sensitive diagnostic tests for norovirus in clinical settings. Increased testing in emergency departments, for example, may intensify infection control measures, such as isolation precautions, and emphasize appropriate hand washing and environmental disinfection. Increasing awareness of the importance of norovirus among healthcare providers, especially during early winter, could help guide clinical management in the ambulatory setting (eg, curtail unnecessary antibiotic use or additional testing). Given the ubiquitous character of norovirus and the public health and economic implications of outbreaks in healthcare establishments, development of systems to exclude nonsevere gastroenteritis cases from ambulatory settings (eg, by telephone triage), may prove prudent and could be time saving for physicians and help reduce overall cost. Similarly, development of an effective preventive measure, such as a vaccine, remains a high priority. Progress is being made in norovirus vaccine development, and an early candidate has shown limited efficacy against homotypic strains in adults [30]. Our study highlights the broad age range that would stand to benefit from such an intervention, as well as baseline numbers of visits and costs associated with norovirus in the ambulatory setting. While this study provides information that could be valuable for future measurements of the impact of prevention strategies, additional carefully designed studies that use sensitive molecular assays and suitable comparison groups (healthy controls) that evaluate norovirus in children and adults with gastroenteritis are still required.

## Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://jid.oxfordjournals.org/). 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.

## Note

***Potential conflicts of interest.*** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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