

# A Retrospective Analysis of Human Parainfluenza Virus in the Pediatric Population

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## ABSTRACT

**Context:** Human Parainfluenza Viruses (HPIVs) are among the most common acute respiratory infections in children and contribute significantly to hospitalizations and emergency room visits in the pediatric population. Differences in clinical presentation and sequelae of the four HPIV serotypes have not been thoroughly characterized. This study describes the clinical symptoms, disease severity, and care demands associated with each of the viral serotypes, which may aid in decision making for the most appropriate available treatment modalities for future pediatric patients and improve quality of care.

### Objectives:

1. Describe and analyze the heterogeneity of HPIV serotypes in clinical presentation and disease outcome in the pediatric population.
2. Analyze oxygen requirement, length of stay, and potential complications in the context of specific viral serotype.
3. Determine whether or not certain HPIV serotypes are predisposed to a more severe course of infection and require escalation of care to the Pediatric Intensive Care Unit (PICU).

**Methods:** This single-center, retrospective, observational study reviewed 40 pediatric patients admitted to Spartanburg Regional Healthcare System (SRHS) with parainfluenza virus during a 15-month period. Inclusion criteria consisted of all patients less than 18 years of age admitted to the general pediatric ward or the PICU with a diagnosis of parainfluenza types 1-4 confirmed on a polymerase chain reaction-based test called FilmArray. Demographic and clinical data were collected and analyzed.

**Results:** The collected data found 75% of patients across all serotypes displayed nonspecific upper respiratory symptoms, while only 35% of patients (primarily HPIV-1 and 2 cases), manifested traditional croup symptoms. The most frequently diagnosed serotype was HPIV-3 and these patients experienced higher rates of bronchiolitis, pneumonia and Upper Respiratory Infection (URI) symptoms compared to other serotypes. While no statistical significance was observed in our small population, serotypes 1 and 4 necessitated greater care demands; with HPIV-1 resulting in the most PICU admissions (50%) and HPIV-4 patients averaging the longest length of stay and requiring the most supplemental oxygen.

**Conclusion:** This single-center, retrospective, observational study suggests that understanding the differences in symptomatology and severity of each serotype may proactively aid in the proper treatment and care of parainfluenza virus in the pediatric population. Further investigative studies with an increased sample size, multiple sites, and longer duration would be beneficial to support the data and further delineate preemptive actions when caring for the pediatric population with HPIV.

**Keywords:** Parainfluenza virus; Respiratory infections; RNA virus

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## INTRODUCTION

Human Parainfluenza Viruses (HPIVs) are single-stranded, enveloped RNA viruses belonging to the Paramyxoviridae family. They are among the most common causes of respiratory tract infections in children, and account for 40% of pediatric hospitalizations for lower respiratory tract infections and 75% of croup cases. Prior epidemiological analyses have determined that socioeconomic factors such as malnutrition, overcrowding, vitamin A deficiency, and environmental toxins can predispose children to HPIV infections. Reduced risk of progression to severe illness has been described in breast-fed infants and patients vaccinated against pneumococcal infections, while immunocompromised hosts remain more liable to poor outcomes [1].

There are four distinct serotypes of HPIV, numbered 1-4, which vary in clinical symptoms, incidence, disease severity, and seasonal occurrence. All HPIV serotypes (Figure 1) share common structures and replication strategies but target different parts of the respiratory tract and may cause different clinical manifestations. HPIV-1 and HPIV-2 replicate in the upper respiratory tract and are more likely to provoke croup; conversely, HPIV-3 replicates in the lower respiratory tract, making patients more susceptible to pneumonia or bronchiolitis [2]. Previous investigations have shown that HPIV type 3 is the most reported parainfluenza virus, followed by types 1, 2, and 4 respectively [3]. The serotypes also vary in circulation patterns, with HPIV-3 and 4 infections occurring throughout the year, and serotypes 1 and 2 appearing seasonally [4].

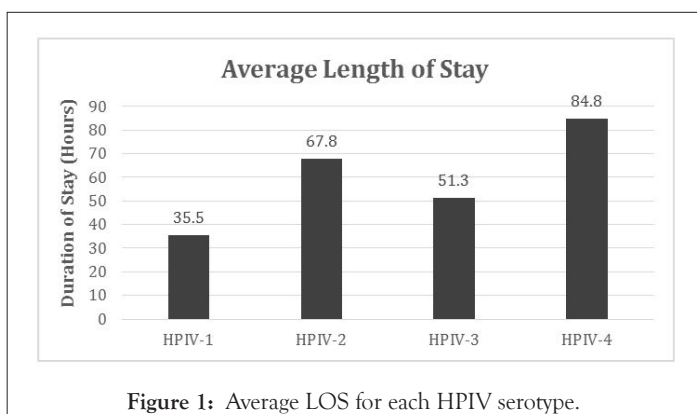


Figure 1: Average LOS for each HPIV serotype.

While previous research has analyzed the virology and epidemiology of HPIV-1-4, differences in clinical presentation and management requirements among serotypes has not been thoroughly investigated. Parainfluenza viruses are associated with a wide spectrum of illnesses including otitis media, pharyngitis, conjunctivitis, croup, tracheobronchitis, and pneumonia. Symptom severity is often influenced by viral serotype, co-infection, and prior medical history. How these factors influence clinical care and overall disease outcome is not well defined.

The objective of this study was to observe and analyze the pediatric patient population diagnosed with HPIV, as well as describe viral serotype presentation and heterogeneity of disease outcome. Although parainfluenza virus is most commonly associated with croup, bronchiolitis, and pneumonia, we postulate that there may be other clinical symptoms as well as risk factors that may be less commonly described that can impact disease outcome. By analyzing this data on viral serotype, patient demographics, past medical history, and the presence of co-infections, this study may

be used in identifying patients who may be at higher risk of more significant disease presentation. Additional analysis of Paediatric Intensive Care Unit (PICU) care needs, supplemental oxygen requirements, length of stay and potential complications in the context of specific viral serotype may aid in decision making for the most appropriate available treatment modalities for future pediatric patients. Ultimately, the goal of the study is to determine whether certain HPIV serotypes are predisposed to a more severe course of disease.

## METHODS

This single-center, retrospective, observational study was conducted by reviewing pediatric patients admitted with parainfluenza virus to the general pediatrics ward or PICU at Self-Reported Health Status (SRHS) from August 2018 to November 2019. Parainfluenza virus presence was confirmed using a polymerase chain reaction based test called FilmArray respiratory panel, which identifies common viral and bacterial pathogens that infect the upper respiratory system. Inclusion criteria consisted of all patients less than 18 years of age admitted to the above units with a diagnosis of parainfluenza serotypes 1-4 confirmed via FilmArray respiratory panel.

Patients were identified through data management software and stratified by parainfluenza serotype for data analysis. The following data were collected: HPIV serotype, demographics (age, gender, race, zip code), past medical history (prematurity, immunodeficiency, prior surgery, congenital heart disease), admission location (general pediatrics vs. PICU), length of stay, clinical presentation (croup, pharyngitis, pneumonia, bronchiolitis, URI), presence of concomitant infection (Respiratory Syncytial Virus (RSV), influenza, rhinovirus/enterovirus, metapneumovirus), clinical management, complications during hospital stay, and patient outcome (discharge home, transfer to higher level of care, death). The data were analyzed to identify patterns within the four parainfluenza serotypes. Chi-square tests were conducted to evaluate differences in disease spectrum (Figure 2) and an ANOVA test was used to compare average length of stay among serotypes.

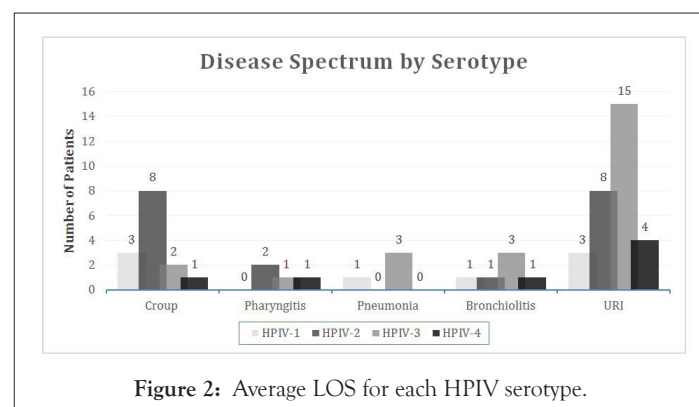


Figure 2: Average LOS for each HPIV serotype.

## RESULTS AND DISCUSSION

Of the 40 patients diagnosed with HPIV 1-4, 6 were diagnosed with HPIV-1 (15%), 12 with HPIV-2 (30%), 17 with HPIV-3 (42.5%), and 5 with HPIV-4 (12.5%) (Figure 3). The most common presenting symptoms across parainfluenza virus serotypes included upper respiratory infection (URI) symptoms (75%), croup (35%), bronchiolitis (15%), pneumonia (10%) and pharyngitis (10%) (Figure 4).

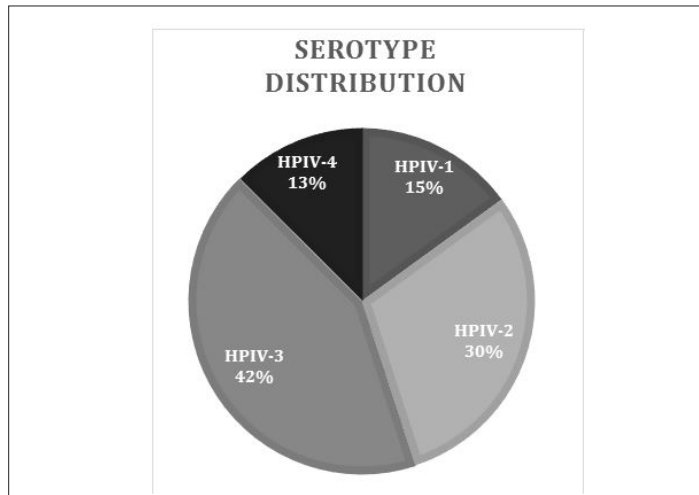


Figure 3: Percentage of patients who tested positive for HPIV serotypes 1-4.

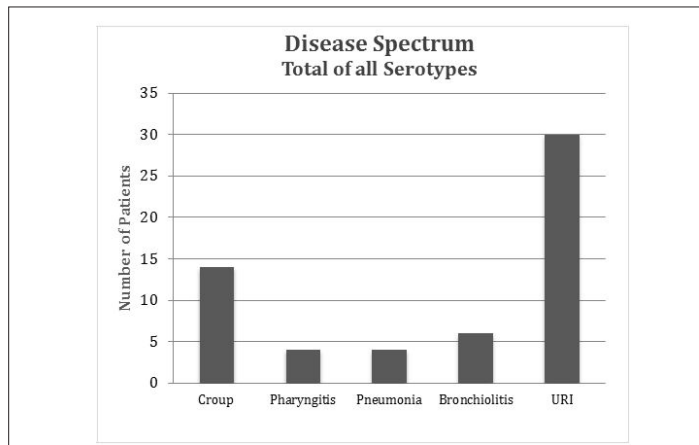


Figure 4: Disease spectrum of all 40 patients. Patients displayed 0, 1, or multiple of the above conditions.

**Group**

While parainfluenza virus is commonly associated with croup, only 35% of patients across all serotypes were noted to have traditional croup-like symptoms (barklike cough, inspiratory stridor). The results demonstrated a significant difference between serotypes and manifestation of croup symptoms ( $p=0.015$ ). HPIV-2 had the highest percentage of patients diagnosed with croup at 66%, followed by HPIV-1 at 50%. HPIV-4 and HPIV-3 demonstrated croup symptoms less frequently, appearing in 20% and 12% of cases, respectively. These findings are consistent with previous literature supporting HPIV 1 and 2 as the most common causes of croup [2,5].

**Bronchiolitis**

Limited to the younger patient population due to the necessity of smaller airways for specific disease presentation, bronchiolitis was not commonly diagnosed in our study. Only 6 of the 40 patients were noted to have bronchiolitis, most frequently with HPIV-3 (18%). Ultimately, there was not a significant difference between serotypes and whether patients had bronchiolitis ( $p=0.891$ ).

**Pneumonia**

While the most common cause of pneumonia and lower respiratory infections are viruses [6], the prevalence of pneumonia during our

study was not substantial. Only 4 of the 40 patients (10%) were diagnosed with pneumonia, and the number of diagnoses did not vary significantly between serotypes ( $p=0.223$ ). Three of the patients with pneumonia tested positive for HPIV-3 and the fourth HPIV-1.

**URI**

HPIV has been noted to be associated with all types of respiratory illnesses, both upper and lower. In our analysis, 75% of patients across all serotypes experienced nonspecific upper respiratory symptoms (cough, congestion, rhinorrhea). HPIV-3 had the highest percentage of patients with URI symptoms (88%). The other serotypes had a similarly high association with URI, with 50% of HPIV-1, 66% of HPIV-2, and 80% of HPIV-4 having this diagnosis, resulting in a difference in prevalence between serotypes that was not statistically significant ( $p=0.251$ ).

**Other disease presentations**

In addition to the above diagnoses, several patients presented with symptoms and diagnoses not commonly associated with parainfluenza virus. One patient was admitted with seizures (HPIV-1), another had viral gastroenteritis (HPIV-3), and one developed myocarditis (HPIV-4). It is unclear if these outliers are true parainfluenza infections, or if they were noted as a co-infection during hospitalization. Pharyngitis was an added respiratory finding in 4 of the 40 patients (10%), and two patients with HPIV-3 were additionally affected with bilateral acute otitis media (5%).

**Inpatient management**

While 29 patients (72.5%) could be managed on the general pediatric ward, 11 (27.5%) required PICU admission (Figure 5) and two patients required escalation to the PICU from the floor (one HPIV-2 and one HPIV-4). Of the different serotypes, HPIV-1 had the highest percentage of patients requiring PICU admission (50%), followed by HPIV-4 (40%). HPIV-2 and HPIV-3 serotypes resulted in PICU admission in only 33% and 11.7% of cases, respectively. These differences between serotypes and requirement for general pediatric ward care ( $p=0.285$ ) or PICU care ( $p=0.238$ ) were not statistically significant. The majority of patients were discharged home (95%), while two (5%) required transfer to an outside facility for higher level of care. One was an HPIV-3 patient with acute respiratory distress syndrome (ARDS) needing support with High Frequency Oscillatory Ventilation (HFOV), the second a HPIV-4 patient with myocarditis needing hemodynamic support with extracorporeal membrane oxygenation (ECMO). Hypoxia requiring supplemental oxygen was most common in HPIV-4 (40%), followed by HPIV-2 (25%).

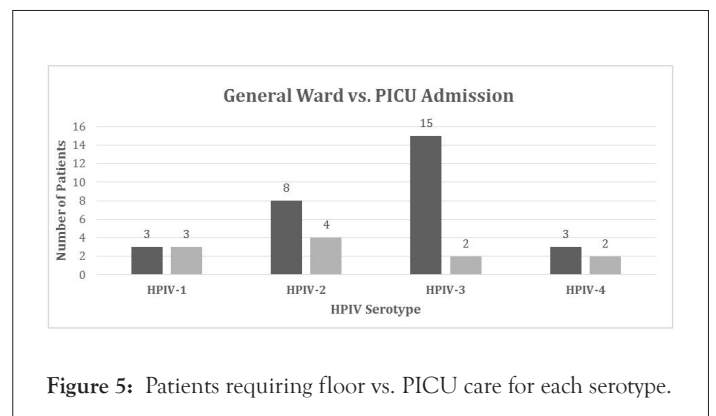


Figure 5: Patients requiring floor vs. PICU care for each serotype.

## Length of stay

Of the patients admitted to the hospital, those with HPIV-4 averaged the longest length of stay (84.8 hours) followed by HPIV-2 (67.8 hours), HPIV-3 (51.3 hours), and HPIV-1 (35.5 hours); however, the differences in length of stay between viral serotypes were not statistically significant ( $p=0.632$ ).

## Co-infection

Human rhinovirus/enterovirus was the leading viral co-infection diagnosed via FilmArray respiratory panel (9 patients), followed by RSV (2 patients) and human metapneumovirus (1 patient). Eight out of the nine patients co-infected with rhinovirus/enterovirus were able to be treated on the general ward, whereas both patients co-infected with RSV required PICU care and supplemental oxygen. Co-infection with RSV also resulted in longer length of stays (Figure 6). While the average duration of inpatient care among all patients was 58.1 hours, patients co-infected with RSV averaged 264 hours. The serotype with the highest proportion of viral co-infections was HPIV-2 (41.7%), followed by HPIV-4 (40%), HPIV-3 (23.5%) and HPIV-1 (16.7%).

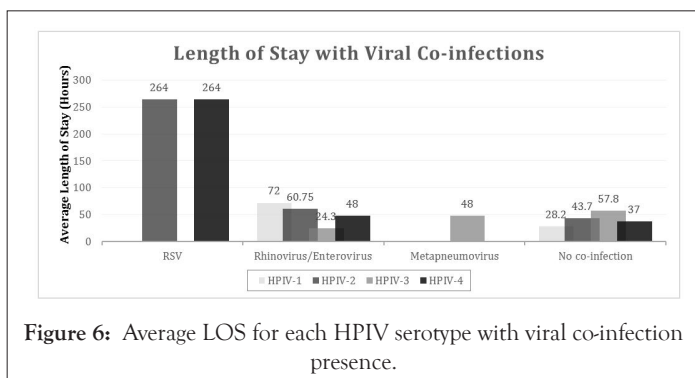


Figure 6: Average LOS for each HPIV serotype with viral co-infection presence.

## DISCUSSION

Human parainfluenza viruses are traditionally associated with croup (laryngotracheobronchitis), which manifests as a seal-bark cough and inspiratory stridor; however, a minority of patients in this study demonstrated these classic symptoms (35% across all serotypes). Patients were more likely to present with vague upper respiratory complaints including non-barking cough, rhinorrhea, and congestion. HPIV-1 and 2 have historically been shown to be the serotypes most associated with croup symptomology [7-8]. This pattern was consistent with our analysis, which demonstrated that 78.6% of patients who displayed croup symptoms were positive for one of these two serotypes. Conversely, HPIV-3 has been recognized to produce lower respiratory tract infection symptoms [9-11]. While not found to be statistically significant, patients diagnosed with HPIV-3 in this study commonly presented with bronchiolitis, pneumonia, and upper respiratory infections symptoms.

Serotypes of HPIV-1 and 4 may warrant closer monitoring due to a higher need for PICU care. The largest percentage of patients who required a higher level of care in the PICU tested positive for HPIV-1 (50%), while patients with HPIV-4 experienced similarly high rates of PICU admission (40%) and endured the longest mean length of stay (84.8 hours). Our data also found that patients afflicted with HPIV-4 required the greatest amount of supplemental oxygen. These findings support previously described trends in HPIV-4 disease progression, including increased risk of hypoxia, lower respiratory tract infections, and abnormal lung findings [11], and

further illustrate the potential for serious morbidity in pediatric patients with this serotype.

Two patients were transferred for escalation of care, both having additional risk factors that made them vulnerable for a more serious disease course and poor outcome. The first patient, a 6-year-old female diagnosed with HPIV-4, was admitted two days post tonsillectomy and adenoidectomy. She was transferred to an outside facility after 72 hours in the SRHS PICU due to myocarditis needing hemodynamic support with Extra Corporeal Membrane Oxygenation (ECMO). The second patient, a 7-year-old female with HPIV-3, had a complicated medical history that included severe developmental delays, microcephaly, seizures, G-tube feeding, home BiPAP, and multiple admissions for respiratory distress. After 48 hours in the PICU, she was transferred with sepsis and Acute Respiratory Distress Syndrome (ARDS) needing support with High Frequency Oscillatory Ventilation (HFOV).

## CONCLUSION

This single-center retrospective observational study indicates that understanding the differences in symptomatology and severity of each parainfluenza serotype may proactively aid in the proper treatment and care of the pediatric population afflicted. There are several limitations to this study including the small sample size of patients, single location site, and short time frame of data collection. Due to the modest number of HPIV infections diagnosed and incorporated into the data analysis, the statistical power of the study is restricted. This observational study invites further investigative studies with an increased sample size, multiple sites, and longer duration to support the data and further delineate preemptive actions when caring for the pediatric population with HPIV.

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