IDWeek 2022
Poster Number : 1459

Prevalence of Enterovirus and Parechovirus in Children with Acute Gastroenteritis and in Healthy Controls over a 7-year Period; 2011-2018

Anjana Sasidharan[1], Brian Lee[1], Kayla Shore[1] , Christopher J Harrison[1], Jennifer E Schuster[1], Mary E. Moffatt[1], Kristen Weltmer[2], Mary E. Wikswo[2], Brian Emery[2], M. Steven Oberste[2] and Rangaraj Selvarangan[1].

[1] Children's Mercy Hospital, Missouri, KC, [2] Centers for Disease Control and Prevention, Atlanta, GA

ABSTRACT

Background:

As of 2017 (WHO, 2017), diarrheal disease ranked second as a cause of worldwide mortality for children under five years of age. Approximately 50-70% of acute gastroenteritis (AGE) is viral in etiology, with commonly detected viruses including norovirus, rotavirus, and adenovirus. However, the epidemiology of enterovirus (EV) and parechovirus A (PeV-A) associated AGE in the United States is not well described. The purpose of our study was to determine the prevalence of EV and PeV-A in children with AGE vs. healthy controls (HC) over a 7-year period.

Methods:

From December 2011 – November 2018, we collected and tested stool samples from children less than 18 years of age prospectively enrolled in Children's Mercy-Kansas City's (CM-KC) site for the CDC's New Vaccine Surveillance Network; 3005 from subjects presenting with AGE and 1097 from HC. Samples from 2011 – 2016 (AGE: 2453; HC:752) and 2017 – 2018 (AGE:552; HC:344) were tested at CDC and CM-KC respectively by a real-time reverse transcription-PCR assay using specific EV and PeV-A primers targeting the highly conserved 5' untranslated region. Additionally, demographic data were collected from the electronic medical records.

Results:

Among 3005 AGE samples, EV was detected in 12.5% (n=386/3004), and PeV-A in 10.3% (n=252/3005). Among 1097 HC samples, EV was detected in 9.0% (99/1096), and PeV-A in 11.9% (130/1097). In 2014-2015 EV detection in AGE was highest (17.9%) among all years and significantly higher (p=0.004) than in HC samples (9.1%), whereas PeV-A detection in AGE was 9.5% vs. 15.6% in HC samples, p=0.008 (Table 1). Co-infections with EV and PeV-A were seen in 55 AGE and 21 HC. Most EV detections (45.1%) were in 1- to 2-year-olds, whereas PeV-A detections (47.3%) were in children <1 year old. Both EV (58.3%) and PeV-A (48.4%) detections were significantly more frequent in male children (p=0.006). The highest frequency of EV detections was in summer to fall months, and for PeV-A in late summer through early winter.

Table 1. Annual Detection of EV and PeV-A in Stools from Children with AGE and from Healthy Controls (HC) during 2011-2018.

	AGE-EV		HC-EV		AGE-PeV-A*		HC-PeV-A*	
Season	Tested	Positive	Tested	Positive	Tested	Positive	Tested	Positive
2011-2012	407	58 (14.3%)	138	14 (10.1%)	408	64 (15.7%)	138	17 (12.3%)
2012-2013	582	76 (13.1%)	229	21 (9.2%)	582	55 (9.5%)	229	27 (11.8%)
2013-2014	557	70 (12.6%)	144	17 (11.8%)	557	58 (10.4%)	144	19 (13.2%)
2014-2015	666	119 (17.9%)	186	17 (9.1%)	666	63 (9.5%)	186	29 (15.6%)
2015-2016	240	27 (11.3%)	55	6 (10.9%)	240	12 (5.0%)	55	1 (1.8%)
2016-2017	347	28 (8.1%)	200	17 (8.5%)	347	42 (12.1%)	201	22 (10.9%)
2017-2018	205	8 (3.9%)	144	7 (4.9%)	205	24 (11.7%)	144	15 (10.4%)
Total	3004	386 (12.9%)	1096	99 (9.0%)	3005	252 (10.6%)	1097	130 (11.8%)

*One stool sample was unavailable for EV testing.

Table 2. Age group distribution of EV and PeV-A from 2011-2018 in Kansas City children

Age	EV(+)	EV(-)		PeV(+)	PeV(-)
< 1 year	154 (31.8%)	1060 (29.3%)		212 (47.3%)	1002 (27.4%)
1- 2 years	219 (45.1%)	1404 (38.8%)		187 (41.7%)	1438 (39.4%)
3-5 years	71 (14.6%)	633 (17.5%)		36 (8.0%)	668 (18.3%)
> 5 years	41 (8.5%)	518 (14.3%)		13 (2.9%)	546 (14.9%)
Total	485	3615		448	3654
Pearson's chi-square	<0.0001			<0.0001	

INTRODUCTION

- Acute gastroenteritis (AGE) is a global health problem and a major contributor to childhood morbidity and mortality worldwide.
- Approximately two million deaths occur due to acute gastroenteritis in children under 5 years of age in the developed and developing countries (1).
- Approximately 50-70% of acute gastroenteritis (AGE) cases are of viral etiology, with commonly indicated viruses including Norovirus, Rotavirus, and Adenovirus, however the incidence of Enterovirus (EV) and Parechovirus (PeV-A) in AGE is less reported in the United States (2, 3).
- Enterovirus and Parechovirus are members of Picornaviridae, a family of small, non-enveloped, positive sense, single-stranded RNA viruses.
- Both EV and PeV-A can cause a wide range of clinical presentations including asymptomatic infections, respiratory infections, gastrointestinal infections, neonatal myocarditis, encephalitis, and sepsis-like disease (4,5).
- Additionally, EV and PeV-A are the most important causes of aseptic meningitis in neonates, with fecal-oral transmission from asymptomatic older siblings increasingly recognized as an important route of infection for this population (6).
- We collected data on EV and PeV-A prevalence in stool samples of children with AGE and healthy controls (HC) over a 7-year period (2011-2018).
- Here we report EV and PeV-A positivity rates in children with AGE and HC, with the aim of gaining a better understanding of EV and PeV-A epidemiology.

METHODS AND MATERIALS

Specimens:

- Network: Samples were enrolled in Children's Mercy, Kansas City for the CDC's New Vaccine Surveillance Network (NVSN).
- Sample collection: 3005 stool samples collected from Acute Gastrointestinal (AGE) and 1009 Healthy control (HC) children.
- Year: 2011-2018
- Age: Children <18 years

Nucleic Acid Extraction/Multiplex testing/Real Time RT-PCR:

- Stool samples from 2011-2016 were tested by the xTAG Gastrointestinal Pathogen Panel (GPP assay), a multiplex PCR for the simultaneous detection and quantification of multiple viral, parasitic, and bacterial targets.
- Samples from 2017-2018 were tested by the Biofire FilmArray Gastrointestinal (GI) Panel.
- For detection of EV and PeV-A, a separate RNA extraction was performed using the MagMAX Microbiome Ultra Nucleic Acid Isolation Kit (Cat#A42458)
- Samples were tested for EV and PeV-A by a separate one-step RT-PCR using specific EV and PeV-A primers targeting the highly conserved 5'untranslated region (UTR).

Data collection:

- The clinical and demographic information of the enrolled subjects were pulled from an electronic database.
- The Study was reviewed and approved by the Institutional Review Board of Children's Mercy.

RESULTS

Table 1 : Overall AGE and HC numbers from 2011-2018

AGE 2011-2018	n
AGE enrolled from 2011-2018	3005
Enterovirus (EV) Tested	3004
Parechovirus (PeV-A) tested	3005

HC 2011-2018	n
HC enrolled from 2011-2018	1099
Enterovirus (EV) Tested	1096
Parechovirus (PeV-A) tested	1097

Figure 1 : Annual distribution of EV and PeV-A in AGE and HC from 2011-2018

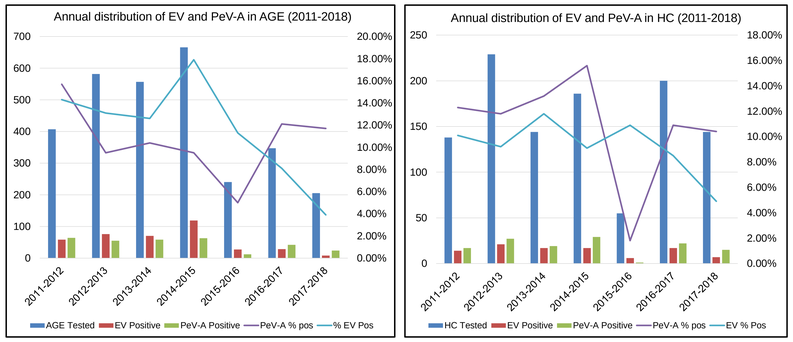

Figure 2 : Seasonal distribution of EV and PeV-A in AGE and HC from 2011-2018

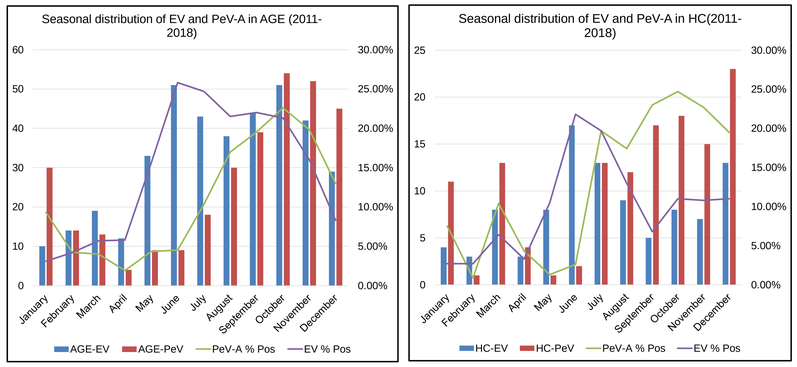

Table 2a: Age categories of EV and PeV-A patients in AGE (2011-2018)

AGE	EV(+)	EV(-)		PeV(+)	PeV(-)
< 1 year	111 (3.7%)	678		144 (4.8%)	645
1- 2 years	170 (5.6%)	1006		137 (4.5%)	1040
3-5 years	66 (2%)	510		29 (1%)	547
> 5 years	39 (1.3%)	424		8 (0.3%)	455
Total	386 (12.8%)	2618		318 (10.6%)	2687
Pearson's chi-square	0.005			<0.001	

Table 2b: Age categories of EV and PeV-A patients in HC (2011-2018)

HC	EV(+)	EV(-)		PeV(+)	PeV(-)
< 1 year	43 (4.3%)	382		68 (6%)	357
1- 2 years	49 (4.5%)	398		50 (4.5%)	398
3-5 years	5 (0.4%)	123		7 (0.63%)	121
> 5 years	2 (0.2%)	94		5 (0.4%)	91
Total	99 (9%)	997		130 (11.8%)	967
Pearson's chi-square	0.006			0.001	

Table 3 : Co-infections of other viral and bacterial targets with EV and PeV-A infections

		EV	PeV-A	Both	Negative
Any Virus					
	No	279 (76.0%)	194 (61.0%)	48 (67.6%)	1963 (66.9%)
	Yes	88 (24.0%)	124 (39.0%)	23 (32.4%)	972 (33.1%)
Any Bacteria					
	No	279 (76.0%)	207 (65.1%)	40 (56.3%)	2289 (78.0%)
	Yes	88 (24.0%)	111 (34.9%)	31 (43.7%)	646 (22.0%)
Any Co-detection					
	No	332 (91.0%)	255 (81.0%)	58 (81.7%)	2555 (88.0%)
	Yes	33 (9.0%)	60 (19.0%)	13 (18.3%)	350 (12.0%)
Common Pathogen Grouping					
	Negative*	264 (71.9%)	191 (60.1%)	44 (62.0%)	1948 (66.4%)
	Norovirus	52 (14.2%)	82 (25.8%)	21 (29.6%)	555 (18.9%)
	Rotavirus	23 (6.3%)	23 (7.2%)	0 (0.0%)	315 (10.7%)
	Adenovirus	12 (3.8%)	18 (8.1%)	2 (3.2%)	87 (4.0%)
	Shigella	19 (5.2%)	11 (3.5%)	5 (7.0%)	70 (2.4%)
	Co-detection**	103 (25.4%)	127 (34.5%)	27 (33.8%)	987 (30.4%)
	Co-detection***	77 (19.0%)	109 (29.6%)	21 (26.3%)	897 (27.6%)

*Negative for Norovirus/Rotavirus/Adenovirus/Shigella
**Co-infections with 2 or more targets: Norovirus/Rotavirus/Adeno/Shigella
***Co-infections with 2 or more targets: Norovirus/Rotavirus/Astrovirus/Sapovirus

Table 4: Clinical features of EV and PeV-A infections among children with AGE.

		EV (N=328)	PeV (N=260)	Both (N=58)	Negative (N=2358)	Significance
Diarrhea -- n (column %)						<0.001
	No	144 (43.9%)	69 (26.5%)	17 (29.3%)	761 (32.3%)	
	Yes	183 (55.8%)	191 (73.5%)	41 (70.7%)	1596 (67.7%)	
	Unknown	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	
Vomiting						0.01
	No	37 (11.3%)	42 (16.2%)	15 (25.9%)	273 (11.6%)	
	Yes	291 (88.7%)	218 (83.8%)	43 (74.1%)	2084 (88.4%)	
	Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	
Fever						0.098
	No	122 (37.2%)	114 (43.8%)	28 (48.3%)	1084 (46.0%)	
	Yes	204 (62.2%)	145 (55.8%)	30 (51.7%)	1264 (53.6%)	
	Unknown	2 (0.6%)	1 (0.4%)	0 (0.0%)	10 (0.4%)	
Eye Appearance						0.011
	Normal	225 (68.6%)	182 (70.0%)	44 (75.9%)	1487 (63.1%)	
	Sunken	70 (21.3%)	60 (23.1%)	10 (17.2%)	682 (28.9%)	
	Unknown	33 (10.1%)	18 (6.9%)	4 (6.9%)	189 (8.0%)	
Antibiotic						0.067
	No	317 (96.6%)	247 (95.0%)	57 (98.3%)	2214 (93.9%)	
	Yes	8 (2.4%)	12 (4.6%)	1 (1.7%)	136 (5.8%)	
	Unknown	3 (0.9%)	1 (0.4%)	0 (0.0%)	8 (0.3%)	
IR Therapy						0.169
	No	321 (97.9%)	251 (96.5%)	57 (98.3%)	2241 (95.0%)	
	Yes	7 (2.1%)	9 (3.5%)	1 (1.7%)	116 (4.9%)	
	Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	
Behavior						0.324
	Normal	53 (16.2%)	41 (15.8%)	13 (22.4%)	341 (14.5%)	
	Fussy/Less playful	186 (56.7%)	138 (53.1%)	36 (62.1%)	1267 (53.7%)	
	Lethargic	87 (26.5%)	79 (30.4%)	8 (13.8%)	721 (30.6%)	
	Seizure	1 (0.3%)	2 (0.8%)	1 (1.7%)	22 (0.9%)	
	Unknown	1 (0.3%)	0 (0.0%)	0 (0.0%)	7 (0.3%)	

DISCUSSION

- In this study we report the detection rates of EV and PeV-A among both children with AGE, as well as HCs.
- EV detection rates among children with AGE (12.9%) and HC (9%) were found to be comparable to prior studies.
- PeV-A detection rates were found to be 10.6% among children with AGE and 11.8% among HC children, falling within the previously reported ranges for both groups.
- There was no significant difference between the PeV-A detection rates of the two groups, indicating PeV-A is frequently shed asymptomatically in children's stool.
- A 2019 study found that children with meningoencephalitis from PeV-A commonly had at least one family member with stool positive for the virus (Izumita et al., 2019).
- Together, these findings indicate asymptomatically shedding of the virus in stool as an important contributor to viral transmission, and likely to incidence of severe disease.
- Majority of EV and PeV-A infections were noted in male children: 58.3% in EV, and 48.4% in PeV-A cases.
- EV infections were most common children among 1-2 years (45.1%), and a higher percentage of PeV-A infections were seen in children <1 year (47.3%).
- Co-detections with Norovirus, Rotavirus, Adenovirus, Astrovirus, Sapovirus and Shigella were seen in both EV and PeV-A infections.
- Limitation of the study: Genotyping data could provide more insight into potential association of specific EV or PeV-A types with AGE.