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Norovirus Illnesses in Children and Adolescents

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BACKGROUND

Norovirus is a leading cause of acute gastroenteritis in the United States[1] and globally[2]. Although norovirus infection causes illness in all age groups, incidence rates are highest among young children.[1,3] In several countries that have introduced national rotavirus vaccination programs, norovirus has replaced rotavirus as the leading cause of medically attended[4–8] and community[8,9] pediatric gastroenteritis. Approximately 99% of the 212,000 annual deaths caused by norovirus occur in developing countries.[10] Although deaths are rare in the United States, norovirus is responsible for approximately 24,000 hospitalizations; 132,000 emergency room visits; and 925,000 outpatient visits in children less than 18 years, at an estimated cost of more than $200 million.[11,12] With norovirus vaccines under development,[13] a review of the virology, epidemiology, clinical presentation, diagnosis, treatment, and prevention of pediatric norovirus is described herein.

NOROVIRUS VIROLOGY

Noroviruses are a genetically diverse group of viruses in the *Caliciviridae* family that cause acute gastroenteritis.[14] The first norovirus was described when a viral particle was observed by electron microscopy in a stool sample derived from a 1968 outbreak in Norwalk, Ohio, leading to the initial name of Norwalk virus.[15] Norwalk virus was the first virus shown to cause gastroenteritis. Since then, other Norwalk-like viruses have been discovered; currently, noroviruses are classified into genogroups GI to GVII.[16] Genogroups GI, GII, and, to a lesser extent, GIV, are known to cause human disease. Globally, viruses of the GII.4 genotype are the leading cause of norovirus disease,[17] include new variants that emerge every 2 years to 4 years,[18,19] and are associated with greater symptom severity and health care burden.[20]

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CLINICAL PRESENTATION AND DISEASE COURSE

Norovirus infections cause acute gastroenteritis, presenting as acute-onset vomiting and/or diarrhea. When present, diarrhea is typically watery and nonbloody and may be accompanied by abdominal cramps, nausea, and fever.[21] Constitutional symptoms, including low-grade fever, generalized myalgias, malaise, headache, and chills, frequently occur. The incubation period lasts 12 hours to 48 hours, and the duration of clinical symptoms is typically 12 hours to 72 hours. Asymptomatic norovirus infection, identified through stool shedding of norovirus in patients without gastroenteritis, has been found in 3% to 10% of children and adults.[22] Although most infections result in full recovery,[23] severe outcomes, such as hospitalization and death, occur, particularly among children ages less than 5 years, adults ages greater than 65 years, and immunocompromised hosts.[1,24–26]

Severity of Norovirus Illness in Children

A meta-analysis of norovirus-associated gastroenteritis in children aged less than 5 years worldwide found that approximately 70% of cases occur within the 6-month to 23-month age range, and fewer than 15% occur before 6 months.[27] In this analysis, the proportion of cases among children less than 12 months increased from community to outpatient to inpatient settings, suggesting that infants more often have severe disease or are more likely to seek medical care and be hospitalized. Gastroenteritis caused by norovirus is generally milder than illness caused by rotavirus.[28] Children less than 5 years diagnosed with norovirus gastroenteritis after presenting to 3 US children's hospitals participating in active surveillance had fewer days of diarrhea, fewer diarrhea episodes, less fever, fewer abnormal behavioral signs, and less hospitalization than those diagnosed with rotavirus.[29] In contrast, children with norovirus gastroenteritis had more days of vomiting and more vomiting episodes than those with an unknown etiology.

Norovirus in Immunocompromised Children

Typically, norovirus outbreaks in hospitalized children with immunocompromising conditions occur by community-acquired infection in an index patient followed by nosocomial transmission to other patients and hospital staff.[30–32] In both retrospective and prospective studies, children with norovirus infection after solid organ or stem cell transplantation are at risk for prolonged viral shedding,[33–37] diarrhea greater than 14 days,[33,34,36–40] and severe outcomes.[33,34,36,37,39,40] Hospitalizations from norovirus gastroenteritis in these studies did not follow the typical seasonal pattern of norovirus. Children with primary immune deficiencies have also been found to have prolonged norovirus shedding after infection.[41,42]

NOROVIRUS TRANSMISSION

Norovirus is highly contagious, and the infectious dose can be as few as 20 viral particles.[43] The most common route for transmission is person to person, either directly through the fecal-oral route, by ingestion of aerosolized vomitus, or by indirect exposure via fomites or contaminated environmental surfaces.[44] Norovirus is also the leading known cause of both sporadic cases[2,45] and outbreaks of foodborne disease, with contamination occurring either

from infected food handlers or directly from foods.[46] Foods often implicated in norovirus outbreaks include leafy greens, fresh fruits, and shellfish, but any food that is served raw or handled after being cooked can be contaminated. Waterborne transmission is less common but possible when drinking or recreational water is not chlorinated.[47]

Peak viral shedding occurs 2 days to 5 days after infection[44] and occurs primarily in stool but can also be present in vomitus. Although norovirus RNA has been detected in stool samples for up to 4 weeks to 8 weeks after symptom resolution in otherwise healthy individuals,[48] the infectivity of the virus beyond the symptomatic period is not well established.

IMMUNITY

Immunity to norovirus is an ongoing field of research relevant to prospects for vaccination. Acquired immunity after infection is likely of limited duration, with protection after volunteer challenge studies lasting for weeks up to 2 years,[49,50] whereas modeling studies suggest protection for up to 9 years.[51] Evidence to support a limited duration of immunity in children is the identification of multiple norovirus infections in children monitored in birth cohort studies, with 25% to 40% of children followed from birth to 3 years in various settings having at least 2 episodes of norovirus gastroenteritis.[52–55] When immunity is acquired, protection may be limited to the initial genotype, because repeat infections by other genotypes do occur.[54,56]

In addition to acquired immunity, innate immunity may be conferred by homozygous mutations in the alpha(1,2) fucosyltransferase (FUT2) gene, which control the expression of histo-blood group antigens on the gut surface epithelium that bind to norovirus.[52,57] These mutations vary by ethnicity and occur in approximately 5% to 50% of different populations worldwide.[58]

NOROVIRUS DIAGNOSIS

Although norovirus gastroenteritis can be suspected by clinical symptoms, confirmatory testing requires laboratory testing of stool specimens (Table 1). Molecular tests, including conventional reverse-transcriptase polymerase chain reaction (RT-PCR) and quantitative, real-time RT-PCR (RT-qPCR), are most sensitive and the gold standard for norovirus detection but are usually only available in public health laboratories and research facilities. RT-qPCR affords several advantages, because it is the most sensitive assay available, can detect GI and GII strains simultaneously, and can limit false-negative results. Interpretation of RT-qPCR results may be complicated by norovirus frequently detected in stool samples of healthy and asymptomatic individuals.[9,59,60] Detection of norovirus in asymptomatic individuals seems more common in developing countries.[22]

Laboratory diagnostics in the clinical setting have recently become more widely available. Molecular-based assays for multiple enteric pathogens, such as xTAG GPP (Luminex Corporation, Toronto, Canada),[61,62] FilmArray gastrointestinal panel (BioFire Diagnostics, Salt Lake City, Utah),[61,63] and Verigene Enteric Pathogens Test (Nanosphere, Northbrook, Illinois)[64] can detect multiple viral, bacterial, and parasitic pathogens simultaneously within

a few hours. The equipment and testing can be expensive, however, and interpretation of positive results with mixed infections can pose challenges for appropriate treatment and management of patients. Norovirus-specific nucleic acid amplification tests are promising for having a short turn-around time for point-of-care testing and have recently received Food and Drug Administration clearance[65] but are not yet commonly used in practice. Other diagnostic tests include electron microscopy, enzyme immunoassay, and immunochromatographic lateral flow assays, although these tests are limited by moderate sensitivity or high cost.[16]

CLINICAL ASSESSMENT AND TREATMENT

The assessment and treatment of gastroenteritis caused by norovirus are similar to those of other causes of viral gastroenteritis. Treatment of diarrhea usually begins at home, with a focus on replacing fluid losses and maintaining adequate nutrition intake.[66] Medical evaluation of children is indicated with young age (eg, age <6 months or weight <8 kg), history of premature birth, chronic medical conditions or concurrent illness, fever, bloody stool, high volume and frequency of diarrhea, persistent vomiting, change in mental status, caregiver concern for dehydration, or poor response to home treatment.[66] At the time of medical evaluation, clinicians should conduct a thorough history and physical examination to assess the level of dehydration and loss of body weight.

Treatment should be based on the degree of dehydration and include 2 phases: rehydration and maintenance (Box 1).[66] The rehydration phase should occur in the first 3 hours to 4 hours of treatment with the goal of replacing the fluid deficit. The maintenance phase should focus on realimentation and returning the patient to an age-appropriate diet. Breastfed infants should continue to nurse throughout treatment. Oral-rehydration solutions (ORS), whose practical use was first studied during cholera outbreaks in Bangladesh and India,[67,68] should be the mainstay of rehydration treatment.[66] Although several ORS formulations are commercially available, all are composed of a balance of carbohydrates, sodium, potassium, chloride, and bicarbonate to encourage rapid rehydration, electrolyte balance, and appropriate osmolarity, and glucose support.[69] Patients with minimal or no dehydration (<3% loss of body weight) may be managed conservatively with ORS provided at home. Patients with mild to moderate dehydration (3%–9%) should be initially medically supervised. Patients with severe dehydration (>9%) should be treated with ORS but may also require intravenous fluids to maintain fluid status. Intravenous fluids may also be required in cases of severe vomiting that precludes oral rehydration.

Aside from general supportive treatment of gastroenteritis, no specific antinorovirus therapy is recommended at this time. Research to identify antiviral treatment strategies is in progress[70,71] and should be bolstered by the recent discovery of human intestinal enteroid cultures to support norovirus replication in vitro.[72] Adjunctive treatments for diarrhea, including use of analgesic, antimotility, antiemetic, antisecretory, and probiotic agents, are commonly used but often without robust supportive evidence.[73]

NOROVIRUS EPIDEMIOLOGY: ENDEMIC DISEASE

The global prevalence of norovirus among cases of acute gastroenteritis is estimated at 17% in hospitalized patients and 24% in the community.[22] A World Health Organization–commissioned analysis estimated 685 million annual norovirus infections (95% uncertainty interval 491 million–1.1 billion) and 212,000 (95% uncertainty interval 161,00–278,000) annual norovirus deaths worldwide.[10] The wide uncertainty intervals reflect current gaps in country-level data, especially from low-income, high-mortality countries. More than half of global cases occur in winter months.[74] One factor in the seasonality of norovirus in high-income countries may be the start of the school year, with evidence to suggest that outbreaks in children begin with the school year and then spread to outbreaks in adults.[75] A systematic review found GII.4 the most common genotype in endemic norovirus gastroenteritis in children, identified in approximately two-thirds of cases.[76]

Estimated rates of norovirus disease in the community, outpatient, emergency, and inpatient settings and for deaths from norovirus in children in high-income countries are summarized in Table 2. Applying rates for studies conducted in the United States to 2016 population estimates from the US Census,[77] the authors estimate the burden from norovirus illness in children aged <18 years to be approximately 4.2 million total illnesses; 815,000 outpatient visits; 130,000 emergency department visits; 24,600 hospitalizations; and 38 deaths (Fig. 1).

EPIDEMIC NOROVIRUS GASTROENTERITIS

Norovirus is the leading etiology of gastroenteritis outbreaks reported to the National Outbreak Reporting System in the United States, accounting for 68% of out-breaks in which a single etiology is identified.[47] Norovirus is most commonly transmitted by person-to-person contact, reported in 66% to 77% of outbreaks, although can also be transmitted by food, water, and environmental routes.[47,78] Although long-term care facilities caring for adults are the most frequently reported setting, schools and day care centers have been reported in 2% to 5% of all norovirus outbreaks.[47,78] Periodic increases in norovirus outbreaks occur in association with the emergence of new GII.4 strains, observed every 2 to 4 years in the past 2 decades.[18]

Foodborne Disease Outbreaks

Norovirus is the leading cause of foodborne disease outbreaks in the United States.[46] Foodborne norovirus outbreaks occur year-round, and infectious food workers are implicated as the source of contamination in 70% of these outbreaks.[46] Globally, norovirus is the leading identified etiology of foodborne illnesses, causing almost 125 million illnesses annually, and the fifth leading identified etiology of foodborne deaths, with almost 35,000 deaths annually.[79] Among children aged less than 5 years, norovirus causes 35 million foodborne illnesses, the third highest after infections from *Campylobacter* and *Escherichia coli*, and 9000 foodborne deaths annually.[79]

Outbreak Prevention and Control

Principles of norovirus outbreak prevention and control include hand hygiene, exclusion of ill persons, and environmental disinfection.[44] For child care centers, the American Academy

of Pediatrics offers additional guidelines for diapering and staff training.[80] Hand hygiene, beginning with proper hand washing with soap and running water for at least 20 seconds, is the most effective way to reduce norovirus contamination on the hands.[81] Alcohol-based sanitizers can be used when soap and water are unavailable but should not be a replacement for proper washing due to conflicting evidence.[81,82] Avoiding bare-hand contact with ready-to-eat foods (ie, food that is eaten raw or food eaten without further cooking) is recommended as an additional preventive strategy. Exclusion and isolation of infected persons are often the most practical means of disrupting norovirus transmission during an outbreak. Ill persons should be excluded during the symptomatic period of their illness as well as a period after recovery while the person is still shedding virus at high levels (typically 24–72 hours). Environmental disinfection is recommended using a chlorine bleach solution or other commercial product registered with the Environmental Protection Agency as effective against norovirus.[83] Particular attention should be given to areas of greatest potential contamination, such as bathrooms and high-touch surfaces. Specific regulations for outbreak prevention and control at child-care and school facilities are determined by state licensing agencies, and address practices, such as handwashing for staff and children, isolation and exclusion of ill children, exclusion of ill staff, diapering, and environmental cleaning.[84] Local school and public health authorities may also consider facility closure to control an outbreak, depending on factors, such as a rising case count, a high attack rate in a defined at-risk population, and input from local stake-holders.[85] Health care providers are encouraged to report suspected and confirmed outbreaks of norovirus to their local health department.

PROSPECTS FOR VACCINATION AGAINST NOROVIRUS

The ubiquity of norovirus in the environment and the high burden of norovirus infection make vaccination against norovirus an appealing prevention strategy. Norovirus vaccines in development have been based on virus-like particles (VLPs), which contain the major capsid antigen but lack genetic material for viral replication.[86] VLPs have been shown to induce humoral, mucosal, and cellular immune responses after oral and intranasal administration.[87] Several norovirus vaccines are currently under development in preclinical and clinical trials using VLPs and involving intranasal, oral, and intramuscular routes of administration.[13,88]

A norovirus vaccination strategy needs to address biological and programmatic challenges.[89] Biologically, norovirus vaccines need to protect against the diversity of norovirus strains that affect humans and the presence of emerging GII.4 strains. Immunity is currently thought to be of limited duration, estimated from 6 months to 9 years and to confer little protection across genogroups.[49,50] Programmatically, young children bear the highest overall incidence of disease and likely drive community transmission[90] and are thus an ideal target for vaccination. It is unknown, however, how norovirus vaccination might interact with other routine childhood vaccinations, and trials of norovirus vaccines have been mostly conducted in adults. Given prior exposure and underlying conditions, the immune response is likely to differ in young children, adolescents, adults, the elderly, and the immunocompromised.

Despite these challenges, norovirus vaccination has the potential to be highly beneficial to society. A simulation model estimated that vaccination could prevent 1 million to 2.2 million

annual cases of norovirus gastroenteritis in the United States, resulting in savings of $2 billion over 4 years.[91] Given the high burden and higher mortality in low-income countries, norovirus vaccination would be of even greater benefit if adopted broadly by national immunization programs.

SUMMARY

Norovirus is the leading cause of acute gastroenteritis in the United States and globally, with higher incidence in children than in other age groups. In the United States, an estimated 4.2 million annual norovirus illnesses in children result in a high burden of medical care and hospitalization. Although deaths from norovirus in US children are rare, norovirus is a leading cause of death from childhood diarrhea in developing countries. Early assessment of dehydration status from diarrhea and appropriate treatment are advised to prevent complications, including death. Norovirus outbreaks should be managed with hand hygiene, exclusion of ill persons, and environmental control. Future prospects for prevention of norovirus include vaccination.

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Box 1

Clinical assessment and treatment of acute diarrhea based on level of dehydration

Minimal or no dehydration (<3% loss of body weight)

- Examination findings: normal mental status, thirst, heart rate, respiratory rate, tears, moist mucosa, skin recoil, capillary refill, urine output, warm extremities
- Immediate rehydration: N/A
- Maintenance treatment: less than 10 kg body weight: 60 mL to 120 mL ORS for each diarrheal stool or vomiting episode; greater than 10 kg body weight: 120 mL to 240 mL ORS for each diarrheal stool or vomiting episode; continue breastfeeding or age-appropriate diet

Mild to moderate dehydration (3%–9% loss of body weight)

- Examination findings: irritable or fatigued mental status, increased thirst, normal to increased heart rate, respiratory rate, slightly sunken eyes, decreased tears, dry mucosa, skin recoil less than 2 seconds, prolonged capillary refill, decreased urine output, cool extremities
- Immediate rehydration: ORS, 50 mL/kg to 100 mL/kg body weight over 3 hours to 4 hours
- Maintenance treatment: same as for minimal or no dehydration

Severe dehydration (>9% loss of body weight)

- Examination findings: lethargic to unconscious mental status, poor thirst or unable to drink, tachycardia (bradycardia in very severe cases), deep breathing, deeply sunken eyes, absent tears, parched mucosa, skin recoil greater than 2 seconds, prolonged and minimal capillary refill, minimal urine output, cold to cyanotic extremities
- Immediate rehydration: iso-osmotic crystalloid intravenous fluids at 20 mL/kg body weight until perfusion and mental status improve; then ORS at 100 mL/kg body weight over 4 hours
- Maintenance treatment: same as for mild to moderate dehydration; if unable to drink, administer through nasogastric tube or intravenous

Adapted from King CK, Glass R, Bresee JS, et al, Centers for Disease Control and Prevention. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. MMWR Recomm Rep 2003;52(RR-16):6; with permission.

KEY POINTS

- Norovirus is a leading cause of both endemic and epidemic gastroenteritis in the United States and globally.
- Norovirus causes approximately 4.2 million illnesses; 815,000 outpatient visits; 130,000 emergency department visits; 24,600 hospitalizations; and 38 deaths annually in children in the United States.
- Most of the global childhood mortality from norovirus illness occurs in developing countries.
- Early assessment of dehydration status and treatment aimed at correcting fluid status are key to preventing severe outcomes from norovirus illness.
- Vaccines against norovirus illness and strategies for defining the target population, vaccination schedule, and delivery mechanism for vaccination are under development.

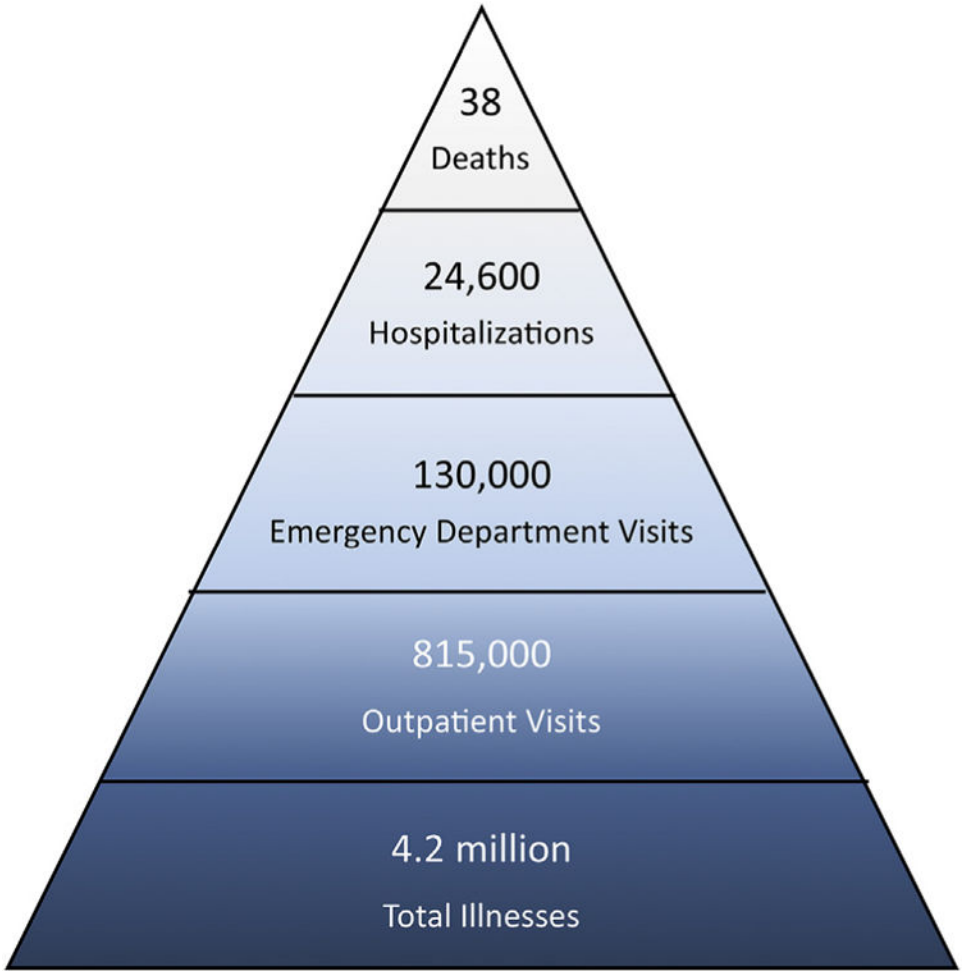

Fig. 1.

Estimates of annual burden (annual number of illnesses and associated outcomes) for norovirus disease for children 0 to 17 years, United States. Data were derived from point estimates of rates of norovirus-associated deaths,[1] hospitalizations,[11] emergency department visits,[12] outpatient visits,[12,94] and illnesses.[94] Population size based on 2016 US Census estimates.

Table 1

Laboratory methods for detection of norovirus

Method	Characteristics	Availability	Use in Clinical Setting?	Use in Outbreak Setting?
Conventional RT-PCR, real-time RT-PCR	• Gold standard test • High sensitivity • Frequently detects viral RNA in asymptomatic and healthy patients	Public health and reference laboratories	Not widely[a]	Yes
Multiple enteric pathogen tests (PCR)	• Detects multiple viral, bacterial, and parasitic pathogens simultaneously • High sensitivity • Expensive	Public health and clinical laboratories	Yes	Yes
Enzyme immunoassay, Immunochromatographic	• Low sensitivity, high specificity	Public health and clinical laboratories	Not recommended for individual patients	Yes, for rapid screening of multiple samples
Electron microscopy	• Detect multiple viral pathogens • Low sensitivity • Expensive	Reference laboratories	No	No

Abbreviations: PCR, polymerase chain reaction; RNA, ribonucleic acid; RT-PCR, real-time polymerase chain reaction.

[a]Individual patient specimens can be tested, such as in an outbreak at a reference laboratory, and positive specimens genotyped, but due to lack of availability in the clinical setting is unlikely to provide results back to the patient in a timely fashion. Some commercial diagnostic laboratories, however, offer their own in-house RT-PCR as do some tertiary-care hospitals.

Table 2

Studies estimating endemic norovirus incidence in children less than 18 years of age in developed countries, by outcome

	Country	Data Period Studied	Study Design	Population	Reported Incidence by Age Group
Deaths					Per 1,000,000 person-years
Hall et al,[92] 2012	US	1999–2007	Retrospective analysis using time-series regression models	Gastroenteritis-associated deaths from National Center for Health Statistics multiple cause-of-death mortality data	0–4 y: 1.3
Hospitalizations					Per 1000 person-years
Lopman et al,[11] 2011	US	1996–2007	Retrospective analysis using time-series regression models	Gastroenteritis-associated hospital discharges from National Inpatient Sample	<5 y: 94 5–17 y: 11
Ruzante et al,[93] 2011	Canada	2001–2004	Retrospective database review	Norovirus hospital discharge codes and Canadian Institute for Health Information, Vital Statistics Registry, National Notifiable Diseases database	<1 y: 5.9 1–4 y: 2.0 5–9 y: 0.8 10–14 y: 0.3 15–19 y: 0.3
Emergency department visits					Per 10,000 person-years
Gastañaduy et al,[12] 2013	US	2001–2009	Retrospective analysis using time-series regression models	Gastroenteritis-associated health care encounters from MarketScan commercial claims and encounters database	0–4 y: 38 5–17 y: 10
Outpatient visits					Per 1000 person-years
Grytdal et al,[94] 2016	US	2012–2013	Retrospective laboratory-based cohort	AGE specimens submitted for routine clinical diagnostics from health maintenance organization in 2 US locations	<5 y: 26 5–15 y: 4
O'Brien et al,[24] 2016	UK	2008–2009	Prospective cohort (IID2 study)	AGE patients presenting for primary health care consultations nationwide	<5 y: 14 5–15 y: 1.5
Gastañaduy et al,[12] 2013	US	2001–2009	Retrospective analysis using time-series regression models	Gastroenteritis-associated health care encounters from MarketScan commercial claims and encounters database	0–4 y: 23 5–17 y: 8.5
Phillips et al,[3] 2010	UK	1993–1996	Prospective cohort (IID1 study)	AGE cases presenting to 70 general practitioner clinics nationwide	<2 y: 64 2–4 y: 15 5–14 y: 4
Bernard et al,[95] 2014	Germany	2001–2009	Retrospective analysis surveillance	National surveillance system for notifiable diseases, Federal Statistical Office, includes sporadic and outbreak cases	<5 y: 4–4.5[a] 5–9 y: 1 10–14 y: 0.4 15–19 y: 0.4–0.6
Werber et al,[96] 2013	Germany	2004–2008	Retrospective analysis surveillance	National surveillance system for notifiable diseases, Federal Statistical Office	0–4 y: 5.4[a] 5–9 y: 1.3 10–19 y: 0.5
Community					Per 1000 person-years
Grytdal et al,[94] 2016	US	2012–2013	Retrospective laboratory-based cohort	AGE specimens submitted for routine clinical diagnostics from health maintenance organization in 2 US locations	<5 y: 152 5–15 y: 22

	Country	Data Period Studied	Study Design	Population	Reported Incidence by Age Group
O'Brien et al,[24] 2016	UK	2008–2009	Prospective cohort (IID2 study)	AGE cases in community nationwide	<1 y: 178 1–5 y: 137 5–15 y: 60
Phillips et al,[3] 2010	UK	1993–1996	Prospective cohort (IID study)	AGE cases in community nationwide	<2 y: 272 2–4 y: 167 5–14 y: 65
de Wit et al,[25] 2001	The Netherlands	1998–1999	Prospective cohort (Sensor)	AGE cases in sample of community practices	<1 y: 740 1–4 y: 900 5–11 y: 481 12–17 y: 157

Abbreviations: AGE, acute gastroenteritis; IID, infectious intestinal disease study; IID2, second infectious intestinal disease study.

[a] If point estimate was not reported in text or table, data points were extracted by digitizing plots.