Severe lower respiratory tract infections are associated with human adenovirus in hospitalised children in a high HIV prevalence area

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Background. Viral causes of lower respiratory tract infections (LRTIs) are associated with increased mortality in children aged <5 years (U5). Human adenovirus (HAdV) has been associated with severe LRTI; however, its relationship with HIV and malnutrition in South Africa (SA) is not understood.
Objectives. To identify the prevalence of and factors associated with HAdV LRTIs in hospitalised U5 childen.
Methods. Clinical and viral data on U5 children hospitalised with severe LRTI from January 2018 to June 2020 at King Edward VIII Hospital, Durban, SA, including results of a multiplex polymerase chain reaction (PCR) panel assay for respiratory viruses, were retrieved from inpatient files and laboratory databases and retrospectively analysed. Standard descriptive statistics and Pearson's $\chi 2$, Fisher's exact and Mann-Whitney tests were used to determine significant associations with HAdV LRTI.
Results. Among the 206 viral assays analysed (15.6% of all LRTI admissions), HAdV was the most common virus identified. The cohort had a median (interquartile range) age of 5 (2 - 13) months, 47.3% had perinatal HIV exposure, and 34.5% had severe acute malnutrition (SAM). No seasonal pattern with HAdV could be demonstrated. SAM and prematurity were significant risk factors for readmission, and perinatal HIV exposure was a significant risk factor for presence of multiple viruses on analysis of a respiratory specimen. Detection of HAdV was not associated with an increased risk of requiring oxygen or ventilatory support.
Conclusion. HAdV was the most common virus found on analysis of multiplex PCR panel results in children hospitalised with severe LRTI in SA, where high rates of HIV exposure may result in increased susceptibility to viral co-infections. The role of HAdV as a cause of severe LRTI in SA infants, who have high rates of HIV exposure, requires greater scrutiny.
Keywords. Adenovirus, lower respiratory tract infection, HIV, children, pneumonia.

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Study synopsis
What the study adds. This study provides retrospective data identifying human adenovirus (HAdV) as the most common cause of severe lower respiratory tract infection (LRTI) in children aged <5 years (U5). The impact of respiratory syncytial virus as a common pathogen in children is well established. The study confirms anecdotal evidence that HAdV is an important disease-causing pathogen associated with LRTI. Children with perinatal HIV exposure and severe acute malnutrition (SAM) may be particularly susceptible.
Implications of the findings. HAdV must be considered a major cause of severe LRTI in U5 children. Children with LRTI who had perinatal HIV exposure and those with SAM need to be tested for HAdV and to be monitored for severe disease.

Lower respiratory tract infections (LRTIs), including bronchitis. bronchiolitis, and pneumonia with or without pleural effusion, are the most common cause of morbidity and mortality in children worldwide, especially in low- to middle-income countries (LMICs).[1] Viruses have been documented to be the leading cause of LRTIs worldwide, especially following the introduction and uptake of *Haemophilus influenzae* and pneumococcal vaccinations.[1] Of the viruses, respiratory syncytial virus (RSV) is the most common LRTI pathogen in both high-income countries and LMICs.[2] Other viruses that commonly cause LRTIs are influenza A and B, human parainfluenza virus (HPIV), human metapneumovirus (HMPV) and human adenovirus (HAdV).[2-5] A multicentre prospective observational study in LMICs identified RSV and HMPV as predictors of hypoxaemia and found an association between in-hospital mortality and these viruses.[5] HAdV was found to

be an important and under-recognised cause of severe LRTI in South Africa (SA).[6]

Risk factors for severe complicated RSV LRTI include premature delivery (<37 weeks' gestation) and asthma.[2,6] Other risk factors for morbidity and mortality include severe acute malnutrition (SAM), severe stunting and underlying cardiac disease.[6,7] With regard to HAdV and LRTI, risk factors identified in previous studies included HIV infection and SAM in almost half and one-third of patients, respectively.[6,7] However, the association of HAdV with LRTI in HIV-uninfected children who were perinatally HIV exposed is not well described. In SA, a study on children <5 years of age (U5) between 2009 and 2012 found that HIV-infected children were at increased risk of hospitalisation for LRTI, with RSV the viral pathogen identified in a high proportion of these cases.[3] HIV exposure and maternal smoking were also found to be risk factors for LRTI in children in their first year of life.[6] Another important pathogen in HIV-infected children was cytomegalovirus.[7]

There is a clear seasonal pattern in RSV infections globally, with differences between the Northern and Southern hemispheres.[8] While the impact of RSV in SA children has been well documented,[6] less is known about the impact and seasonal pattern of HAdV. There is robust evidence on the association of HAdV with severe LRTI, including long-term sequelae such as chronic lung disease and bronchiolitis obliterans.[7,9]

The objective of the present study was to describe the clinical characteristics of U5 children hospitalised with severe LRTI who tested positive for HAdV on a multiplex polymerase chain reaction (PCR) panel assay for respiratory viruses. In addition, we aimed to identify whether a seasonal pattern is associated with HAdV infections, and to determine whether there are specific risk factors associated with HAdV LRTI in a population of children with high prevalences of SAM and perinatal HIV exposure.

Methods

This retrospective cohort study reviewed the respiratory virus multiplex PCR results obtained from processing respiratory specimens of hospitalised children with LRTI, aged 1 - 59 months, between 1 January 2018 and 30 June 2020 at King Edward VIII Hospital (KEH), Durban, SA. KEH is a referral hospital that caters for a population with high U5 rates of SAM (9.1% of all U5 hospitalisations, accounting for 40.8% of in-hospital mortality in this age range).[10] This nutritional burden is compounded by a high prevalence of HIV infection in all paediatric hospitalisations and high mortality due to HIV (36.8% of all U5 mortality is HIV related).[10,11] Children diagnosed with severe LRTI are referred from other institutions, especially if they require higher levels of care, i.e. oxygen therapy, high-care monitoring, and non-invasive and invasive respiratory support.

Study definitions

For this study, a cohort of patients was selected for inclusion from a larger group of all doctor-diagnosed LRTI admissions to the institution (history of cough, tachypnoea with and without chest indrawing). Patients included in the study cohort were those who satisfied the following criteria for severe LRTI: presence of cough or difficult breathing and tachypnoea (age dependent) in addition to a general danger sign (usually poor feeding); chest indrawing or stridor in a calm child; presence of hypoxia at presentation (oxygen saturation <90% in room air); need for a high-care bed (as determined by the attending doctor); or need for ventilation as per international guidelines.[12] The definition of severe LRTI used in this study followed the general practice of the institution, where resource constraints require these patients (the potential study cohort) to be admitted to a high-care unit where more intensive nursing and medical cover can be provided (in a well-resourced environment, they would be admitted to an intensive care unit). From this potential study cohort, we excluded those with a proven bacterial aetiology (i.e. a positive blood culture or positive Gram stain), those subsequently categorised as having mild LRTI (not requiring oxygen and discharged within 24 hours), those with moderate LRTI (not requiring oxygen but requiring >24 hours of admission), and those with a diagnosis of upper airway obstruction (croup). The patients who satisfied all inclusion and exclusion criteria and had been tested with a multiplex PCR panel for respiratory viruses were included in the study.

The time period of the study was initially intended to reflect 3 calendar years, to enable us to fully identify and describe any seasonal patterns associated with respiratory viral pathogens. The COVID-19 pandemic resulted in premature cessation of data collection in June 2020, after 30 months.

Demographic and clinical variables

Demographic data were accessed through the DigiData system (DigiData, South Africa) used for inpatient hospital records. The nutritional status of each child was determined by calculating the World Health Organization (WHO) weight-for-age *z*-score (WAZ score) and weight for height,[13] using the IGROWUP macro for Stata (WHO Anthro version 3.2.2; StataCorp, USA). SAM was defined as a WAZ score ≤3[13] and/or the presence of nutritional oedema. The HIV status of patients was classified as perinatally HIV exposed or HIV unexposed, and further as HIV positive or HIV negative. Prematurity was defined as gestational age <36 weeks at birth documented in the Road to Health book or neonatal unit discharge documents. Routine laboratory investigations recorded were total white cell count (WCC) and C-reactive protein (CRP) level. The predominant radiological findings on the admission chest radiograph were described by the admitting doctor (paediatrician) within 24 hours of admission, using the following categories: no obvious abnormalities detected; interstitial infiltrates; multifocal opacities/consolidation; pleural effusion; and features of acute respiratory distress syndrome. These categories are used by all admitting doctors and have been adapted from the commonly used radiological categorisation of paediatric chest radiographs.[14]

Quality control measures included a primary data capture sheet to enter demographic, clinical, laboratory and radiological information for every patient who had multiplex PCR panel tests for respiratory viruses done (Supplementary file 1, available online at https://www.samedical.org/file/2206), with additional secondary verification of the radiological categorisation for each patient and the laboratory data.

Laboratory testing

Testing was done on respiratory specimens obtained during the first 24 - 48 hours of admission. The specimens included nasopharyngeal aspirates, nasal swabs and endotracheal aspirates. Specimens were immersed in viral transport medium and transported at 4 - 8°C to the National Health Laboratory Service (NHLS) Department of Virology

at Inkosi Albert Luthuli Central Hospital within 72 hours of collection. Specimens were tested using a real-time multiplex PCR panel assay for respiratory viruses. Viruses that were reported were adenovirus, influenza A and B viruses, HPIV types 1 - 3, and RSV. The PCR panel testing did not include the subtyping of viruses.

Data management

De-identified data were obtained from the NHLS Central Data Warehouse, including results of multiplex PCR panel testing for respiratory viruses from all requesting healthcare facilities in KwaZulu-Natal (KZN) Province for the stipulated period. The DigiData system used in the hospital for inpatient hospital records was used to obtain demographic data and enter them on primary data capture sheets. All data were curated into a password-protected database for further analysis.

Data analysis

The data collected were analysed using Stata 17 (StataCorp, USA). Descriptive statistics such as frequencies and percentages were used to summarise categorical data. Measures of central tendency mean and median and measures of dispersion, including standard deviation and interquartile range (IQR), were used to calculate numerical variables. Pearson's χ^2 test or Fisher's exact test was used for categorical categories, and the Mann-Whitney test was used for numerical data to test the null hypothesis for risk factors such as gestational age, nutritional status, perinatal HIV exposure, and HIV infection. A p-value <0.05 was considered to be statistically significant.

Ethics approval

Ethical approval was obtained before data collection from the University of KwaZulu-Natal Biomedical Research Ethics Committee (ref. no. BREC/00001178/2020), and gatekeeper permission was obtained from KwaZulu-Natal Department of Health, King Edward VIII Hospital and the NHLS.

Results

A total of 216 patients (16.4% of all 1 319 LRTI hospitalisations) fulfilled the inclusion criteria and had a multiplex PCR panel for respiratory viruses requested at the time of admission (Fig. 1). Of these, 10 were excluded from analysis because either the specimen had leaked while in transit to the laboratory or the information required was unavailable for that patient.

The median (IQR) age of the patients whose specimens were analysed was 5 (2 - 13) months, and 55.3% of patients were male (Table 1). Over a third (35.9%) were premature deliveries, and 41.6% had previously been admitted to the hospital for LRTI. With regard to growth parameters, 37.9% and 27.3% were classified as underweight and stunted, respectively. Just over a third (34.5%) were classified as having SAM. Nearly half (47.3%) had perinatal HIV exposure; however, only 9.9% were HIV infected.

The median (IQR) WCC (n=199 patients) was 11.7 (9.1 - 17) × 10^9/L and the median CRP level (n=162) was 13.5 (10 - 35) mg/L. Most patients (80.8%) required oxygen therapy on admission, and 21.4% required invasive ventilation during their hospitalisation. Radiological categorisation by the admitting paediatrician (n=204) showed that 55.9% of the patients had interstitial infiltrates with or without hyperinflation, 23.0% multifocal opacities/consolidation, and only 16.2% no documented abnormalities detected.

Table 1. Clinical characteristics of patients who had multiplex polymerase chain reaction panel testing for respiratory viruses

Characteristic	n (%)
Gender (n=206)	
Male	114 (55.3)
Female	92 (44.7)
Gestational age (n=198)	
Term	127 (64.1)
Preterm (<37 weeks)	71 (35.9)
Nutritional categorisation	
Weight for age (n=203)	
Normal	126 (62.1)
Underweight (≤2 z-score)	77 (37.9)
Weight for height (n=203)	
Not severely malnourished	133 (65.5)
SAM	70 (34.5)
Height for age (n=183)	
Normal	133 (72.7)
Stunted (≤2 z-score)	50 (27.3)
HIV status (n=203)	
Perinatal HIV exposure	
Exposed	96 (47.3)
Not exposed	107 (52.7)
HIV laboratory result	
Negative	183 (90.1)
Positive	20 (9.9)
Readmission status (n=197)	
First admission	115 (58.4)
Repeat admission	82 (41.6)
Oxygen requirement (n=198)	
No oxygen required	38 (19.2)
Oxygen required	160 (80.8)
Invasive ventilation (n=201)	
No ventilation required	158 (78.6)
Ventilation required	43 (21.4)
Radiological categorisation (n=204)	
No abnormalities noted	33 (16.2)
Interstitial infiltrates with or without hyperinflation	114 (55.9)
Multifocal opacities/consolidation	47 (23.0)
Pleural effusion	6 (2.9)
ARDS like	4 (2.0)

SAM = severe acute malnutrition; ARDS = adult respiratory distress syndrome.

Of the 206 specimens taken for multiplex PCR panel testing for respiratory viruses, 90 (43.7%) yielded one virus per specimen, 37 (18%) two viruses and 6 (2.9%) three viruses. No viruses were identified in the remaining 73 specimens (35.4%). HAdV was the most common virus isolated (n=69) followed by HPIV-3 (n=49) and RSV (n=43) (Fig. 1).

The positivity rates for HAdV, HPIV-3 and RSV on multiplex PCR panel testing for repiratory viruses on specimens from all healthcare facilities in KZN, including KEH, during the 30-month study period

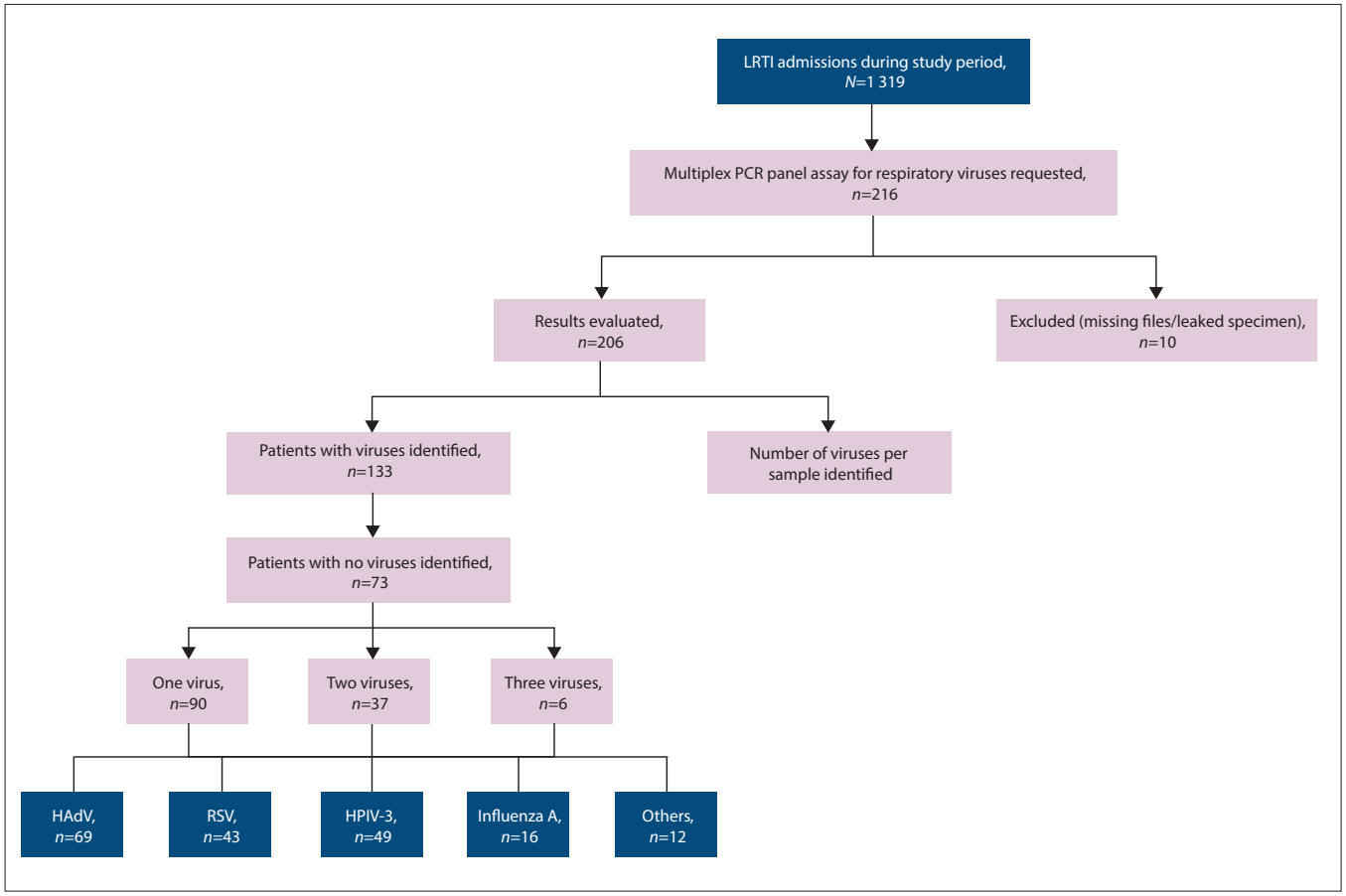

Fig. 1. Flow diagram illustrating the results of analysis of specimens from children aged <5 years with LRTIs. (LRTI = lower respiratory tract infection; PCR = polymerase chain reaction; HAdV = human adenovirus; HPIV-3 = human parainfluenza virus type 3; RSV = respiratory syncytial virus.)

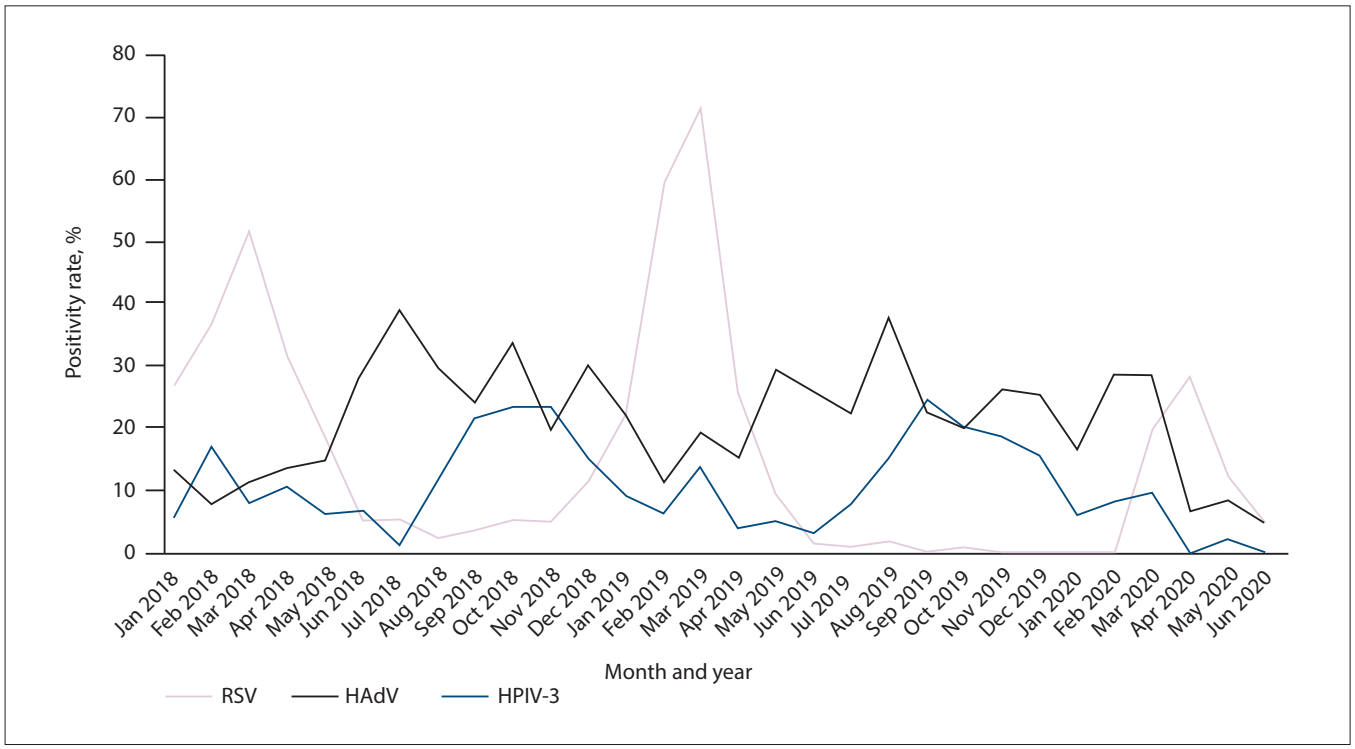

Fig. 2. Seasonal pattern of HAdV, HPIV-3 and RSV in KwaZulu-Natal Province over the study period. (HAdV = human adenovirus; HPIV-3 = human parainfluenza virus type 3; RSV = respiratory syncytial virus.)

is illustrated in Fig. 2. The positivity rate was used to demonstrate the seasonality of these viruses, if any. A clear seasonal pattern was identified specifically for RSV, with average peaks between February and March over the 30 months. For the 2020 period, the peak for RSV was between March and April and was lower than the previous years. There was an increase in the positivity rate for HPIV-3 from September to November; however, HPIV-3 was also detected during other months. For HAdV, no clear pattern was identified over the 30 months.

Patients in whom HAdV was the only virus detected were less likely to require oxygen on admission or invasive ventilation at any point in their admission than patients with other viruses or patients with no virus. Table 2 compares oxygen and invasive ventilation requirements in the analysed groups.

On assessing the risk factors for LRTI readmission, it was found that children with perinatal HIV exposure or HIV-infected children appeared less likely to have readmissions. Malnourished and overweight patients seemed more likely to be readmitted (p=0.02), as were those who had been born prematurely (p=0.001) (Table 3). A family history of asthma did not increase the risk of LRTI readmission.

On assessing the risk factors for having multiple viruses per specimen, patients with perinatal HIV exposure were more likely to have multiple viruses than those who were not HIV exposed (p=0.03) (Table 4).

Table 2. Comparison of oxygen and invasive ventilation requirements of patients with and without HAdV (N=206)

Management required	HAdV, *n* (%)	No HAdV, *n* (%)	Total, *N*	*p*-value
Oxygen therapy				0.61
No	14 (36.8)	24 (63.2)	38	
Yes	52 (32.5)	108 (67.5)	160	
Unknown	3	5	8	
Invasive ventilation				0.54
No	51 (32.3)	107 (67.7)	158	
Yes	16 (37.2)	27 (62.8)	43	
Unknown	2	3	5	

HAdV = human adenovirus.

Table 3. Risk factors associated with readmission†

Risk factor	No, *n* (%)	Yes, *n* (%)	Total, *N*	*p*-value
Gestational age (n=192)				0.001*
Premature	30 (43.5)	39 (56.5)	69	
Term	83 (67.5)	40 (32.5)	123	
Nutritional category weight/age (n=194)				0.3
Normal	76 (62.8)	45 (37.2)	121	
Underweight	38 (52.1)	35 (47.9)	73	
Nutritional category height/age (n=194)				0.3
Normal	79 (61.2)	50 (38.8)	129	
Stunted	34 (52.3	31 (47.7)	65	
Nutritional category weight/height (n=196)				0.02*
Normal	83 (64.8)	45 (35.2)	128	
SAM	31 (50.0)	31 (50.0)	62	
Obese	1 (16.7)	5 (83.3)	6	
Perinatal HIV exposure (n=195)				0.02*
Not exposed	53 (51.5)	50 (44.8)	103	
Exposed	62 (67.4)	30 (32.6)	92	
HIV infection (n=195)				0.23
Negative	102 (57.6)	75 (42.4)	177	
Positive	13 (72.2)	5 (27.8)	18	
Family history of asthma (n=191)				0.2
No history of asthma	93 (60.4)	61 (39.6)	154	
History of asthma	18 (48.6)	19 (57.4)	37	

SAM = severe acute malnutrition.
*Significant ($p<0.05$).
†Figures based on patients for whom data on readmission were available.

Risk factors associated with HAdV in LRTI hospitalisations

On univariate analysis of various risk factors for children with HAdV, no significant associations were found with gestational age, perinatal HIV exposure, HIV infection and malnutrition when compared with patients with all other types of viruses found and those without any viruses detected. Table 5 shows these risk factor analyses with the three most commonly found viruses, HAdV, RSV and HPIV-3. No significant associations were found when we compared these risk factors among patients with the three most commonly found viruses, excluding patients with no virus. When comparing patients who had been born prematurely with those born at term, more of the former (n=17/71; 23.9%) than the latter (n=18/124; 14.5%) had RSV (p=0.1).

Discussion

In the present study, HAdV was the most common viral respiratory pathogen detected in children hospitalised with severe LRTI. The role of HAdV in severe LRTI, resulting in hospitalisation and mortality, is of increasing concern worldwide.[8,9] The prevalence of HAdV in our cohort was 33.5%, higher than in previous SA studies, which reported figures ranging between 19% and 26% of isolates in children with LRTI.[3,6] These figures are, however, much higher than those reported elsewhere in Africa and in China.[2,15-18] HAdV has been noted in cases of severe LRTI, and our cohort had similar disease severity to many of these studies.[8,15-18] Detection of HAdV on nasopharyngeal aspirate or nasal swab specimens in the absence of control groups may not prove that HAdV caused the LRTI; however, the increased frequency with which HAdV is seen in such cases requires further investigation.[19]

In HIV-infected children in the era of antiretroviral treatment, an association has been noted with HAdV detection.[20] In our cohort, of whom nearly half were perinatally HIV exposed, the increased presence of HAdV in severe LRTI admissions was notable.

Studies have documented that HIV-exposed, uninfected infants are more susceptible to LRTI than HIV-unexposed infants.[21] The higher HAdV rates in our cohort may be related to the high rate of HIV exposure; however, other factors such as the severe LRTI inclusion criteria and high rates of SAM may also have played a role. Our study also showed that children with perinatal HIV exposure and HIV-infected children had a significantly increased rate of multiple viruses detected on admission. While HIV-infected children have been noted to have an increased risk of polymicrobial infections with multiple bacterial, viral and fungal pathogens,[19,20] further investigation is required with regard to viral pathogens.

HAdV infections have been noted to be associated with severe LRTI,[15-18] and the present study corroborates this finding, although HAdV did not confer an increased risk for oxygen requirement or invasive ventilation when comparing patients with HAdV and those with RSV/HPIV-3. A more definitive study comparing patients with mild, moderate and severe LRTI and the roles of various viral pathogens within these categories is needed, with HAdV subtyping.[21] The seasonality of RSV has been well documented in SA, and the present study confirms the previously described peak between February and April in KZN,[22] and no HAdV seasonality, as described elsewhere in Africa.[23]

As found in other studies,[6,7] patients in our cohort who had been born prematurely were more likely to have readmissions and to be positive for RSV on testing. However, prematurity in our cohort

Table 4. Risk factors associated with detection of multiple viruses at admission†

Risk factor	0 or 1 virus, *n* (%)	Multiple viruses, *n* (%)	Total, *N*	*p*-value
Gestational age (*n*=195)				0.3
Premature	94 (75.8)	30 (24.2)	124	
Term	58 (81.7)	13 (18.3)	71	
Nutritional category weight/age (*n*=201)				0.9
Normal	100 (79.4)	26 (20.6)	126	
Underweight	59 (78.7)	16 (21.3)	75	
Nutritional category height/age (*n*=201)				0.9
Normal	106 (79.7)	27 (20.3)	133	
Stunted	53 (77.9)	15 (22.1)	68	
Nutritional category weight/height (*n*=203)				0.5
Normal	104 (78.2)	29 (21.8)	133	
SAM	53 (82.8)	11 (17.2)	64	
Obese	4 (66.7)	2 (33.3)	6	
Perinatal HIV exposure (*n*=203)				0.03*
Not exposed	91 (85.0)	16 (15.0)	107	
Exposed	70 (72.9)	26 (27.1)	96	
HIV infection (*n*=203)				0.3
Negative	147 (80.3)	36 (19.7)	183	
Positive	14 (70.0)	6 (30.0)	20	

SAM = severe acute malnutrition.
*Significant ($p<0.05$).
†Figures based on patients for whom data were available.

Table 5. A comparison of risk factors for severe lower respiratory tract infection by virus category (HAdV, RSV and HPIV-3)*

	HAdV				RSV				HPIV-3			
Risk factor	**Neg., *n* (%)**	**Pos., *n* (%)**	**Total, *N***	***p*-value**	**Neg., *n* (%)**	**Pos., *n* (%)**	**Total, *N***	***p*-value**	**Neg., *n* (%)**	**Pos., *n* (%)**	**Total, *N***	***p*-value**
Gestational age												0.6
Premature	53 (74.6)	18 (25.4)	71	0.07	54 (76.1)	17 (23.9)	71	0.1	55 (77.5)	16 (22.5)	71	
Term	77 (62.1)	47 (37.9)	124		106 (85.5)	18 (14.5)	124		92 (74.2)	32 (25.8)	124	
Perinatal HIV exposure												0.7
Not exposed	72 (67.3)	35 (32.7)	107	0.8	93 (86.9)	14 (13.1)	107	0.07	83 (77.6)	24 (22.4)	107	
Exposed	63 (65.6)	33 (34.4)	96		74 (77.1)	22 (22.9)	96		72 (75.0)	24 (25.0)	96	
HIV infected												0.2
Negative	123 (67.2)	60 (32.8)	183	0.5	152 (83.1)	31 (16.9)	183	0.4	142 (77.6)	41 (22.4)	183	
Postive	12 (60.0)	8 (40.0)	20		15 (75.0)	5 (25.0)	20		13 (65.0)	7 (35.0)	20	
Nutritional category weight for age												0.2
Normal	80 (63.5)	46 (36.5)	126	0.4	103 (81.7)	23 (18.3)	126	0.8	100 (79.4)	26 (20.6)	126	
Wasted	53 (70.7)	22 (29.3)	75		61 (81.3)	14 (18.7)	75		54 (72.0)	21 (28.0)	75	
Nutritional category height for age												0.6
Normal	84 (63.2)	49 (36.8)	133	0.3	114 (85.7)	19 (14.3)	133	0.07	102 (76.7)	31 (23.3)	133	
Stunted	49 (72.1)	19 (27.9)	68		51 (75.0)	17 (25.0)	68		52 (76.5)	16 (23.5)	68	
Nutritional category weight for height and nutrional oedema												0.7
Normal	85 (63.9)	48 (36.1)	133	0.3	108 (81.2)	25 (18.8)	133	0.8	103 (77.4)	30 (22.6)	133	
SAM	47 (73.4)	17 (26.6)	64		52 (81.3)	12 (18.8)	64		48 (75.0)	16 (25.0)	64	
Overweight	3 (50.0)	3 (50.0)	6		6 (100)	0	6		4 (66.7)	2 (33.3)	6	
Family history of asthma												0.73
Yes	107 (68.6)	49 (31.4)	156	0.1	124 (79.5)	32 (20.5)	156	0.07	119 (76.3)	37 (23.7)	156	
No	21 (55.3)	17 (44.7)	38		35 (92.1)	3 (7.9)	38		30 (78.9)	8 (21.1)	38	

*In this table, patients who were positive for HAdV are compared with all other patients who did not have HAdV (they either had other viruses or no viruses), This comparison is replicated for patients with RSV and HPIV.
HAdV = human adenovirus; RSV = respiratory syncytial virus; HPIV-3 = human parainfluenza virus type 3; Neg. = patients with no virus plus patients with virus other than specified; Pos. = virus alone or with other viruses; SAM = severe acute malnutrition.

conferred no increased risk of HAdV. Larger studies with high-risk premature cohorts need to assess the association with HAdV infection.[24]

Children with compromised immune function have been documented as being at increased risk of HAdV infection for various reasons.[18,21,23]. The role of SAM specifically remains elusive in terms of the risk of virally induced LRTI.[25] In our cohort, of whom nearly one-third were severely acutely malnourished, stunted or underweight, HAdV did not confer an increased risk when compared with RSV or HPIV-3.

Study limitations

This study was a retrospective file review of a cohort with incomplete and missing data. The sample was from single-institute data. The COVID-19 pandemic and associated lockdowns affected viral respiratory multiplex PCR panel testing from March 2020 onwards, impacting on data collection. Criteria for determining the need to request a multiplex PCR panel assay for respiratory viruses were based on admission practices in the institution, which could potentially bias the selection and impact on the generalisability of the study results. Our study did not assess mortality, length of stay, or the incidence of persistent lung disease. The cohort was restricted to patients with severe LRTI only, so comparisons with mild and moderate cases could not be drawn. Lastly, we did not document longitudinal outcomes in this study.

Conclusion

The most common virus found on multiplex PCR panel testing for respiratory viruses in a cohort of infants with severe LRTI in SA was HAdV. Perinatal HIV exposure may result in increased susceptibility to viral co-infections. The role of HAdV as a cause of severe LRTI in SA infants with high rates of perinatal HIV exposure requires greater scrutiny.

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