HHS Public Access

Author manuscript

J Pediatr. Author manuscript; available in PMC 2024 July 01.

Published in final edited form as:

J Pediatr. 2023 October ; 261: 113551. doi:10.1016/j.jpeds.2023.113551.

A Comparison of Pathogen Detection and Risk Factors among Symptomatic Children with Gastroenteritis Compared with Asymptomatic Children in the Post-rotavirus Vaccine Era

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Abstract

Objective—To describe demographics, pathogen distribution/seasonality, and risk factors in children seeking care for acute gastroenteritis (AGE) at a midwestern US emergency department during 5 postrotavirus vaccine years (2011–2016), and further, to compare the same data with matched healthy controls (HC).

Study design—AGE and HC participants <11 years old enrolled in the New Vaccine Surveillance Network study between December 2011 to June 2016 were included. AGE was defined as ≥3 diarrhea episodes or ≥1 vomiting episode. Each HC's age was similar to an AGE participant's age. Pathogens were analyzed for seasonality effects. Participant risk factors for AGE illness and pathogen detections were compared between HC and a matched subset of AGE cases.

Results—One or more organisms was detected in 1159 of 2503 children (46.3%) with AGE compared with 99 of 537 HC (17.3%). Norovirus was detected most frequently among AGE (n = 568 [22.7%]) and second-most frequently in HC (n = 39 [6.8%]). Rotavirus was the second most frequently detected pathogen among AGE (n = 196 [7.8%]). Children with AGE were significantly more likely to have reported a sick contact compared with HC, both outside the home (15.6% vs 1.4%; $P < .001$) and inside the home (18.6% vs 2.1%; $P < .001$). Daycare attendance was higher among children with AGE (41.4%) compared with HC (29.5%; $P < .001$). The *Clostridium difficile* detection rate was slightly higher among HC (7.0%) than AGE (5.3%).

Conclusions—Norovirus was the most prevalent pathogen among children with AGE. Norovirus was detected in some HC, suggesting potential asymptomatic shedding among HC.

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Declaration of Competing Interest

The other authors declare no conflicts of interest.

Data Statement

Data sharing statement available at www.jpeds.com.

The proportion of AGE participants with a sick contact was approximately 10 times greater than that of HC.

Each year, an estimated 958 million diarrheal episodes occur worldwide among children <5 years of age; acute gastroenteritis (AGE) is considered the fifth leading cause of death.[1] Before rotavirus (RV) vaccines were routinely recommended for children in 2006, the most common pathogen causing diarrhea-related mortality worldwide among children <5 years of age was RV, representing 37% of all deaths attributable to diarrhea and 5% of all deaths under 5 years of age.[1,2] During the pre-RV vaccine era, an estimated 55 000–70 000 US hospitalizations and 410 000 clinic visits were attributed to RV annually.[3] After universal recommendation of infant vaccination in 2006, rates of RV detection in AGE patients from the National Respiratory and Enteric Virus Surveillance System decreased from 26% during the prevaccine period (2000–2006) to 6% during the postvaccine period (2017–2018 season).[4] Peak detection rates during winter-spring seasons also decreased from 43.1% to 14.0%.

With substantial decreases in pediatric US hospitalizations and emergency department (ED) visits attributed to RV in the post-RV vaccine era, norovirus (NoV) has become the most commonly detected gastrointestinal pathogen in the US.[5–10] In addition, RV infections shifted to a biennially higher detection rates during the post-RV vaccine era, whereas NoV continues to be prevalent each year with peak infections occurring during winter months.[4–8,10,11]

Risk factors associated with pediatric AGE symptoms (eg, AGE contact, daycare attendance, environmental contamination) have also been described; however, additional data from population-based, laboratory confirmed, prospective, active surveillance for AGE pathogens by case control studies can expand our understanding of AGE pathogen prevalence and community transmission patterns.[6,10,12–14] To better understand the risk and health outcomes associated with pathogens causing AGE among US children, the New Vaccine Surveillance Network (NVSN), a population-based, prospective, laboratory confirmed, active surveillance network funded by the Centers for Disease Control and Prevention of 7 US medical institutions (https://www.cdc.gov/surveillance/nvsn/index.html), has maintained surveillance in children with AGE symptoms and matching healthy controls (HC) during the post-RV vaccine era. Although an overarching aim of this network is to prospectively monitor RV vaccine effectiveness, data and stool samples are collected prospectively and systematically, allowing periodic analysis of a variety of AGE-related pathogens, including viral, bacterial, and parasitic organisms. Stools are tested per protocol using molecular multiplex gastrointestinal pathogen assays. The aim of this study was to describe the epidemiology and clinical presentation of AGE over 5 consecutive post-RV vaccine years (2011–2016) based on the subset of NVSN-enrolled children attending the ED at the Kansas City site, and further, to compare risk factors between matched AGE and HC groups.

Methods

NVSN Enrollment

Enrolled participants were >14 days and ≤10 years old, had NVSN protocol-defined AGE and sought medical care at the ED of Children's Mercy Kansas City, Missouri, from December 2011 to June 2016; ED patients who were subsequently admitted were included in the analysis. Surveillance was year-round (September through August) except the initial 2011/2012 season that started December 2011. Detailed methods and NVSN scope were previously described.[7,15,16] Briefly, AGE was defined as ≥3 diarrhea episodes within 24 hours or ≥1 vomiting episode within 24 hours, or both; symptoms had to be present for <10 days. Systematically enrolled HC had to attend a scheduled well-child visit in an outpatient clinical care site within ±14 days of an enrolled AGE participant of a similar age group (ie, <6 months, 6–11 months, 12–23 months, 24–59 months, and ≥60 months). Per protocol, HC had no history of AGE symptoms for 14 days before enrollment. AGE stools were collected within 10 days of symptom onset and HC stools within 5 days of enrollment. Families provided demographic, epidemiologic, and clinical data. Immunization histories were obtained through Kansas and Missouri state vaccine registries and/or through the participant's medical provider.

Children were enrolled via written consent from parent/s or legal guardian. This study was reviewed and approved by the Institutional Review Board of Children's Mercy Kansas City and the Centers for Disease Control and Prevention.

Pathogen Testing

Stools were stored at −80 °C until total nucleic acids were extracted with an automated EasyMag extraction system (bioMerieux, Durham, NC).[17] Samples were tested via Luminex GPP assay (Luminex Corp, Austin, TX) along with positive and negative controls per manufacturer's instructions. Targets includes viruses (RV, NoV, and adenovirus 40/41), bacteria (*Clostridium difficile*, *Shigella, Salmonella, Campylobacter*, *Escherichia coli* O157, enterotoxigenic *E coli* [ETEC], shiga-like toxin producing *E coli* [STEC], *Vibrio cholera*, and *Yersinia*) and parasites (*Cryptosporidium*, *Giardia*, and *Entamoeba histolytica*).

Samples that were given a target call of invalid by the Luminex data analysis software on initial testing were repeated, per manufacturer, and if both results were invalid, the patient's stool sample was excluded from the analysis (n = 35). Because Luminex Corp had released notes on false-positive detection of *Salmonella*, *E histolytica*, *Giardia*, and *Cryptosporidium* by the multiplex Luminex GPP assay and our relatively high Luminex detection rate of these 3 organisms in nonsymptomatic HC, each Luminex detection was confirmed by a second methodology. Using manufacturers' instructions, Progastro SSCS assay was used to confirm *Salmonella* (Hologic Inc, Marlborough, MA) and RIDA Gene Parasitic Stool Panel to confirm *Giardia lamblia*, *Cryptosporidium* spp., *Entamoeba histolytica* (R-Biopharm, Creve Coeur, MO). If the *Salmonella*, *E histolytica*, *Giardia*, and *Cryptosporidium* detected by Luminex GPP assay was not confirmed by a repeat testing assay, the sample was categorized as negative for that organism. The American Academy of Pediatrics recommends not testing children <12 months of age for *C difficile* owing to the high rate of asymptomatic

colonization.[18] As a result, data on *C difficile* detections in children <12 months were collected but were categorized as negative owing to the uncertainty in whether the child was a *C difficile* carrier or not. For this analysis, samples with ≥2 detected organisms were considered codetections.

Case Control Subsample

Per NVSN protocol, participant enrollment is performed with the intended goal to have AGE and HC be similar as possible with regards to visit date, age, and race/ethnicity. However, because significant differences in patient demographics were noted between AGE and HC, we created a matched analytic dataset using a subset of our AGE and HC participants (case control subset). This dataset was created using a propensity score model that accounted for sampling time frame (ie, calendar month and year), patient race, and patient ethnicity. HC and AGE who did not have a corresponding comparator (ie, AGE and HC, respectively) within 14 days of their screened data were excluded from the propensity model. To further ensure balance, the propensity score models were stratified by 5 patient age groups (<6 months, 6–11 months, 12–23 months, 24–59 months, and ≥60 months). Optimal pair matching, which included sampling without replacement, was implemented with an intended goal of a 2:1 ratio of AGE:HC. This case control subset was used for demographic, risk factor, and seasonality comparisons between AGE and HC.

RV Vaccination Status

RV vaccination status was determined from provider records for all participants to quantify RV vaccine adherence of children who had RV detected. A complete schedule was defined as 3 doses of any vaccine or combination of vaccines, or 2 doses of monovalent vaccine. Participant vaccination status was classified as either unvaccinated, partial, or complete. RV vaccination dates were used to identify which AGE/HC children received the vaccine within 7 days of stool specimen collection.

Statistics Analyses

Patient demographics (age group, gender, race/ethnicity) among the AGE participants were compared based on whether a pathogen was detected (positive) or not (negative). Select clinical symptoms (eg, maximum temperature, any diarrhea, number of vomiting episodes) and seasonality effect were contrasted between pathogens using the entire AGE subset. The case control subset was used to compare the potential risk factors for AGE illness (eg, current daycare ≥4 hours/week, exposure to persons with AGE in the prior week, number of persons residing in household). Last, pathogen detections were compared between matched AGE and HC.

Pearson's χ^2 test was used to compare categorical distributions and the Kruskal-Wallis test was used for continuous outcomes. Unadjusted logistic and quantile regression models compared risk factors and clinical presentations for each organism compared with the negative group. Reported *P* values for contrasting organisms were adjusted for multiple comparisons using the Sidak method. Unadjusted logistic models were used to compare risk factors between AGE and HC. The *MatchIt* package in R (R Core Team; Vienna, Austria)

was used for creating the case control subset. All analyses were completed using Stata (StataCorp, College Station, TX).

Results

A total of 5223 eligible children were approached for enrollment. Of those, 3238 children with AGE (62.0%) were enrolled. Of these enrolled participants, 2598 (80.2%) provided a stool specimen. Among these 2598 participants, 2503 (96.3%) had GPP assay results and were included in the analysis. A total of 1159 AGE participants (46.3%) tested positive for ≥1 pathogens. The case control subset contained 537 HC and 1093 matched AGE participants; AGE and HC were matched in a 2:1 ratio, with the exception of participants <6 months (1.5:1). Of the 537 HC, 99 (17.3%) were test positive compared with 47.5% in matched AGE subset (519/1093; $P < .001$).

AGE Cohort: Demographics and Pathogen Detection

When AGE participants having ≥1 detected pathogen were compared with AGE participants having no pathogens detected, those 12–23 months old were significantly over-represented (29.4% vs 20.2%), and those ≥60 months old were under-represented (18.4% vs 25.5%) (Table I). The distributions of sex, ethnicity, and race were similar between AGE test-positive and AGE test-negative groups. The AGE test-positive group had a slightly higher but nonsignificant proportion of Hispanic/Latino children compared with the AGE test-negative group (32.3% vs 28.9%, respectively). A comparison of clinical presentation by pathogen detection is provided in Table II.

NoV was the most frequently detected pathogen among children with AGE (n = 568 [22.7%]), followed by RV (n = 196 [7.8%]) (Table III). Among the children with AGE and RV detected, only 2 had received a RV vaccine within the last week, that is, might have been shedding vaccine virus. Among bacterial pathogens, *Salmonella* was the most common (n = 159 [6.4%]) followed by *C difficile* (participants ≥1 years of age; n = 132 [5.3%]) and *Shigella* (n = 113 [4.5%]).

Codetections occurred in 206 of 2503 AGE participants (8.2%) (Figure 1). In general, codetection proportions were higher for a bacterial pathogen (eg, *Salmonella*, 53.5%; *C difficile*, 54.5%) compared with a viral pathogen (eg, NoV, 20.8%; RV, 27.6%). Among codetections, nearly three-quarters (72.8% [n = 150]) of these 206 children had both a viral and a bacterial pathogen detected, followed by 11.2% (n = 23) who had multiple bacterial pathogens detected, 10.2% (n = 21) with multiple viral pathogens, and 5.8% (n = 12) who had a parasitic and bacterial/viral codetection. Most codetections in AGE participants (75%) included NoV, *Salmonella, C difficile*, and/or RV.

Case Control Analysis: Pathogen Detection and Risk Factors

In the case control analysis, NoV was more commonly detected among matched AGE participants (n = 240 [22.0%]) compared with HC (n = 39 [6.8%]) (Table III). *C difficile* was the most commonly detected pathogen among HC (n = 40); the detection rate was slightly higher in HC than those with AGE (7.0% vs 5.3%, respectively). RV was detected in 15 HC; however, 10 of 15 of these HC had received a RV vaccination at their prior well-check visit

within 1 week of stool specimen submission, suggesting most of the RV detections in HC may represent RV vaccine strain shedding. Only a single child with AGE had received RV vaccine within 7 days of stool collection. The detection rate of *C difficile* and *E coli* (*E coli* O157, ETEC, or STEC) did not differ significantly between matched AGE and HC.

Nearly one-quarter (23.8%) of AGE participants <24 months old tested positive for NoV, with a corresponding 7.5% NoV positivity among HC <24 months (Figure 2). Positivity rates for viral pathogens decreased with increasing age of enrolled participants, whereas for some bacterial organisms (eg, *Shigella* in children with AGE and *C difficile* in HC) the opposite effect was observed. Codetection occurred in 2.3% of all HC (13/579) and was predominately detection of a viral and bacterial organism (n = 8 [61.5%]). NoV and *C difficile* were the 2 most common organisms (both 30%) among HC participants with codetections.

Children with AGE and HC used in the case control analyses were similar in terms of age, sex, and race/ethnicity (Table I). As shown in Table IV, AGE participants were significantly more likely to report a sick contact compared with HC, both for contacts outside the home (15.6% vs 1.4%; OR, 13.01; 95% CI, 6.35–26.64) and inside the home (18.6% vs 2.1%; OR, 10.66; 95% CI, 5.90–19.27). The proportion with household income ≤$25,000 was higher among children with AGE (53.7%) than among HC (37.2%; OR, 1.96; 95% CI, 1.59–2.49). No significant differences in median household size were noted between matched AGE and HC participants. Children with AGE were also more likely to report daycare attendance compared with HC (41.4% vs 29.5%).

Case Control Analysis: Seasonality Effects

When considering all organism detections (ie, single-infection + codetections), year-to-year patterns for some organisms were similar between AGE and HC participants. Seasonal fluctuations in NoV among AGE have corresponding seasonal fluctuations among HC (Figure 3). Intermittent increases in *Shigella* detections were observed for both AGE and HC and correspond with the timing of a known concurrent local community outbreak (Figure 4). Pathogens such as NoV, RV, and *Salmonella* (among AGE) demonstrated consistent expected seasonal and annual patterns. Conversely, other organisms appear to have had a constant presence (eg, adenovirus 40/41, *C difficile*) or exhibited sporadic outbreaks (eg, *Shigella*).

Discussion

In our analysis of 2503 children seen in the ED for AGE symptoms over 5 years of NVSN surveillance at our site, an AGE pathogen was detected by a multiplex molecular assay in 46.3% of samples. Nearly two-thirds (63.5%) of all detections in children with AGE were viruses. In the case control subset, AGE cases were more likely to report contact with a sick person or daycare attendance than HC. Our case control data are distinct from some other pediatric case control studies in that we performed a comprehensive evaluation that included multiple bacterial and parasitic organisms in the multiplex GPP, as well as viral pathogens.[6,12,14,17]

NoV was one of the most prevalent pathogens detected. Nearly one-quarter (22.0%) of AGE participants and 6.8% of HC in our matched sample were NoV test positive. This NoV predominance is similar to that of other studies during the post-RV vaccine era including prior multisite NVSN studies, where NoV was detected in 15%−22% of children with AGE but only 4%−8% of HC.[6,10,11]

We also detected NoV in an annual seasonal pattern similar to that previously described, consistently peaking during winter months.[6] In our study, we also observed that the minor fluctuations in prevalence of NoV detection, both season to season and month to month, in children with AGE were mirrored but in much smaller numbers among HC. Our prior 2-site NVSN study of AGE inpatients and matched HC demonstrated a clear NoV seasonality pattern in Kansas City, similar to our AGE patient and HC study; a clear seasonality pattern had been less notable for the Texas study site in pediatric inpatients.[10] A UK study found that asymptomatic NoV shedding was detected in 15%−20% of HC during winter months and in 5%−10% during the summer, mirroring the pattern among HC in our study.[19] Because HC, by definition, have no recent diarrhea or vomiting symptoms, a greater understanding of the frequency of prolonged NoV shedding within the community is needed, especially during community outbreaks.

Despite substantial declines in rates of RV detection in the post-RV vaccine era (26% prevaccine vs 6% postvaccine), our study performed over a decade into the RV vaccine era revealed RV as the second most common pathogen among all our AGE participants, a highly vaccinated group (75% AGE were partially or fully vaccinated against RV).[4] Our 7.8% RV detection rate was somewhat lower than other NVSN studies at other sites or among inpatients (10%−14%) during the RV-vaccine era.[6,10]

Bacterial pathogens such as *E coli* (*E coli* O157, ETEC, or STEC) and *Shigella*, which frequently cause diarrheal symptoms in developing countries, accounted for only 11.8% of all detections among children with AGE in our study.[20–22] Our matched sample of AGE and HC participants demonstrated that both groups had similar rates of detection of *C difficile* and *E coli* (raising the question of pathogenicity even when detected in children with AGE in the US). Additionally, children with AGE and HC exhibit similar seasonal patterns for select pathogens.

Interestingly, despite our analysis including *C difficile* detections only in children ≥12 months of age, *C difficile* was the most common organism detected in HC (7.0%). The detection rate for *C difficile* would have been higher had *C difficile* detections in children <12 months been included. The detection of *C difficile* in young children with AGE presents a dilemma for clinicians given that young children often are colonized with *C difficile*.[18,23] *C difficile* polymerase chain reaction results should be interpreted with caution because the assay used may merely detect colonization by a toxigenic *C difficile* strain and not the toxin that mediates the disease. Although our data provide further support of *C difficile* also being a colonizer in older children, continued research is needed to determine the true prevalence of *C difficile* colonization in children of all ages, particularly those >60 months of age.

Two recent studies of children with AGE and HC NVSN found overall pathogen codetection rates of 1%−6% for AGE inpatients and 1%−2% for HC.[6,10] Results from our study showed similar codetection rates among all enrolled AGE and HC (8.2% and 2.3%, respectively). When an organism was detected in our study, codetection rates varied by organism, ranging between 20% and 60%. Among the 2 most common bacteria detected in children with AGE (*C difficile* and *Salmonella*), more than one-half represented a codetection. Indeed, NoV or RV was codetected in approximately 40% of samples with *C difficile* or *Salmonella* detection, suggesting that *C difficile* and *Salmonella* may not always be the AGE-causing pathogen or that viral AGE may enhance these bacterial pathogens. Therefore, assessing clinical presentation and exposure history is essential to assess likely etiology and to avoid unnecessary antibiotic treatment.

The proportion of participants either having contact with another sick individual or attending daycare was significantly higher for the case control AGE group compared with the HC group, despite similar distributions in patient age, sex, and race/ethnicity. In our study, the proportion of children with AGE having a sick contact was approximately 10 times that of HC. Halasa et al found that sick contact exposure in AGE patients was 7 times higher than in HC (30% vs only 4%).[6] Approximately 40% of children with AGE were reported to attend daycare compared with 29% of HC, similar to another study reporting preschool/school attendance of 41% among AGE and 32% among HC children.[6]

Our study has limitations. The study was performed at a single site in 1 Midwest US metropolitan area. The data represent only enrolled participants. A total of 38% of eligible AGE ED cases that were approached for study participation during the study time period were not enrolled. Both factors may affect the generalizability of our results. Our study time period was 2011–2016, which may not represent current AGE epidemiology. Further, parental reporting of clinical symptoms and risk factors during the prospective interviews may have introduced recall bias. However, the data collected in this study used a standardized protocol and questionnaire as in prior NVSN studies. Last, although the matching decreased notable differences in patient demographics (ie, age, race/ethnicity) between the original AGE and HC groups, unmeasured confounders may have affected the differential distributions in risk factors and pathogen detection when comparing AGE and HC groups.

Our data from the Midwest US show that viruses were detected more commonly than bacteria in stools from AGE participants attending the ED. After NoV, RV remains the second most common virus detected in AGE >10 years into the RV vaccine era. Our data also reveal that NoV was the second most commonly detected pathogen among asymptomatic children. Whether asymptomatic children with NoV-positive stools are contagious should be investigated. Last, *C difficile* detection rates were slightly higher among asymptomatic children compared with children experiencing AGE symptoms. ■

Acknowledgments

This work was supported by the US Centers for Disease Control and Prevention (cooperative agreement number CDC-RFA-IP16-004). The funder contributed with data interpretation and writing the manuscript. The findings and

conclusions in this report are those of the author(s) and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

B.R.L.'s institution received funding from Merck for an unrelated study. C.J.H.'s institution received funding from Merck, GSK, and Pfizer for unrelated studies. Since the completion of the study, F.H. is employed by Sanofi US.

Glossary

AGE	Acute gastroenteritis
ED	Emergency department
ETEC	Enterotoxigenic *E coli*
HC	Healthy control
NoV	Norovirus
NVSN	New Vaccine Surveillance Network
RV	Rotavirus
STEC	Shiga-like toxin producing *E coli*

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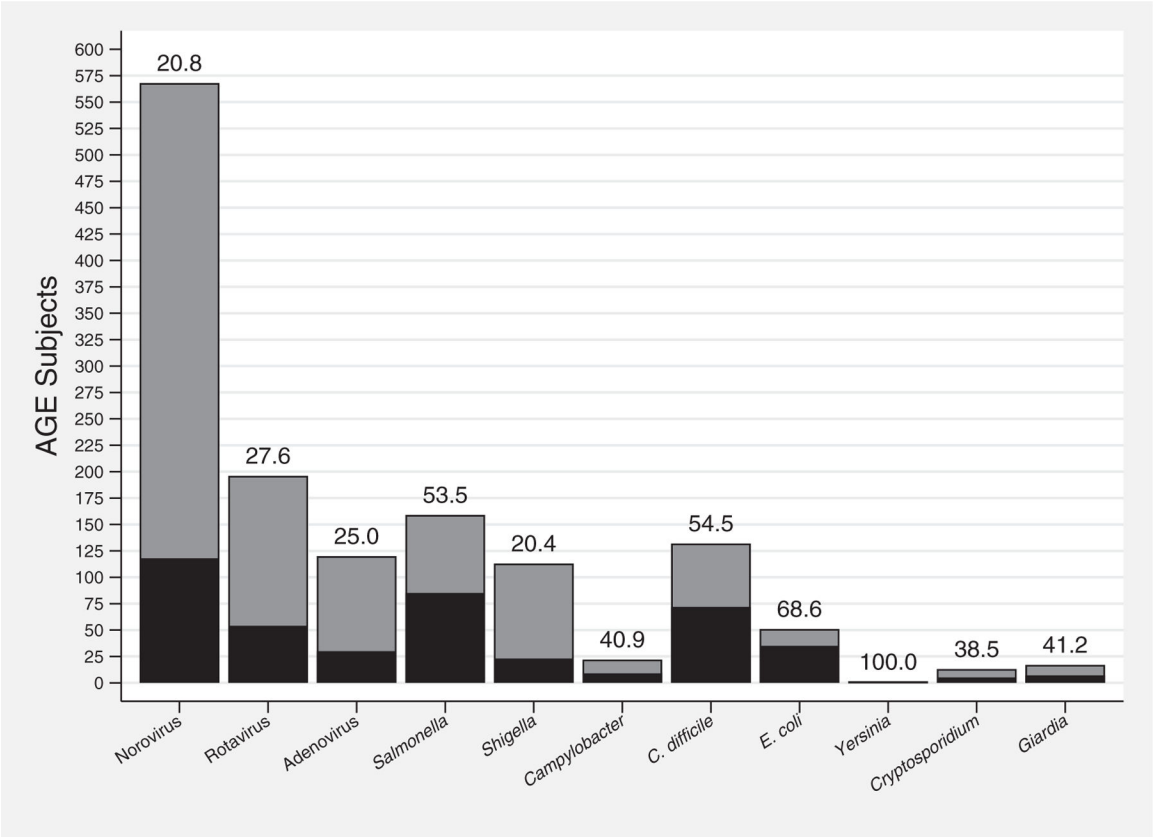

Figure 1.

Frequency of pathogen detections among enrolled AGE participants (n = 2503). Number above the bar indicates the percent with codetection. Gray portion indicates single-pathogen, black portion indicates co-detection.

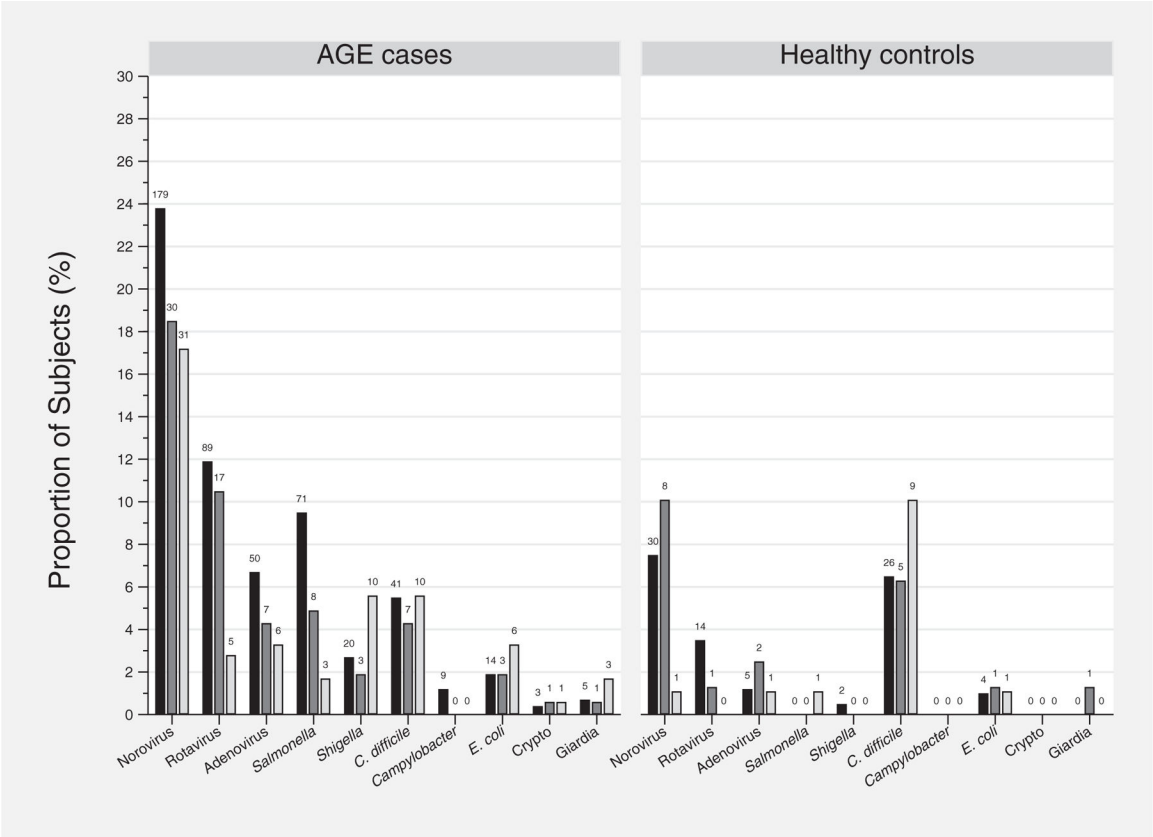

Figure 2.

Prevalence of organism detection by age group and AGE/HC status. Number above the bar denotes the number of detections. Black bar indicates children 0 through 23 months, darker gray for children 24 through 59 months, and light gray for children ≥60 months.

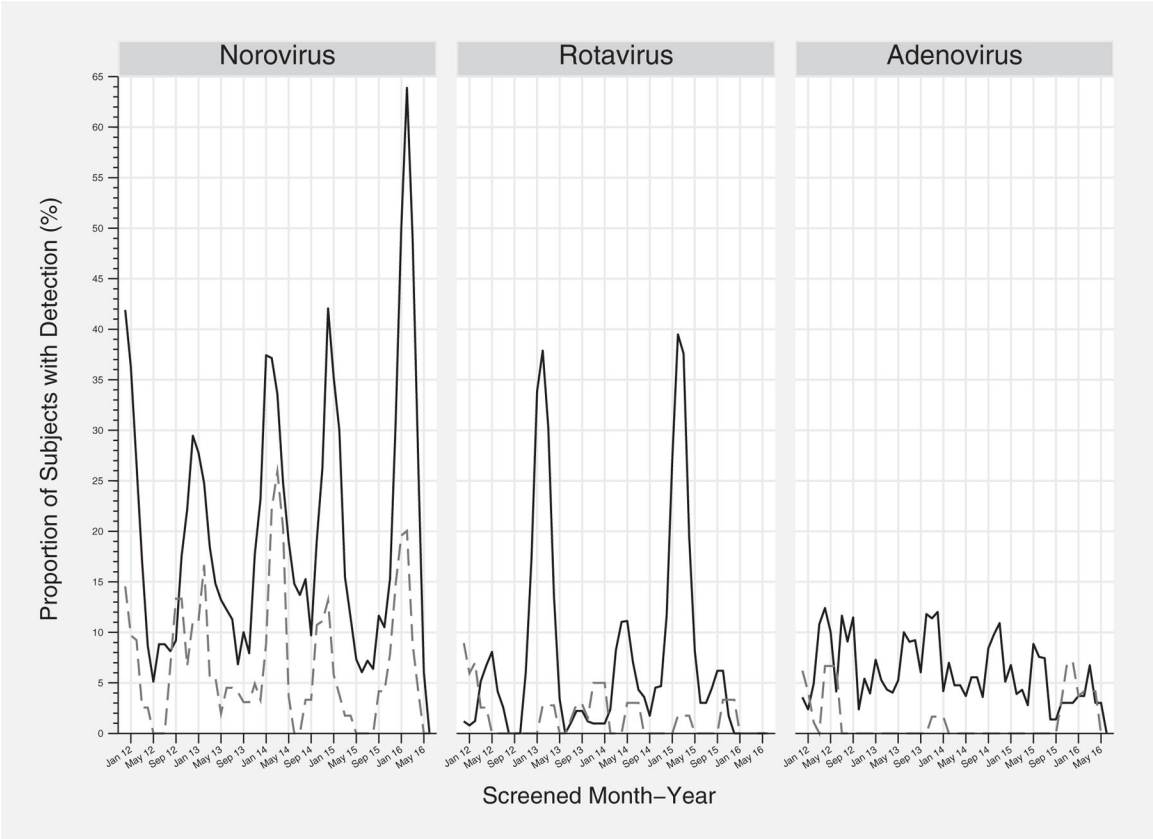

Figure 3.

Seasonality of viral pathogens. Solid black line indicates AGE cases, whereas dashed-gray line represents Healthy controls.

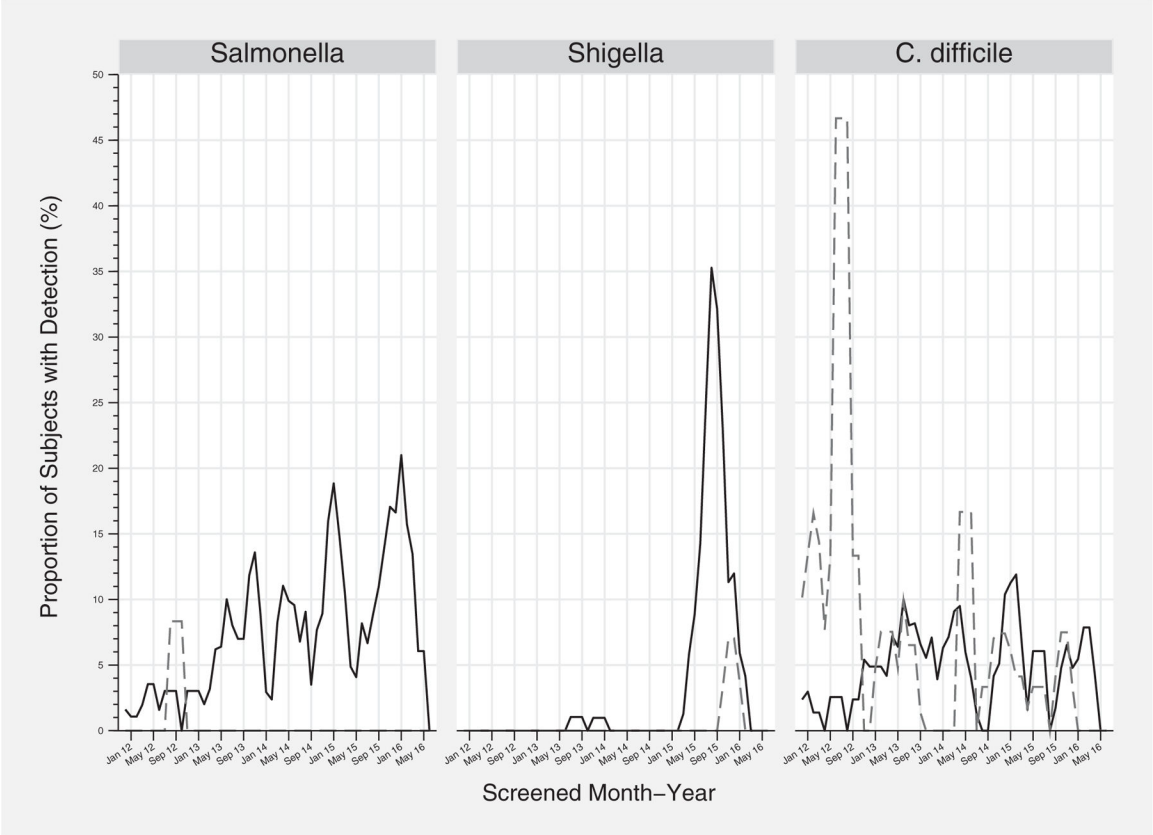

Figure 4.

Seasonality of bacterial pathogens. Solid black line indicates AGE cases, whereas dashed-gray line represents Healthy controls.

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Table I.

Patient demographics

Characteristics	AGE cases (n = 2503)				AGE cases and HC subjects in case control sample (n = 1666)			
	No pathogen detected (n = 1344)	≥1 Pathogen (n = 1159)	Difference in proportion (%)	*P* value	AGE (n = 1093)	HC (n = 573)	Difference in proportion (%)	*P* value
Age, months								
<6	111 (8.3)	86 (7.4)	0.8 [–1.3 to 2.9]	.437	155 (14.2)	104 (18.2)	−4.0 [–7.7 to −0.2]	.034
6–11	184 (13.7)	202 (17.4)	−3.7 [–6.6 to −0.9]	.01	246 (22.5)	123 (21.5)	1.0 [–3.1 to 5.2]	.627
12–23	272 (20.2)	341 (29.4)	−9.2 [–12.6 to −5.8]	<.001	350 (32.0)	175 (30.5)	1.5 [–3.2 to 6.2]	.537
24–59	434 (32.3)	317 (27.4)	4.9 [1.4 to 8.5]	.007	162 (14.8)	81 (14.1)	0.7 [–2.9 to 4.2]	.707
≥60	343 (25.5)	213 (18.4)	7.1 [3.9 to 10.4]	<.001	180 (16.5)	90 (15.7)	0.8 [–2.9 to 4.5]	.689
Sex								
Female	595 (44.3)	546 (47.1)	−2.8 [–6.8 to 1.1]	.155	499 (45.7)	289 (50.4)	−4.8 [–9.8 to 0.3]	.063
Male	749 (55.7)	613 (52.9)	2.8 [–1.1 to 6.8]	.155	594 (54.3)	284 (49.6)	4.8 [–0.3 to 9.8]	.063
Ethnicity								
Hispanic	388 (28.9)	374 (32.3)	−3.4 [–7.0 to 0.2]	.065	193 (17.7)	95 (16.6)	1.1 [–2.7 to 4.9]	.58
Non-Hispanic	956 (71.1)	785 (67.7)	3.4 [–0.2 to 7.0]	.065	900 (82.3)	477 (83.2)	−0.9 [–4.7 to 2.9]	.643
Unknown	0 (0.0)	0 (0.0)	–	–	0 (0.0)	1 (0.2)	−0.2 [–0.5 to 0.2]	.344
Race								
Asian	9 (0.7)	4 (0.3)	0.3 [–0.2 to 0.9]	.26	7 (0.6)	3 (0.5)	0.1 [–0.6 to 0.9]	.769
Black	577 (42.9)	472 (40.7)	2.2 [–1.7 to 6.1]	.265	572 (52.3)	313 (54.6)	−2.3 [–7.3 to 2.7]	.373
Multiracial	99 (7.4)	96 (8.3)	−0.9 [–3.0 to 1.2]	.393	97 (8.9)	64 (11.2)	−2.3 [–5.4 to 0.8]	.132
Other race	18 (1.3)	18 (1.6)	−0.2 [–1.2 to 0.7]	.654	23 (2.1)	4 (0.7)	1.4 [0.3 to 2.5]	.031
Unknown/refused	284 (21.1)	264 (22.8)	−1.6 [–4.9 to 1.6]	.32	96 (8.8)	45 (7.9)	0.9 [–1.8 to 3.7]	.517
White	357 (26.6)	305 (26.3)	0.2 [–3.2 to 3.7]	.889	298 (27.3)	144 (25.1)	2.1 [–2.3 to 6.6]	.349

Values are number (%) or absolute difference [95% CI].

Table II.

Symptoms associated with AGE cases in pediatric subjects with the most commonly detected organisms compared with AGE cases with no organism detected used as the reference group for statistical analysis

Symptoms	NoV (n = 450)	RV (n = 140)*	Adenovirus (n = 90)	*C difficile* (n = 60)	*Shigella* (n = 90)	*Salmonella* (n = 74)	*Campylobacter* (n = 13)	No organism detected (n = 1344)
Fever	186 (41.4)†	85 (61.2)	35 (38.9)‡	31 (51.7)	67 (74.4)†	46 (62.2)	12 (92.3)†	749 (55.9)
T_{max}	101 [100.5–103]†	102 [101–103]	101 [101–102]	102 [101–104]	102 [102–103]	102.5 [101–103]	102 [101–103]	102 [101–103]
Diarrhea	294 (65.3)§	127 (90.7)†	81 (90.0)†	34 (56.7)	79 (87.8)†	50 (67.6)	12 (92.3)†	775 (57.7)
Episodes	4 [2–6]	6 [3–10]†	6 [3–8]†	4.5 [3–6]	7 [5–10]†	5 [3–10]	7.5 [5.5–11.5]‡	4 [3–6]
Emesis	426 (94.7)†	129 (92.1)	80 (88.9)	54 (90.0)	59 (65.6)†	57 (77.0)	5 (38.5)‡	1158 (86.2)
Episodes	5 [3–8]†	5 [3–7]§	3 [2–5]	4 [2–7]	3 [2–4]	3 [2–6]	5 [4–6]	4 [2–6]

T_{max}, maximum temperature.

Sample: AGE ED cases with select pathogens compared with no organism detected (N = 2261). Values are number (%) or median [IQR].

*RV (exclude <1 week after RV vaccine).

†$P < .001$; reference group: no detections.

‡$P < .01$.

§$P < .05$.

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Table III.

Pathogen detections

		Case-control Sample			
	All AGE cases (n = 2501–2503)	AGE cases (n = 1092–1093)	HC (n = 560–570)		
Pathogen	**Positive (%)**	**Positive (%)**	**Positive (%)**	**Difference in detection rates in cases vs HC (%)**	***P* value**
NoV	568 (22.7)	240 (22.0)	39 (6.8)	15.1 [11.9 to 18.3]	<.001
RV	196 (7.8)	111 (10.2)	15 (2.6)	7.5 [5.3 to 9.7]	<.001
Adenovirus	120 (4.8)	63 (5.8)	8 (1.4)	4.4 [2.7 to 6.0]	<.001
C difficile	132 (5.3)	58 (5.3)	40 (7.0)	−1.7 [–4.2 to 0.8]	.160
Salmonella	159 (6.4)	82 (7.5)	1 (0.2)	7.3 [5.7 to 8.9]	<.001
Shigella	113 (4.5)	33 (3.0)	2 (0.4)	2.7 [1.5 to 3.8]	<.001
Campylobacter	22 (0.9)	9 (0.8)	0 (0.0)	0.8 [0.3 to 1.4]	.030
E coli	51 (2.0)	23 (2.1)	6 (1.1)	1.1 [–0.1 to 2.2]	.120
E coli O157	21 (0.8)	8 (0.7)	5 (0.9)	−0.1 [–1.1 to 0.8]	.750
ETEC	20 (0.8)	10 (0.9)	1 (0.2)	0.7 [0.1 to 1.4]	.077
STEC	15 (0.6)	6 (0.5)	0 (0.0)	0.5 [0.1 to 1.0]	.076
Vibrio	0 (0.0)	0 (0.0)	0 (0.0)	–	–
Yersinia	1 (0.0)	1 (0.1)	0 (0.0)	0.1 [–0.1 to 0.3]	.470
Cryptosporidium	13 (0.5)	5 (0.5)	0 (0.0)	0.5 [0.1 to 0.9]	.106
Entamoeba	0 (0.0)	0 (0.0)	0 (0.0)	–	–
Giardia	17 (0.7)	9 (0.8)	1 (0.2)	0.6 [0.0 to 1.3]	.105

Denominator ranges in column headers reflect number tested for each pathogen. Values are number (%) or absolute difference [95% CI].

Table IV.

Bivariate comparison of risk factors for AGE infection between HC and matched AGE subjects

Risk factors	HC (n = 573)	AGE cases (n = 1093)	OR (95% CI)	*P* value
Breastfeeding (ever)	386 (67.4)	755 (69.1)	1.08 (0.87–1.34)	.489
Attend daycare currently, >4 h/wk	169 (29.5)	452 (41.4)	1.69 (1.36–2.09)	<.001
Sick contact outside household	8 (1.4)	170 (15.6)	13.01 (6.35–26.64)	<.001
Sick contact inside household	12 (2.1)	203 (18.6)	10.66 (5.90–19.27)	<.001
Household income				
≤$25,000	213 (37.2)	587 (53.7)	1.96 (1.59–2.41)	<.001
$25,001-$50,000	68 (11.9)	124 (11.3)	0.95 (0.69–1.30)	.751
$50,001-$100,000	28 (4.9)	82 (7.5)	1.58 (1.02–2.45)	.041
>$100,000	4 (0.7)	37 (3.4)	4.98 (1.77–14.05)	.001
Unknown/refused	260 (45.4)	263 (24.1)	0.38 (0.31–0.47)	<.001
Total household members	4 [3–5]	4 [3–5]	1.04 (0.79–1.37)	.778

The household members is a median [IQR.]