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Epidemiology and clinical outcomes of non-COVID viral respiratory infections in children from a low-middle-income country

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Abstract

Acute lower respiratory infections are one of the leading causes of morbidity and mortality in children globally. There is a lack of data reflecting the true burden of viral lower respiratory tract infections from low-middle-income countries like Pakistan. This study aims to describe the epidemiology and outcome of viral lower respiratory infection.

This was a cross-sectional and retrospective study carried out from January 1, 2019, to December 31, 2021. We identified 13 different non-COVID viral respiratory pathogens. The statistical association was assessed between different factors, *i.e.*, viral respiratory pathogens, with invasive and non-invasive mechanical ventilation, inotropic support, and mortality. A p-value of <0.05 was taken as significant. Among 234 patients, 187 (80%) had positive viral polymerase chain reaction (PCR). Males were predominant (n=137, 58%). The most common respiratory pathogen was the respiratory syncytial virus (RSV) (n=62, 26%), followed by entero/rhinovirus (n=24, 10%). Half of the patients (n=92, 50%) had a pediatric intensive care stay, and all required non-invasive mechanical ventilation (hi-flow). One-fifth of patients (n=34, 18%) required invasive mechanical ventilation and inotropic support. Overall, 8 (4%) patients with positive viral PCR died during the hospital stay. All the patients had associated comorbidity.

RSV is the most common respiratory pathogen identified. Non-invasive mechanical ventilation, particularly high-flow therapy, is crucial in managing patients with viral illnesses, though a subset may still require invasive support. These findings highlight the importance of preventive strategies, including vaccination, which could significantly reduce the burden of viral infections, minimize the need for intensive care interventions, and lower morbidity and mortality.

Key words: respiratory viruses, non-COVID viruses, respiratory syncytial virus, influenza, virus.

Introduction

Acute lower respiratory infections are one of the leading causes of morbidity and mortality in children globally, accounting for 16% of mortality in children under 5 years in 2015 [1]. The global under-five mortality rate declined by almost 60 percent from 93 deaths per 1,000 live births in 1990 to 38 deaths in 2019. In context to Pakistan, it comes under the top 10 countries with the highest numbers of deaths (thousands) for children under 5 years, in 2019 [2].

Pneumonia and diarrhea are still the leading causes of childhood mortality in developing countries [3]. However, there has been a remarkable improvement in the mortality indicator. These reductions are consistent with decreasing the prevalence of some key risk factors i.e., increasing socioeconomic development, vaccination and preventive interventions, improved access to care, and quality of care in hospitals [4]. Younger infants in low-income and lower-middle-income countries are at greater risk of hospitalization and increased morbidities because of various factors. They are also at an increased risk of dying from viral etiologies e.g., respiratory syncytial virus, Influenza, and Human Metapneumovirus associated acute lower respiratory infections than older children and those in upper-middle-income and high-income countries [5].

Respiratory syncytial virus (RSV) peaks in the late summer months and influenza in April to June. Significant associations are present between the detection of human parainfluenza 3 and human rhinovirus with the month mean dew point. A significant relationship exists between the Human parainfluenza virus and the temperature, and the dew point [6]. The incidence of acute respiratory infections is higher in the winter season [7]. This environmental epidemiology is essential to understanding peak respiratory and gastrointestinal disease in younger children. Most of these viral illnesses don't mount prolonged and life-long immunity; hence a potential recurrence is possible. Effective identification of viral pathogens is important to prevent transmission, set up appropriate management, identify high-risk populations, identify viruses to isolate the patients, and ensure antibiotic stewardship. RSV and influenza virus infection cause significant mortality due to complications like acute respiratory distress syndrome (ARDS) among infants not managed timely than comparable to those observed in hospitalized children [8].

The COVID-19 pandemic led to significant shifts in the patterns of respiratory viral infections, with preventive measures like mask-wearing, social distancing, and school closures resulting in a temporary reduction in illnesses such as RSV and influenza [9]. There is a paucity of data reflecting the true burden of viral lower respiratory tract infections from developing countries, including Pakistan. Severe respiratory viral diseases sometimes mimic severe bacterial pneumonia and lead to mismanagement with irrational use of antibiotics. The limited availability of viral Polymerase Chain Reaction (PCR) testing is one of the foremost issues that is crucial for detecting and identifying viral infections accurately. Shortage of PCR machines and reagents, resulting in delays in diagnosing and monitoring infectious diseases. Moreover, the cost associated with PCR testing is prohibitively high for many individuals and healthcare facilities, making it difficult for those with limited resources to get tested promptly. Additionally, a lack of skilled human resources trained to perform these tests further contributes to the problem, as accurate testing and interpretation require specialized knowledge and training [10].

Vaccination like the influenza vaccine plays an important role in preventing viral pneumonia. We aim for this study to describe the epidemiology, clinical outcomes, and short-term complications of viral lower respiratory infection. This will lead to a better understanding of the severity of viral respiratory illnesses, resource utilization, and predictors of length of hospital stay and mortality in severe viral lower respiratory tract infections. It is also important to know the number of PICU admissions because it involves a comprehensive assessment and the provision of specialized medical attention to address acute illnesses, especially respiratory infections. Utilization within the PICU is an essential aspect that requires careful management and allocation to cater to the varying needs and severity of patient's conditions. Efficient utilization of resources in the PICU, including medical equipment, skilled healthcare professionals, laboratory investigations, and medication, is necessary to ensure optimal care for each patient.

Materials and Methods

This was a cross-sectional data at multidisciplinary pediatric intensive care units (PICU), special care units, and pediatrics wards at Aga Khan University Hospital (AKUH), one of the major private tertiary care referral Hospitals in Karachi Pakistan from January 1st, 2019, to December 31, 2021. Aga Khan University Hospital (AKUH) is JCIA accredited and renowned for its advanced facilities, comprehensive services, and commitment to delivering high-quality patient care. The Department of Pediatrics at AKUH provides exceptional health care to neonates, infants, children, and adolescents. The team consists of highly skilled and experienced pediatricians, nurses, and support staff who are committed to providing personalized care to young patients and their families. The department offers a wide range of specialties, including neonatology. Pediatric cardiology, nephrology, gastroenterology, genetics, metabolic, neurology, 13-bed special care units, 24-bed neonatal, 8-bed pediatric, and 4-bed cardiac intensive care units. Aga Khan University Hospital has separate specialized emergency department services for the children.

All children from one month to 18 years with viral respiratory illness to whom nasopharyngeal viral PCR test was performed were included in the study. The sample was collected using a nasopharyngeal swab under respiratory negative pressure isolation, placed in a transport medium, and sent to the lab within four hours. The viral pathogens were checked for PCR. The nasopharyngeal viral PCR is a real-time, nested multiplexed polymerase chain reaction test designed to simultaneously identify nucleic acids from 15 different viruses (*Supplementary material - Annexure I*) and bacteria associated with respiratory tract infection, from a single nasopharyngeal swab (NPS) specimen. Internal controls are used to monitor all stages of the test process [11].

The sensitivity of a single RT-PCR test of upper respiratory tract samples in hospitalized patients is 82%. Sensitivity increases to 90% when patients are tested twice [12].

All children who fulfilled the eligibility criteria were enrolled in the study. Data Collectors were not blinded.

An ERC # 2022-6953-20414 was assigned. The study participants were assigned a unique study identification number to maintain confidentiality. The authors had no access to the information that could identify individuals. Data was collected on a structured proforma including demographics (i.e., age, weight-for-age, gender), clinical information (i.e., the reason for admission, need for intensive care, the requirement for inotropic support, invasive/non-invasive ventilation, etc.), laboratory information (radiology findings of the chest, viral respiratory panel (via nasal swab performed on all enrolled patients), and outcome variables (i.e., mortality, hospital length of stay, invasive and non-invasive mechanical ventilation). Respiratory pathogens identified and trends in different seasons i.e., summer or winter were also recorded on a pre-designed proforma. Radiologically, bronchiolitis was defined as peribronchial cuffing, haziness, airspace shadowing, pneumonia as collapse, consolidation, infiltration, opacification and fluid as pleural effusion, pulmonary plethora, mass, subcutaneous emphysema. We acknowledged the reporting of the initial two X-rays for uniformity among all patients.

Data was entered and analyzed in SPSS version 23. Descriptive analysis was used to determine the characteristics of individuals and demographic features. A cross tab was performed to analyze the outcome and association between exposure (respiratory pathogens) and outcome i.e., discharged home or died. The Chi-square test was applied to determine the association of different factors with the development of viral respiratory infection and its outcome. A p-value of <0.05 was taken as significant. Missing variables were adjusted at the analysis level.

Results

During the study period 234 patients were tested for viral respiratory PCR. Most of them were males (n=137, 58%). The median age was 9 months. According to the WHO z-score, (n=86, 37%) of patients were undernourished i.e., weight for height z-score was <3rd centile while (n=75, 32%) were stunted i.e., weight for age z-score was <3rd centile. Among 234 viral PCR tests performed, 187 (187/234= 80%) patients were PCR positive. Thirteen different types of respiratory pathogens were isolated in 187 patients (Figure 1).

Respiratory syncytial (RSV) virus was the most common respiratory pathogen (n=62, 26%) followed by entero/rhinovirus i.e., (n=24, 10%). One-fifth (18%) of patients have co-infection i.e., two respiratory pathogens identified. More viruses were identified during the month of summer (March-September) i.e., (n=155, 66%) as compared to winter (October-February) i.e., (n=79, 34%). The median hospital length of stay was 5 days. Most of the tests were performed on the 2nd day of admission (Mean ±SD; 2.3±1.5). Radiologically, pneumonia was the most frequent finding (n=94, 40%) along with bronchiolitis (n=66, 28%). (n=39, 16.6%) of patients had chest X-rays reported as normal.

Among 187 viral PCR-positive patients, (n=34, 18%) required invasive mechanical ventilation, and (n=92, 50%) required non-invasive mechanical ventilation (hi-flow). While looking at the frequently isolated viruses, (n=32, 40%) of patients with positive RSV required non-invasive mechanical ventilation (hi-flow), (n=9, 11.3%) mechanical ventilation. Of those who had rhino/enterovirus positive, (n=11, 21%) were on mechanical ventilation, (n=38, 73%) were on non-mechanical ventilation (hi-flow). Of patients with positive human metapneumovirus, (n=6, 22%) required mechanical ventilation, (n=20, 74%) were on non-mechanical ventilation (hi-flow). Eleven (29%) of patients with influenza required mechanical ventilation, (n=26, 68%) non-mechanical ventilation (hi-flow)

One-fifth (n=36, 19%) of the study population require inotropic support. Overall, (n=8, 4%) patients with positive viral PCR died during the hospital stay. Among those who died, 3 patients had positive human rhino/enterovirus, and 2 patients had human rhino/enterovirus + human metapneumovirus. One patient had positive parainfluenza virus, one with RSV, and one with RSV+ human rhino/enterovirus. All the patients had associated comorbidity, i.e., global developmental delay, congenital heart disease, metabolic disorder, and septic shock (pan-resistant Acinetobacter), except one with RSV+ human rhino/enterovirus with acute respiratory distress (Table 1).

Discussion

Our study demonstrates that respiratory syncytial virus is the most identified respiratory pathogen.

Respiratory tract infections are well-recognized as one of the leading causes of childhood morbidity and mortality globally. Pathogens may be detected in both symptomatic and asymptomatic children [13].

In a large study from Shenzhen Children's Hospital, China, involving 30,443 hospitalized children under 14 years, RSV was also reported as the most identified virus [14]. Similar results were found in another study done at a university in Islamabad, Pakistan [15].

Our study found that many patients were co-infected with more than one respiratory virus. A prospective study from the Netherlands found that 22.5% of patients had multiple viral infections, defined as the presence of two or more respiratory pathogens [16].

Our study revealed that the detection of common respiratory viruses notably peaked during the summer months.

In Taiwan, data from MacKay Memorial Hospital revealed that viral detection rates were highest during the summer and autumn seasons [17].

In our study, among the patients who died, three had positive human rhino/enterovirus, and two had co-infection with human rhino/enterovirus and human metapneumovirus. Additionally, one patient had the parainfluenza virus, another had RSV alone, and a third had RSV with human rhinovirus/enterovirus. Importantly, all patients who died had at least one associated comorbidity.

In a Jordanian study, 32% of PCR-positive patients required oxygen support, and 9% of these required PICU care [18]. Comparatively, in Colombia, at the Misericordia Foundation Hospital, 93.1% of pediatric patients with viral respiratory infections needed oxygen, with a mortality rate of 1.3%. Deaths were more likely among children with comorbidities [19].

In a cohort from the Children's Hospital of Philadelphia, RSV-associated ARDS mortality was not commonly seen, while those who died of rhino/enterovirus had more than one virus detected and comorbidities [20].

Another key observation in our study was the nutritional status of patients. A substantial proportion of children with non-COVID viral respiratory infections were undernourished, based on low weight-for-height, while many others were stunted based on low weight-for-age, both falling below the 3rd centile.

In a case-control study from Bangladesh, the viral causes of pneumonia in children with severe malnutrition were primarily attributed to RSV, influenza, human parainfluenza virus, and human metapneumovirus [21]. A systematic literature review from Arizona State University reported that children with higher rates of mortality when malnourished and experiencing a respiratory infection [22].

Strengths and Limitations

- This is the first study in the region on non-COVID respiratory pathogens during COVID-19.

- Viral pathogens are identified via a PCR test, which has high sensitivity.
- Data is statistically significant.
- This is a single-center study.
- The viral PCR test is expensive and is performed on a limited number of patients, so it is difficult to comment on the actual prevalence of respiratory viruses.
- It's a retrospective study so there are chances of missing data.
- We could not follow the patient post-discharge so could not comment on long term outcomes.

Conclusions

The respiratory syncytial (RSV) virus is the most common respiratory pathogen identified. Non-invasive mechanical ventilation, particularly high-flow therapy, plays a crucial role in managing patients with viral illnesses, though a subset may still require invasive support. These findings highlight the importance of preventive strategies, including vaccination, which could significantly reduce the burden of viral infections, minimize the need for intensive care interventions, and lower morbidity and mortality in a resource-limited setting. Future multicenter studies would be valuable to validate and expand upon our findings across broader contexts.

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Online supplementary material:
Annexure I. Collection of nasopharyngeal samples. Reproduced from: BioFire Diagnostics L. [11].

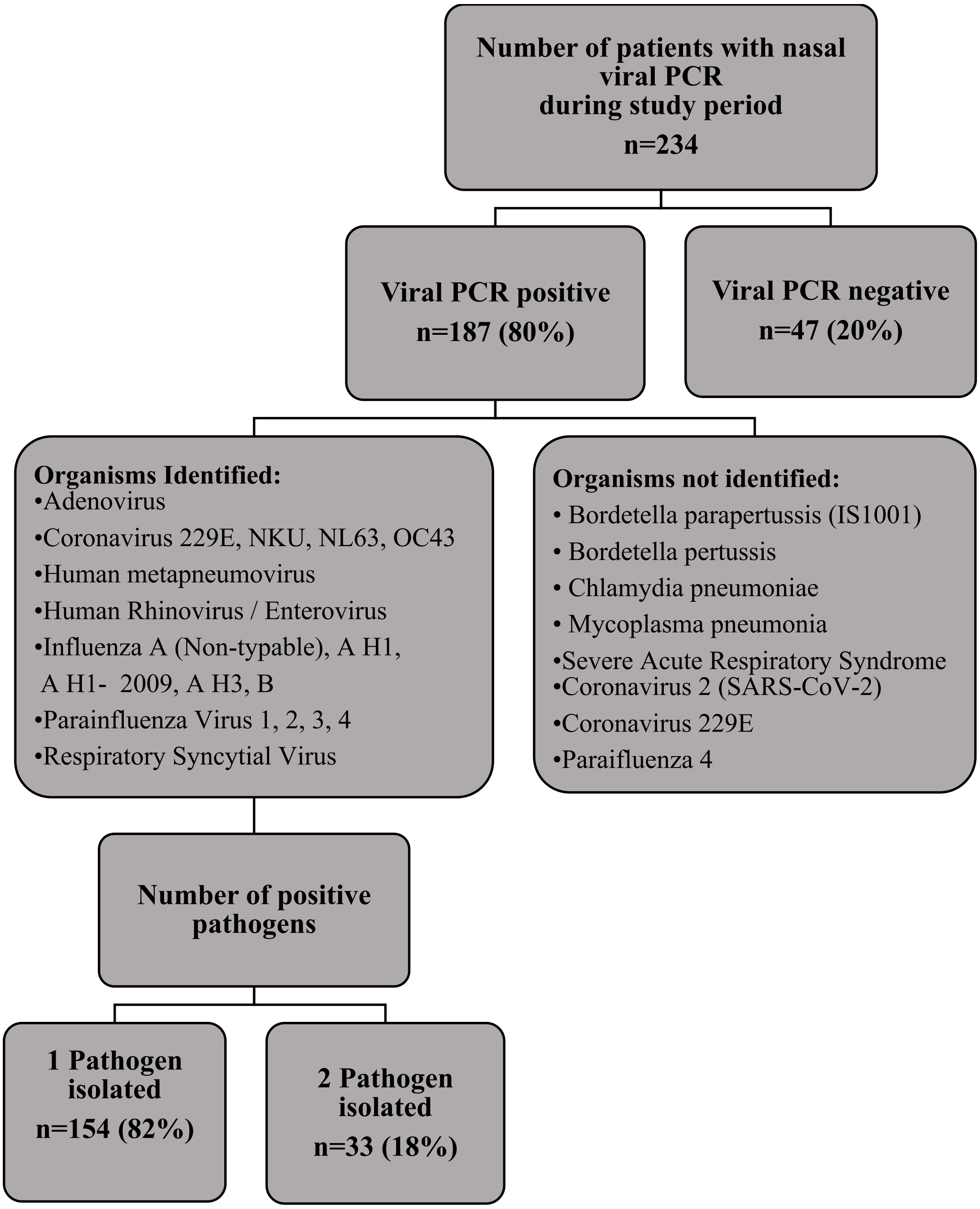

Figure 1. Number of patients with positive viral PCR.

Table 1. Demographic features, respiratory pathogens, and their associations.

Demographics		
		N = 234, (%)
Gender (Male)		137 (58)
Age (Median (Range): 9 months (0-24 months)		
Weight for age Z-score (Undernourished) ($<3^{rd}$ centile)		86 (37)
Height for age Z-score (Stunting)		75 (32)
Respiratory pathogens		
Respiratory syncytial virus (RSV)		62 (26)
Entero/Rhinovirus		24 (10)
Humanmetapneumo virus		19 (8)
Parainfluenza		18 (7)
Influenza		19 (7)
Humanmetapneumo virus + RSV		2 (1)
Humanmetapneumo virus + Entero/Rhinovirus		5 (2)
Human entero/rhinovirus + RSV		15 (6)
Human entero/rhinovirus + Parainfluenza virus		4 (2)
Human entero/rhinovirus + Influenza B		1 (0.4)
Adenovirus + RSV		1 (0.4)
Human entero/rhinovirus + Coronavirus OC43		2 (0.9)
Coronavirus	*Coronavirus OC43*	1 (0.4)
	Coronavirus NL63	1 (0.4)
	Coronavirus HKU 1	1 (0.4)
Influenza A + Humanmetapneumo virus		1 (0.4)

Respiratory pathogens and their associations

Respiratory pathogens	**PICU stay (N and %) / p-value**	**Mechanical ventilation**		**Inotropic support (N and %) / p-value**	**Mortality**
		Invasive (N and %) / p-value	**Non-invasive (high flow) (N and %) / p-value**		
Viral PCR	*109 (58.3) p<0.005	*34 (18.2) p<0.005	*109 (58.3) p<0.005	*36 (19.3) p<0.005	8
RSV	*32 (40) p<0.005	9 (11.3)	*32 (40.0) p<0.005	*9 (11.3) p<0.005	2
Rhino/enterovirus	*38 (73.1) p<0.005	11 (21.2)	38 (73.1)	13 (25.0)	3
Humanmetapneumo virus	20 (74.1)	6 (22.2)	20 (74.1)	5 (18.5)	2
Influenza	26 (68.4)	11 (28.9)	26 (68.4)	12 (31.6)	1

*p-value <0.005