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Rotavirus and adenovirus in children evaluated for viral gastroenteritis at a single healthcare center in the Eastern Province of Saudi Arabia: A perspective of two decades

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Abstract:

BACKGROUND: The aim of this study was to determine the distribution of rotavirus and adenovirus in pediatric patients evaluated for viral gastroenteritis in a hospital in the Eastern Province of Saudi Arabia for 22 years.

MATERIALS AND METHODS: This was a retrospective study based in a secondary healthcare center in Saudi Arabia. Laboratory and demographic data were collected from hospital records for all pediatric patients (up to 14 years old) evaluated for viral gastroenteritis by rotavirus/adenovirus antigen detection kit from January 2000 to December 2022. Data were analyzed utilizing SPSS version 28.0. Categorical data were presented as frequency and percentages, whereas mean and standard deviations were computed for continuous variables. Chi-square test and t-test were used to determine statistical significance.

RESULTS: The overall yields of antigen detection were 13.6% for rotavirus and 2.6% for adenovirus. Coinfection with both viruses was documented in 0.5% of the study population. Rotavirus was persistently detected in the past two decades with varying frequency, but the detection of adenovirus showed intervals of at least three consecutive years of zero confirmed cases. Before 2013, when the rotavirus vaccine was introduced in Saudi Arabia, rotavirus was much more prevalent than adenovirus (30% compared to 3.8% in 2010), but they became equally prevalent a decade after the introduction of the vaccine. Rotavirus gastroenteritis showed three different peaks in the year, in March, July, and December. Each peak was followed by a gradual decrease in prevalence before the next peak. Adenovirus, in contrast, was detected consistently around the year at rates between 2% and 5%.

CONCLUSION: Rotavirus and adenovirus gastroenteritis have changed in prevalence in the past two decades. We found distinct seasonal patterns associated with rotavirus and adenovirus gastroenteritis. The utilization of virological testing for pediatric gastroenteritis with syndromic testing panels is to be encouraged to improve the knowledge of the true prevalence of enteric viruses.

Keywords:

Adenovirus, antigen test, rotavirus, Saudi Arabia, viral gastroenteritis

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Introduction

Viral causes of gastroenteritis result in around 60% of all diarrheal episodes in children.[1,2] They are significant in both developing and developed countries owing to their relative resistance to hygienic and sanitary interventions.[1,2] They include rotavirus, norovirus, astrovirus, sapovirus, enteric adenovirus, parechovirus, enterovirus as well as other typically nonenteric infections

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that may manifest as diarrhea and vomiting such as influenza and coronaviruses.[3-8]Enteric viruses are also detected as part of co-infections, for which clinical significance has not been determined.[9]

Despite its self-limiting nature, gastroenteritis poses a significant public health problem. In 2015, it was estimated that 2.39 billion episodes of diarrheal illness occurred globally.[10] Rotaviral disease is associated with 200,000 deaths worldwide, most of which are in developing nations with little access to rehydration therapy.[11] It is estimated that the mortality rate associated with rotavirus gastroenteritis is 15 per 100,000 population in Saudi Arabia. A study in Oman revealed that the direct costs associated with a 3-day hospitalization as a result of rotaviral gastroenteritis reach 1.8 million US dollars per year.[12]

Before the introduction of rotavirus vaccine as part of Saudi Arabia's routine immunization program, the median prevalence of the virus in episodes of pediatric gastroenteritis was estimated at 30%, mostly detected in patients under 2 years of age.[2]

Some studies that serotyped strains from acute gastroenteritis by enzyme-linked immunosorbent assay using monoclonal antibodies,[13] showed a predominance of G1 and G4 serotypes, with high proportions of untypable strains. Another study which employed a more advanced modality, electropherotyping, and reverse transcriptase-polymerase chain reaction of the viral protein 7 and viral protein 4 genes, resulted in successful G-P typing of 93% of strains.[14] In line with earlier results, 89% of the typed strains were of G1P[8] serotype.[14]

To our knowledge, only one retrospective study in Jeddah demonstrated a reduction in the prevalence of rotavirus Group A from 38.5% 1 year before vaccine implementation to 13.2% 3 years after[15]

Data on viral etiologies other than rotavirus detected in cases of acute gastroenteritis in pediatric patients in Saudi Arabia are scarce. Little is known about the circulating serotypes of adenovirus implicated in episodes of acute gastroenteritis in children in Saudi Arabia. A large-scale study involving 3000 diarrheal stool samples reported 15 different serotypes, with serotypes 40 and 41 as the most common.[16]

Multiple knowledge gaps warrant research on viral gastroenteritis in Saudi Arabia. The current distribution of enteric viruses in terms of prevalence, severity, and seasonality is largely unknown. Further, the clinical burden of rotavirus in Saudi Arabia almost a decade after the introduction of the rotavirus vaccine is not well defined.

The self-limiting nature of viral gastroenteritis and the limited impact on treatment decreases routine viral diagnostic testing. However, prompt diagnosis of viral gastroenteritis optimizes antimicrobial stewardship[17] and decreases unnecessary health-resources expenditure.[17] This is demonstrated in the reduction of endoscopic and radiologic procedures, as well as shortened hospital stays.[17] Data are accumulating that major enteric viruses cause chronic gastroenteritis in HIV-positive and immunocompromised individuals, resulting in a prolonged viral shedding, which may persist in these patients for weeks to years as opposed to 20–40 days in immunocompetent individuals.[18] Recognition of such cases could prevent community- and hospital-based transmission. Detection of enteric viruses in episodes of viral gastroenteritis facilitates timely management of outbreaks.[19]

The aim of this study was to determine the distribution of rotavirus and adenovirus gastroenteritis in pediatric patients evaluated for viral gastroenteritis in a hospital in the Eastern Province of Saudi Arabia over a period of 22 years.

Materials and Methods

This study spans the period from January 1, 2000 to December 31, 2022 in patients aged up to 14 years old evaluated for viral gastroenteritis with the rotavirus/adenovirus antigen detection kit. It was a retrospective study in a 550-bed secondary healthcare center, including the Emergency Department in Al-Khobar, Saudi Arabia, serving patients from Dammam, Khobar, and Dhahran cities. Ethical approval was obtained from the Institutional Review Board (IRB) vide Letter No. IRB-PGS-2022-1-226 dated June 9, 2022 with a waiver of informed consent since there was no direct relation with human subjects in this study.

Duplicate samples within 2 weeks were excluded since most cases of acute gastroenteritis resolve within that period.[20] If duplicate samples were invariably positive or negative, a single positive or negative episode was counted accordingly. When any discrepancy in results was encountered (two duplicates in our study), we counted a single positive episode. This is justified by the plausibility of intermittent viral shedding and the performance of the assays.

This analysis targeted rotavirus/adenovirus lateral flow assays (LFAs) – the only available test at the hospital – ordered over the last 22 years (from 2000 to 2022). Results of the rotavirus/adenovirus antigen testing and associated parameters were retrieved from the electronic medical records. We collected data on age at testing, gender, nationality, and exact date of testing

for each documented result of rotavirus/adenovirus antigen detection assay.

LFA from the following providers was used: (1) Vikia Rota-Adeno (Biomerieux, Lyon, France), (2) Rota-Adeno (VitaAssay, Huesca, Spain), and (3) Rota-Adeno (Meridian Bioscience, Milano, Italy). There is no standard testing algorithm, and the testing decision is usually based on the need for improved diagnostic certainty.

Data included in the study were tabulated in IBM SPSS software Version 28.0 (Released 2021, Armonk, NY, USA: IBM Corp). Frequency statistics were used to summarize data on the results of the rotavirus/adenovirus assays, nationality, sex, seasonality, and annual trends. Descriptive statistics were used to summarize data on the age of patients across different classifications. A $P < 0.05$ was determined as the level of statistical significance.

Results

A total of 580 diarrheal episodes were evaluated for rotavirus and adenovirus gastroenteritis by antigen detection assays from 2000 to 2022. Demographic data plotted against rotavirus/adenovirus antigen results are summarized in Table 1. Of the tested population, 54.3% of patients were males (n = 315) and 45.7% were females (n = 265). The majority of patients were Saudis (n = 493, 85%). The mean age of children tested for viral gastroenteritis was 3.2 years (standard deviation ± 3.7) [Table 1]. There was no significant difference in overall mean age across genders or nationalities (P = 0.241 and 0.455, respectively).

The overall yields of antigen detection were 13.6% for rotavirus (79/580) and 2.6% for adenovirus (15/580). Coinfection with both rotavirus and adenovirus was documented by antigen testing in 0.5% of the study population (n = 3). Cases of co-infection were exclusively seen in children 5 years old or younger, all of which were documented in the 2016 winter season. There was no significant difference in rotavirus or adenovirus detection in the genders (P = 0.139 and 0.33 for rotavirus and adenovirus, respectively). No significant difference was observed in the proportion of cases positive for rotavirus or adenovirus between Saudi and non-Saudi patients (P = 0.773 and 0.855 for rotavirus and adenovirus, respectively). The mean age did not differ significantly among the children who tested positive or negative for rotavirus antigen (P = 0.059), and the finding was the same for both the children who tested positive or negative for adenovirus (P = 0.165) [Table 1].

Rotavirus and human adenovirus annual detection rates have shown distinct patterns [Figure 1]. Rotavirus was persistently detected over the past two decades with varying frequency, but there were intervals of at least three consecutive years of zero confirmed cases in the detection of adenovirus. During the era of pre-vaccination against rotavirus, before 2013, the difference in the annual rate between the two viruses was wide and in favor of rotavirus. In 2010, for instance, 30% of evaluated children tested positive for rotavirus antigen as opposed to only 3.8% positive for adenovirus gastroenteritis. A decade after the rotavirus vaccine introduction; however, rotavirus gastroenteritis annual rates gradually declined to equal those of adenovirus gastroenteritis. In 2021 and 2022, the rates of the two viruses were equal [Figure 1]. Owing to the unavailability of testing reagents, only one or no samples were tested annually from 2004 to 2007. Therefore, these years are not represented in Figure 1.

Both rotavirus and adenovirus were found to be year-round enteric viruses with distinct peak patterns [Figure 2]. Rotavirus gastroenteritis showed three different peaks in the year; in March, July, and

Table 1: Demographic characteristics of patients tested for viral gastroenteritis over the period 2000–2022 in a hospital, Eastern Province, Saudi Arabia

	Rotavirus antigen result			Adenovirus antigen result		
	Negative *N* (%)	Positive *N* (%)	*P-value*	Negative *N* (%)	Positive *N* (%)	*P-value*
Sex						
Male (*n*=315)	266 (84.4)	49 (15.6)	0.139	305 (96.8)	10 (3.2)	0.33
Female (*n*=265)	235 (88.7)	30 (11.3)		260 (98.1)	5 (1.9)	
Nationality						
Saudi (*n*=493)	425 (86.2)	68 (13.8)	0.773	480 (97.4)	13 (2.6)	0.855
Non-Saudi (*n*=87)	76 (87.4)	11 (12.6)		85 (97.7)	2 (2.3)	
Age group (years)						
≤5 (*n*=478)	410 (85.8)	68 (14.2)	0.27	465 (97.3)	13 (2.7)	0.33
6–10 (*n*=68)	60 (88.2)	8 (11.8)		66 (97.1)	2 (2.9)	
11–14 (*n*=34)	31 (91.2)	3 (8.8)		34 (100)	0	
Mean age (Years)	3.24	2.4	0.059	3.16	1.82	0.165

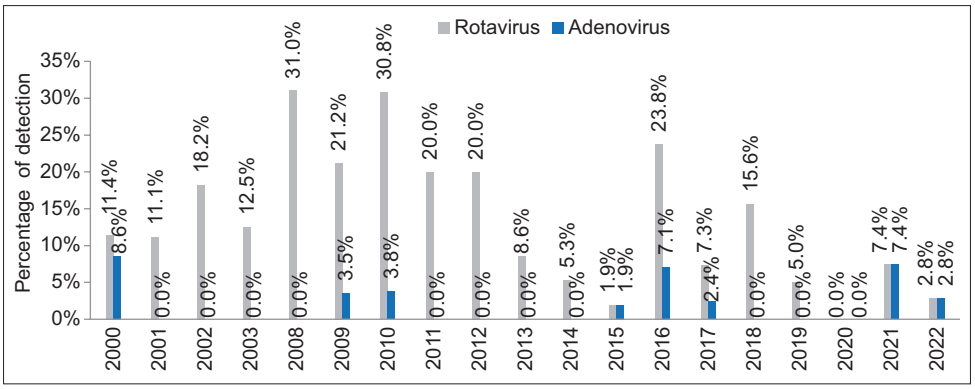

Figure 1: Annual rates of rotavirus and adenovirus gastroenteritis among patients evaluated in a hospital in Saudi Arabia from the year 2000 to 2022(*).*No testing was conducted in the study center from 2004 to 2007 due to intermittent reagent availability, and this duration is thus not represented in the figure

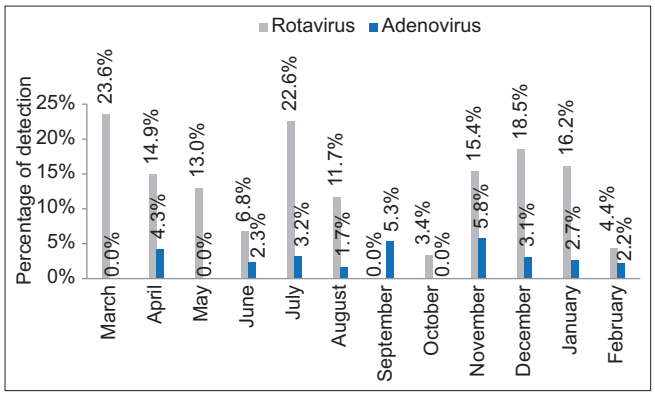

Figure 2: Seasonality of rotavirus and adenovirus gastroenteritis in patients evaluated in a hospital in Saudi Arabia from the years 2000 to 2022

December, each peak followed by a gradual decrease in the prevalence before the second peak [Figure 2]. Adenovirus, in contrast, was detected consistently through the year between in the range of 2% and 5%.

Discussion

The prevalence of viral antigen detection in our study was higher in children of up to 5 years old than in older children between the ages of 6 and 14 years. This finding is in line with the notion that rotavirus infection is almost universal early in life in unvaccinated children, and it confers partial protection against subsequent rotavirus infections.[21,22]

Our study did not compare vaccinated and unvaccinated children at a single point of time as that data were not available. However, a real-life observation that covers the two periods with respect to the introduction of rotavirus vaccination in Saudi Arabia (here referred to as the prevaccination era and the postvaccination era) has been demonstrated. This is the first survey to be done on the frequency of rotavirus and adenovirus gastroenteritis over two decades in a single Saudi healthcare center. We report an annual rate of pediatric rotavirus as high as 31% in 2008 (in the prevaccination era), as opposed to only 7.7% and 2.8% of cases confirmed as rotavirus gastroenteritis in 2021 and in 2022, respectively, approximately 9 years after the vaccine had been introduced locally. The absence of cases in 2020 is most probably due to distancing policies and reduced hospital visits during the COVID-19 pandemic. Most local studies on rotavirus gastroenteritis had been conducted before the rotavirus vaccine was introduced in the national vaccination schedule. During the pre-vaccination era (i.e., before 2013), the median prevalence of rotavirus in episodes of pediatric gastroenteritis was estimated as 30%, mostly in patients under 2 years of age.[2] Some studies have reported lower detection rates, but those included both adults and children, which dilute the overall rate.[13] In 2008, a study conducted in Makkah and Jeddah demonstrated that 22% of gastroenteritis episodes were rotavirus positive.[23] In Najran, a study reported a proportion of 17% of rotavirus-positive gastroenteritis in 2012.[24] In Riyadh, an outstanding 65.5% prevalence of rotavirus gastroenteritis led the authors to speculate a newly introduced genotype that was not present before.[1] This was not, however, directly proven in the corresponding study population. The techniques used in local studies to detect rotavirus antigen vary from enzyme immunoassays to immunochromatographic techniques. Since most of the studies did not utilize typing methods, it is difficult to clearly attribute this variance in prevalence to a particular factor.

Few local studies have covered the postvaccination era in Saudi Arabia. A retrospective study in Jeddah demonstrated a reduction in the prevalence of rotavirus Group A by antigen test from 38.5% 1 year before vaccine implementation to 13.2% 3 years after vaccine implementation.[15] The median age of rotavirus-induced gastroenteritis in the previous study sample increased after vaccination from 16 months to 44 months. Similar to our findings, a recent study in Riyadh described a further decrease in the proportion of rotavirus detection.[25]

Albeit from a sample size of 100, the authors reported that only 2% of the cases were confirmed as rotavirus gastroenteritis in children in 2022.

While rotavirus was far more commonly reported than adenovirus in the prevaccination era, we found a gradual decrease in cases of rotavirus gastroenteritis during the postvaccination era. The annual rate of detection currently is now equal to those of adenovirus gastroenteritis at 2.8% each. Indeed, a recent study in Riyadh showed an opposite distribution of prevalence.[25] In a majority of pediatric patients, adenovirus was detected in 7% of cases, whereas only 2% of patients tested positive for rotavirus. The authors found a female predominance for adenovirus gastroenteritis (a female-to-male ratio of 5:2), whereas the rotavirus antigen was exclusively detected in males. The study sample size, however, was not powered to describe the epidemiology of viral gastroenteritis. In our study population, we did not find a relationship between the detected viruses and gender. Overall, the accumulating data demonstrate a shift in the distribution of enteric viruses in children in the past. Since adenovirus and rotavirus were the only viruses sought in our study population, we cannot completely outline the changes in the prevalence of other enteric viruses.

This is the first study to survey the seasonality of rotavirus and adenovirus gastroenteritis in the Eastern Province of Saudi Arabia. We found that rotavirus cases were detected throughout the year with peaks in winter, early spring, and mid-summer. Seasonality patterns of rotavirus yielded variability across Saudi provinces which are also geographically and demographically diverse.[15]In Jeddah, for instance, cases of rotavirus-associated gastroenteritis appeared to peak in winter.[15] In Al-Taif, maximum rates were observed in the warmer months.[2] In Riyadh, however, a large-scale study of more than 1000 samples revealed no significant seasonal peaks of rotavirus gastroenteritis.[1]

Adenovirus appears to be an infrequently detected enteric pathogen in our study population. The overall proportion of adenovirus gastroenteritis was 2.6%. Notably, our analysis showed that detection of adenovirus in diarrheal stools was regularly interrupted by at least three consecutive years with no reports of adenovirus gastroenteritis. However, the laboratory policy is not standardized to consistently report adenovirus if not specifically requested by the ordering physician. This may have influenced the prevalence of the virus in our study sample and is attributable to the inherent documentation limitations of retrospective studies. The proportion of confirmed adenovirus gastroenteritis cases varies at different rotavirus vaccination eras and with different viral antigen detection techniques employed. A study conducted in Al-Qassim in 2006 showed that 7.7% of young children were positive for adenovirus antigen detected through an enzyme immunoassay.[26] A similar figure of 7.4% was reported from Makkah and Jeddah in 2008, also using an enzyme immunoassay.[23] In 2010, a higher proportion reported in Jeddah documented 16.2% of adenovirus gastroenteritis episodes. Based on data from Najran (2013), however, using an immunochromatographic technique, only 3.6% of gastroenteritis episodes were attributed to adenovirus.[24]

There are not much data on the seasonality of adenovirus gastroenteritis in different Saudi regions. We found that adenovirus was detected generally all year round with no major peaks in any specific season. A study in Riyadh showed that no cases of adenovirus gastroenteritis were documented in summer, whereas most cases were detected in autumn and early winter.[25] In consonance with our findings, the persistence of adenovirus gastroenteritis in the summer was reported by another study that combined samples from the Western and the central regions of Saudi Arabia.[27]

Coinfection with rotavirus and adenovirus was variably reported by a few studies in Saudi Arabia, primarily during the prevaccination era. Since most local studies only targeted rotavirus antigens, available data come from studies that included adenovirus and infrequently norovirus through antigen detection methods. We reported an 0.5% overall rate of rotavirus and adenovirus coinfection, representing 3% of positive episodes. As highlighted above, the adenovirus reporting system is also likely to affect the true prevalence of coinfection. Data from Al-Qassim revealed that 5% of gastroenteritis patients with positive viral antigens tested positive for both rotavirus and adenovirus.[26] This included the detection of different combinations of rotavirus, adenovirus, and norovirus. A retrospective study that analyzed more than 3000 episodes of gastroenteritis in Jeddah showed that 22.9% of the positive samples had had coinfection with rotavirus and adenovirus.[28] Indeed, the authors found that adenovirus was significantly more likely to accompany rotavirus than be detected in isolation (21.7% vs. 12.2% of rotavirus-positive and rotavirus-negative samples, respectively).[28] Our data showed that coinfection was detected in children younger than 5 years of age. Reviewed studies did not describe the age group and other clinical and epidemiological characteristics associated with coinfection. Owing to the limited target spectrum and the prevaccination timing of these studies, there is a current knowledge gap on the prevalence and impact of coinfection in enteric viruses. Further studies with more inclusive assays will improve our understanding of this entity.

The extended trend analysis in this study shows a generally low testing frequency, approximately two cases per month. The infrequent testing for enteric viruses generally reflects the reliance on clinical diagnosis for most diarrheal episodes. Routine microbiological testing for gastroenteritis is not always mandatory. It has been recommended that children aged 5 years or less should be tested for infectious pathogens if diarrhea did not improve by day 7, if the patient has been abroad recently, or in any diagnostic uncertainty.[29] Testing is strongly recommended for patients who are immunocompromised, present with blood or mucus in stool, or are suspected to be septicemic.[29] Another factor that may have influenced the utilization of enteric virus testing assays is unawareness of the availability of the test.

The presented study is not without limitations and barriers to generalizability. The quality of documentation and the retrospective design precluded the analysis of additional data, such as the severity of gastroenteritis attacks, vaccination status as well as the indication for testing. Furthermore, the uncertainty on reporting policy for adenovirus impedes our impression of the accurate epidemiological view of the virus. Finally, the current study is based on the diagnostic tests conducted by the study center, which only target rotavirus and adenovirus by antigen detection. Further studies using more sensitive and inclusive assays such as syndromic multiplex panels are recommended to enhance our knowledge of the epidemiology of enteric viruses in the Eastern Province of Saudi Arabia.

Conclusion

The distribution of the prevalence of rotavirus and adenovirus gastroenteritis has changed over the past two decades. Rotavirus has become less commonly detected a decade after the introduction of the rotavirus vaccination into the national immunization schedule. We found rotavirus cases detected all year round with peaks in winter, early spring, and mid-summer. Adenovirus was detected generally all year round with no major peaks in specific seasons. We report a low utilization of virological tests for pediatric gastroenteritis, which maintains the knowledge gap on circulating enteric viruses. With the adoption of newer virological assays, further studies with broader detection ranges are encouraged.

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Conflicts of interest

There are no conflicts of interest.

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