Enteric viruses other than rotavirus and norovirus in children under 5 years of age with gastroenteritis in Argentina, 2010–2021. A descriptive study

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ABSTRACT

Introduction. Data on the frequency of enteric adenoviruses, sapoviruses, and astroviruses in cases of sporadic acute gastroenteritis in Argentina are scarce.

Methods. Descriptive design of a selection of fecal samples of children with diarrhea younger than 5 years referred between 2010 and 2021, with a previous negative result for rotavirus and norovirus. The presence of enteric adenovirus, sapovirus, and astrovirus was tested by molecular methods, with subsequent genotyping of positive samples.

Results. At least 1 of the tested viruses was detected in 226 (39.4%) of the 574 selected samples. Specifically, adenovirus, sapovirus, and astrovirus were detected in 30.7%, 5.6%, and 3.1% of the samples, respectively. The most frequent viruses detected were adenovirus 41, sapoviruses GI.1 and GI.2, and astrovirus 1. Non-classic astroviruses were detected in 2 samples.

Conclusions. Despite being less frequent, these enteropathogens are responsible for a large number of sporadic diarrhea events. Therefore, their study and surveillance contribute significantly to reduce the gap of undiagnosed cases.

Keywords: human adenovirus infections; sapovirus; human astrovirus; diarrhea; Argentina.

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INTRODUCTION

Acute gastroenteritis is one of the most relevant diseases for pediatric public health worldwide.¹ In Argentina, prior to the introduction of the rotavirus vaccine into the Expanded Program of Immunization (2015), approximately 500 000 to 600 000 cases per year in children younger than 5 years were reported to the National Health Surveillance System.² However, after this strategy was implemented, a rapid decrease of 20% in acute diarrhea cases of any etiology was observed.³

In the case of acute non-inflammatory diarrhea in children younger than 5 years, several studies indicate that the most frequent etiology of this event is assumed to be viral. The most frequently detected enteropathogens in this age group are rotavirus A (RVA) and norovirus (NV).4-6 Prior to the introduction of a specific vaccine, RVA was identified in approximately 25% to 30% of the samples studied,⁷ with a subsequent decrease in prevalence of more than 50% as of 2016.3,7 In addition, noroviruses have attracted attention in recent years due to a high frequency of detection, mainly associated with the implementation of molecular methods and an increase at the expense of the decrease in rotavirus-associated cases in places with acceptable vaccination coverage.⁸ However, the proportion of acute, non-inflammatory diarrhea of unknown etiology remains high.^{4,6} Other diarrhea-causing viruses described for decades are enteric adenoviruses (AdV), sapoviruses (SaV), and astroviruses (AstV), but these are sometimes underestimated due to lack of knowledge or because the differential diagnosis is not considered important, since the treatment of cases of acute, non-inflammatory diarrhea is symptomatic.

AdVs cause a wide spectrum of diseases, including neurological, respiratory, eye, and gastrointestinal infections. AdVs are classified into 7 subgenera (AdV A-F) and more than 50 serotypes have been identified in humans. AdVs belonging to the F species (serotypes 40 and 41) are the most frequently associated with gastrointestinal conditions. Their circulation is not influenced by seasonal patterns and, although they are distributed worldwide, their prevalence varies between 2% and 15%.^{9,10} Recently, enteric AdV serotype 41 was detected in numerous cases of severe acute hepatitis in immunocompetent children, although their pathogenic role is unknown.¹¹ SaVs cause acute gastroenteritis mainly in children younger than 5 years. However, they have been detected as a causative agent of epidemic outbreaks in all age groups.¹² Given that SaV belongs to the same family as noroviruses, it has similar characteristics and is most frequently identified in autumn and winter. From a molecular perspective, SaV is divided into 5 genogroups; 4 of them (GI, GII, GIV, and GV) infect humans and these, in turn, are subclassified into 18 genotypes.¹³

Human AstVs are distributed worldwide, with a higher incidence in the winter. AstVs mainly affect children younger than 2 years, but, like most viral enteropathogens, infection poses a higher risk in immunosuppressed patients and older adults. Genetically, they are classified into 2 groups: i) classic AstVs, which include 8 serotypes, and ii) new AstVs, of which the MLB and VA variants have been documented in human fecal samples. Classic AstVs are those detected in the majority of cases, with an overall prevalence between 2% and 9%, while new AstVs have been isolated very sporadically worldwide.¹⁴

In Argentina, although these pathogens have been described as causative agents of acute gastroenteritis outbreaks,¹ there are no current studies on their frequency in acute sporadic diarrhea in children younger than 5 years. The only precedent is a study of viral etiology in 66 symptomatic patients more than 2 decades ago, in which the most frequently detected agents were rotavirus and norovirus.¹⁶

Therefore, the objective of this study was to analyze the frequency of detection of enteric AdVs, SaVs, and AstVs in fecal samples with negative results for rotavirus and norovirus in children younger than 5 years with symptoms of diarrhea in Argentina.

METHODS

This was a descriptive study on fecal samples from children younger than 5 years with symptoms of diarrhea; the samples were referred to the Laboratory of Viral Gastroenteritis of the National Institute for Infectious Diseases (Instituto Nacional de Enfermedades Infecciosas, INEI)-National Administration of Health Institutes and Laboratories (Administración Nacional de Laboratorios e Institutos de Salud, ANLIS) "Dr. Carlos G. Malbrán" in the period between 2010 and 2021, with a previous negative result for rotavirus A and norovirus. The samples belonged to the archival collection sent by members of the National Surveillance Network for Viral Gastroenteritis to the National Reference Laboratory for special tests and/or epidemiological purpose.

For sample selection, samples with a negative result for rotavirus and norovirus were retrieved from the database. Of these, for each year of the aforementioned period, every fifth sample (accounting for approximately 20%) was selected to be studied through a systematic sampling strategy. In the event that the volume of any of the selected samples was not sufficient, it was replaced by the next one, according to the registry.

The samples were previously diluted in a 1:10 ratio with sterile saline solution and then centrifuged. The supernatant was used to perform semi-automated nucleic acid extraction using the KingFisher[™] Flex system (Thermo Scientific, Massachusetts, United States). Extracts were pooled in groups of 4, then each pool was screened for enteric AdVs by PCR and for SaVs and classic AstVs by real-time RT-PCR.¹⁷ Nonclassic AstVs (MLB1 and VA1) were tested by end-point RT-PCR with visualization of the amplification products on a 2% agarose gel.¹⁸ In the case of detection of any of the viruses, the same procedure was carried out for each sample within the pool, individually.

Subsequently, the genotype of the positive samples for any of the enteropathogens studied was assessed by amplification and sequencing of the region of genetic variability (hexon, overlapping open reading frame [ORF] 1 and 2, and ORF1b for enteric AdV, SaV, and AstV, respectively).^{19–21} The detection frequency proportion for each of the viruses studied and the identified genotypes were described.

Although this study used human clinical samples whose personal or epidemiological data could be linked to the subjects, obtaining a consent was impractical or would have been very difficult because these patients had consulted for a single acute event 3 to 10 years prior to conducting the study. Likewise, the clinical samples were anonymized and, since this study did not consider data linked to the patient as variables of analysis, its conduct did not represent any risk, so obtaining an informed consent was not deemed necessary.22 This study was approved by the Research Ethics Committee of the National Institute for Epidemiology (Instituto Nacional de Epidemiología, INE)-ANLIS "Dr. Juan H. Jara", under code Degiuseppe B-03/2023.

RESULTS

Of the panel of 2876 fecal samples with a negative result for rotavirus A and norovirus in the 2010–2021 study period, 574 were selected. Of these, at least 1 of the viruses studied was detected in 226 samples (39.4%). The most frequent pathogen detected was enteric AdV (176, 30.7%), followed by SaV (32, 5.6%) and AstV (18, 3.1%) (*Table 1*). Mixed infections were identified in 14 samples (2.4%); the most frequent combination was AdV and SaV in 56.3% of cases. The 3 viral enteropathogens were detected in only 1 sample.

The analysis disaggregated by year showed that the detection of a viral etiology ranged from 13.0% (2010) to 53.3% (2020). Enteric AdVs were detected during the entire study period and in a higher relative proportion, except in 2020, when AstV was identified in a higher number of cases (*Table 1*). Likewise, SaV was detected practically throughout the entire study period, with the exception of the sample group from 2010. In addition, the detection of AstV was rather inconsistent: it was identified in 8 of the 12 years included in the study period (2011–2013, 2015–2016, and 2019–2021).

In relation to genetic diversity, the genotype of 140 enteric AdVs (79.5%), 18 SaVs (56.3%), and 17 AstVs (94.4%) was correctly identified. Of the 2 types belonging to subgenus F, AdV-41 was the most frequently detected. In the SaV-positive samples, only genotypes 1 and 2 of genogroup I were detected, in the same proportion. In addition, AstV showed greater diversity because 7 genotypes were identified, of which the most frequent one was the AstV-1 genotype. Likewise, it is worth highlighting the detection of non-classic AstV MLB1 in 2 samples (1 in 2015 and 1 in 2016) as the only viral enteropathogen present (*Figure 1*). No non-classic AstV VA strains were detected.

DISCUSSION

This study provides evidence on the detection and diversity of viral enteropathogens in cases of acute diarrhea in children. Enteric AdVs were the most frequently detected agents (30.7%). Some studies carried out in Turkey and Ethiopia also detected higher proportions of enteric AdVs,^{9,23} while others conducted in Brazil found a lower relative frequency.¹⁰ Despite the variability in prevalence, the most frequent genotype was AdV41. SaV was detected less frequently (5.6%), similar to the reports of studies carried out in the

Year	Received samples ^a	Selected samples	AdV		Sa	SaV		AstV		Overall detection		Mixed infections⁵	
	n	n	n	%	n	%	n	%	n	%	n	%	
2010	230	46	6	13.0	0	0	0	0	6	13.0	00		
2011	235	47	18	38.3	4	8.5	1	2.1	23	48.9	1	2.1	
2012	141	28	2	7.1	1	3.6	1	3.6	4	14.3	0	0	
2013	135	27	10	37.0	2	7.4	1	3.7	13	48.1	1	3.7	
2014	320	64	22	34.4	6	9.4	0	0	28	43.8	2	3.1	
2015	322	64	20	31.3	4	6.3	4	6.2	28	43.7	1	1.	
2016	325	65	23	35.4	4	6.2	5	7.7	32	49.2	4	6.1	
2017	327	65	23	35.4	5	7.7	0	0	28	43.1	3	4.6	
2018	316	63	20	31.7	2	3.2	0	0	22	34.9	0	0	
2019	324	65	25	38.5	2	3.1	1	1.5	28	43.1	0	0	
2020	74	15	3	20.0	1	6.7	4	26.7	8	53.3	2	13.3	
2021	127	25	4	16.0	1	4.0	1	4.0	6	20.0	0	0	
Total	2876	574	176	30.7	32	5.6	18	3.1	226	39.4	14	2.4	

TABLE 1. Overall and annual percent distribution of adenovirus, sapovirus, and astrovirus detection in fecal samples of children younger than 5 years. Argentina, 2010–2021

n: number. AdV: adenovirus. SaV: sapovirus. AstV: astrovirus.

^a Samples received at the Laboratory of Viral Gastroenteritis with a previous negative result for rotavirus A and norovirus.

^b The mixed infections detected distributed as follows: 8 AdV+SaV (1 in 2011, 2 in 2014, 1 in 2015, 1 in 2016, and 3 in 2017);

3 AdV+AstV (1 in 2013, 1 in 2016, and 1 in 2020); 2 SaV+AstV (1 in 2016 and 1 in 2020); 1 AdV+SaV+AstV (2016).

United States and the United Kingdom, in which the prevalent genogroup was also GI.²⁴ AstV was identified in the lowest proportion (3.1%). This relative frequency is similar to that described in Brazil and Italy, although higher values have been observed in Uruguay.²⁵ It is worth mentioning that AstV showed the greatest genetic diversity because 7 of the 8 genotypes described so far were identified, with a predominance of genotype 1.





In addition, the finding of non-classic AstV MLB1 represents the first report of detection in our country. Although its identification was sporadic, as previously described in Brazil, Australia, Japan, and the United States,¹⁴ it evidences its worldwide circulation and suggests its introduction into baseline surveillance systems.

A fraction of the samples showed mixed infections (2.4%), which is in line with previous studies carried out in India and Europe.^{26,27} Likewise, an even higher proportion would be expected considering the possibility of detecting any of these 3 viruses in samples positive for rotavirus and norovirus, or with any bacterial or parasitic pathogen. This type of finding is still challenging because it is not clear whether the detection of more than 1 agent is associated with greater clinical severity or whether any of them could act as a co-pathogen, favoring the infection by another microorganism.²⁸

These results highlight the importance of the contribution of the diagnosis of enteric viruses other than rotavirus and norovirus to the etiology of noninflammatory diarrhea of unknown origin. Globally, differences have been observed in the relative prevalence of these viruses.^{4,6} Therefore, it is important for children's health care centers to be aware of the local or regional epidemiology regarding the circulation of AdV, SaV, and AstV to assess the need to include their detection into the usual diagnostic algorithms and in what type of patients it would be worth implementing them. Mainly, because in a context of implementation of a specific rotavirus vaccine, the relative frequency of these agents may change. Likewise, a diagnostic approach that considers viral etiology beyond rotavirus will allow for improvements in daily practice and patient care by reducing the potential unnecessary use of antibiotics. In general, the detection of AdV in clinical laboratories is more accessible due to the use of immunochromatographic tests that identify both AdV and rotavirus simultaneously. Instead, the methods of choice to detect SaV and AstV involve molecular techniques. However, in recent years, methodological advances have allowed the development of molecular design kits that detect multiple enteropathogens by rapid and simple procedures.29,30

This study has certain limitations. First of all, since the sampling excluded samples diagnosed with rotavirus and norovirus, it is not possible to establish a net prevalence among the most frequent viral pathogens. Likewise, in the past 2 years of the study period, the number of samples in the collection was low because, during the SARS-CoV-2 pandemic, surveillance activities for events other than COVID-19 decreased drastically for multiple reasons, mainly due to the fact that healthcare providers were committed to other tasks and, in addition, due to the decrease in consultations during the period of social isolation. Secondly, molecular detection was performed using the sample pooling strategy. This is a frequent practice used in surveillance studies aimed at optimizing resources. While one might expect a dilution effect that would have prevented the detection of any of these pathogens, the viral load of excretion in the acute diarrhea period is high enough to be detected. In addition, in all positive pools, at least 1 positive sample was subsequently detected when the 4 samples were tested individually. Besides, the panel included samples from different geographical regions of Argentina due to the national nature of the surveillance network. However, the sampling process, the quantities of specimens selected, and the number of positive specimens do not allow us to analyze the frequency of detection at a provincial or regional level.

Although both the procedures for shipping samples for epidemiological surveillance purposes and the nature of the sampling do not allow the data to be interpreted as prevalence, the findings of this study are consistent with those described in the bibliography. Therefore, these findings reinforce the evidence of the circulation of these agents in the child population of Argentina and reveal a reduction of approximately 40% in the gap of cases of diarrhea of unknown etiology. This type of study represents a starting point for further studies that consider other aspects, such as seasonality, sociodemographic profile, and its association with the risk of requiring hospitalization to prioritize factors that allow predicting not only the etiology, but also the prognosis of this condition. And, above all, the ultimate goal is monitoring the associated disease burden to delineate prevention and control strategies targeted at this high impact event in the pediatric population.

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