

# Epidemiology and Clinical Presentation of Parainfluenza Type 4 in Children: A 3-Year Comparative Study to Parainfluenza Types 1–3

Holly M. Frost,<sup>1,a</sup> Christine C. Robinson,<sup>2</sup> and Samuel R. Dominguez<sup>3</sup>

<sup>1</sup>Department of Pediatrics, University of Colorado School of Medicine and Children's Hospital Colorado; <sup>2</sup>Department of Pathology and Clinical Medicine, Children's Hospital Colorado; and <sup>3</sup>Department of Pediatric Infectious Diseases, University of Colorado School of Medicine and Children's Hospital Colorado, Aurora

**Background.** Human parainfluenza viruses (HPIVs) are among the most common causes of respiratory tract infections in children. Little is known about the epidemiology and clinical presentation of HPIV type 4.

**Methods.** A retrospective chart review and comparison of patients positive for HPIV types 1–4 by multiplex polymerase chain reaction between 2009 and 2012 at Children's Hospital Colorado was performed. Patients who had only direct fluorescent antibody testing performed or concurrent viral infections were excluded.

**Results.** Of 11 533 samples, 752 (6.5%) were positive for HPIV. After exclusion criteria, 316 samples were included in the study. HPIV-4 had year-round prevalence with biennial peaks in odd-numbered years. HPIV-4 and HPIV-3 had similar clinical presentations. 50.8% and 51.5% of patients with HPIV-3–4 had hypoxia compared to 20.3% and 33.3% of patients with HPIV-1–2 ( $P < .01$ ). HPIV-1 (23.6%) and HPIV-2 (24.2%) were more associated with stridor than HPIV-3 (6.6%) and HPIV-4 (0%) ( $P < .01$ ). No patients with HPIV-4 had croup. Patients with HPIV-4 had similar lengths of stay and mortality as those with HPIV-1–3.

**Conclusions.** This is the first large-scale analysis of HPIV-4 clinical and epidemiologic features. HPIV-4 was most similar to HPIV-3 in clinical presentation. HPIV-4 had year-round prevalence with peaks in the autumn of odd-numbered years. HPIV-4 is a common respiratory pathogen capable of causing significant morbidity in children.

**Keywords.** parainfluenza virus; parainfluenza virus type 4; paramyxovirus; respiratory virus; epidemiology; infection; children.

Human parainfluenza viruses (HPIVs) are among the most common causes of acute respiratory tract infections in children [1–6]. Four HPIV serotypes (types 1–4) have been identified. Previous attempts to identify HPIV-4 have proved difficult as HPIV-4 has little cytopathic effect in culture, direct fluorescent antibody (DFA) panels have not routinely included HPIV-4, and HPIV-4 serology is time consuming with limited commercial

availability. As a result, most studies have focused primarily on types 1–3, leaving the epidemiology and clinical significance of HPIV-4 largely unknown [1–3, 7–9]. The recent development of multiplex polymerase chain reaction (PCR) capable of detecting HPIV-1–4 has aided in the detection of all HPIVs from respiratory specimens [10]. There are 2 subtypes of HPIV-4, 4a and 4b, both of which have been implicated in causing human disease [7]. Prior studies suggest that HPIV-4 may be associated with both upper and lower respiratory tract infections in children [7, 10–16]. However, these studies have primarily been conducted outside North America and are limited by small sample sizes and often included patients with concurrent respiratory viral infections, making it difficult to assess the true clinical significance or epidemiology of HPIV-4 in pediatric patients. This retrospective study aims to further characterize the epidemiology and disease associations of HPIV-4 in comparison to HPIV-1–3 in pediatric patients.

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<sup>a</sup>Present affiliation: Marshfield Clinic, Minocqua and Marshfield Clinic Research Foundation, Marshfield, Wisconsin.

Correspondence: Holly M. Frost, MD, Marshfield Clinic, Marshfield Clinic Research Foundation, 9601 Townline Road, Minocqua, WI 54548 (frost.holly@marshfieldclinic.org).

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## METHODS

Children's Hospital Colorado (CHCO), an academic tertiary care center located in Aurora, Colorado, has approximately 430 000 outpatient visits, 86 000 emergency department visits, and 4000 inpatient stays each year. In addition, the laboratory receives specimens from 5 satellite locations along the Colorado Front Range.

Specimens from children with respiratory symptoms were collected and sent to the CHCO Clinical Virology Laboratory when detection of respiratory viruses was ordered for routine clinical care. Specimen types were nasopharyngeal washes, tracheal aspirates, or bronchoalveolar lavages.

From January 2009 to November 2011, the type of testing performed was guided by an algorithm. The testing algorithm that was recommended to clinicians is provided as a [Supplementary Figure](#). In general, outpatients were tested by a DFA for respiratory syncytial virus (RSV), influenza A and B, adenovirus, HPIV-1–3 (Light Diagnostics, Millipore), and human metapneumovirus (Diagnostic Hybrids). Hospitalized patients or high-risk outpatients were tested by DFA, with negative or inadequate specimens reflexively tested by a multiplex respiratory virus PCR (RVP). DFA and RVP were performed concurrently on patients in intensive care and immunocompromised inpatients or outpatients with viral cultures for cytomegalovirus and herpes simplex virus added. DFA testing was discontinued by the laboratory in November 2011; RVP was the sole test performed thereafter.

The respiratory virus PCR used was xTag Respiratory Virus Panel, respiratory virus PCR (RVP) (Luminex Molecular Diagnostics), which can detect 16 respiratory viruses and subtypes including influenza A (seasonal subtypes H1 and H3), influenza B, HPIV-1–4, adenovirus, RSV A and B, human metapneumovirus, human coronaviruses 229E, OC43, HKU1, and NL63, and human rhinovirus/enterovirus. xTag Respiratory Virus Panel is able to detect, but not differentiate, between HPIV-4a and HPIV-4b. Nucleic acids for RVP were extracted on BioRobot EZ1 extractors using Virus Minikits v2.0 (Qiagen) per the manufacturer's instructions.

The study period was January 2009–April 2012. Only patients with specimens positive for HPIV-1–4 by RVP during that time were included because only RVP could distinguish between HPIV types. Patients who only had only DFA, without PCR performed, were excluded. Patients with concurrent viral infections (defined as a positive DFA, viral culture, or RVP result for another virus), positive serology for Epstein-Barr virus, or a positive bacterial culture from a normally sterile site (ie, blood, cerebral spinal fluid, pleural fluid) were also excluded. For patients who were repeatedly positive for HPIV, chart review was performed only on the initial positive result to avoid attributing new clinical symptoms to persistent nucleic acid or viral shedding from previous infection.

Retrospective electronic chart review of all cases was performed using REDcap electronic data capture [17]. Data collected included demographic information, subjective symptoms, physical exam findings, hospital course and management, radiographic findings, and laboratory results. Fever was defined as a temperature  $>38.0^{\circ}\text{C}$  ( $100.4^{\circ}\text{F}$ ) by either history or exam. Hypoxia was defined as oxygen saturation  $<90\%$ . Children's Hospital Colorado is located at an altitude of 5471 feet (1668 meters) and many children are discharged home on oxygen, so these data were captured if available.

Research and data collection protocols were approved by the Colorado Multiple Institutional Review Board. Waiver of informed consent was approved for retrospective chart review of study participants. Statistical analysis was performed with SAS software version 9.3. HPIV distribution and categorical data were compared using Fisher exact test or  $\chi^2$  test. Continuous variables were analyzed using 1-way analysis of variance, Wilcoxon rank-sum test, or Kuskal-Wallis test. Clinical significance was defined as  $P < .05$ .

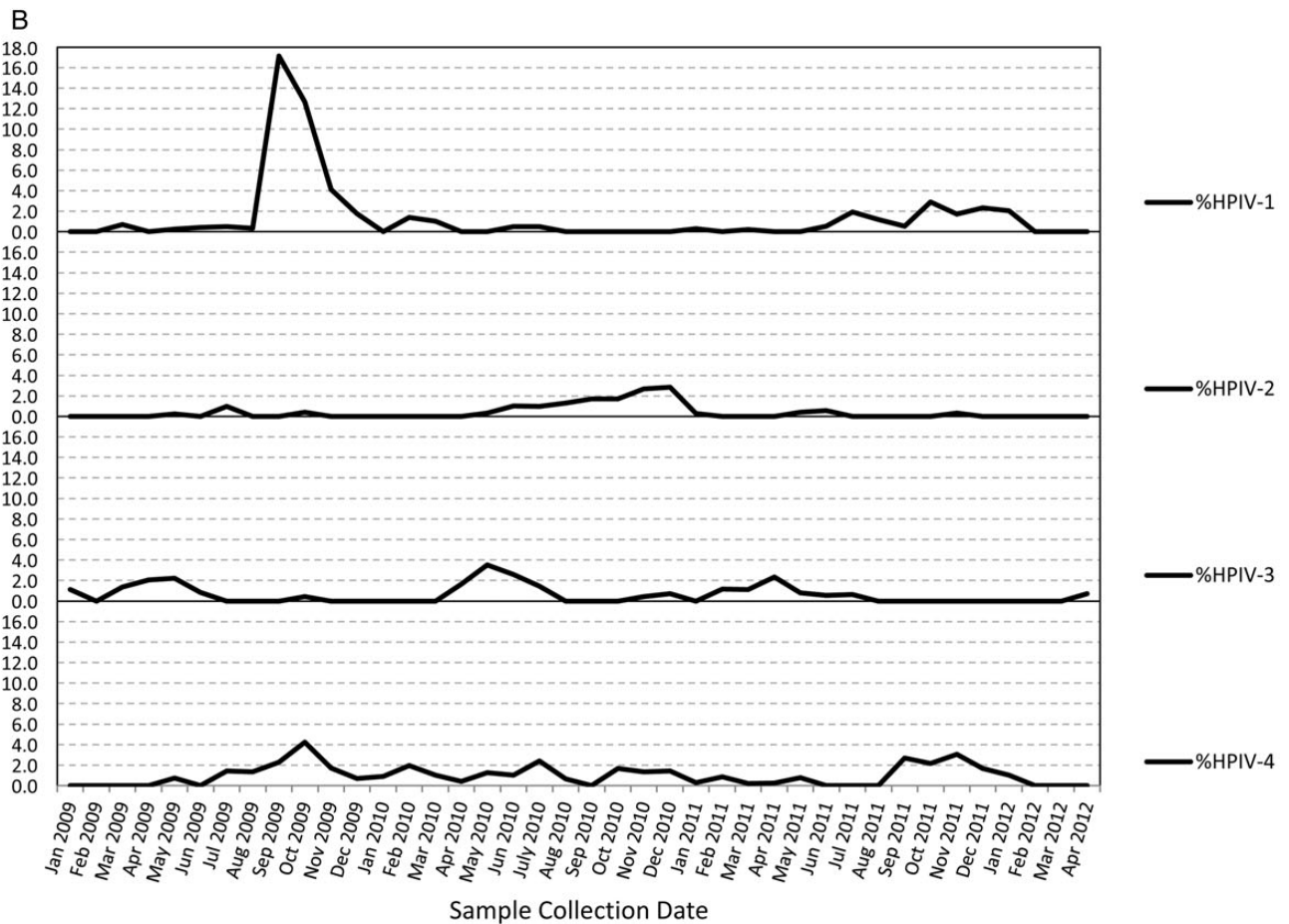
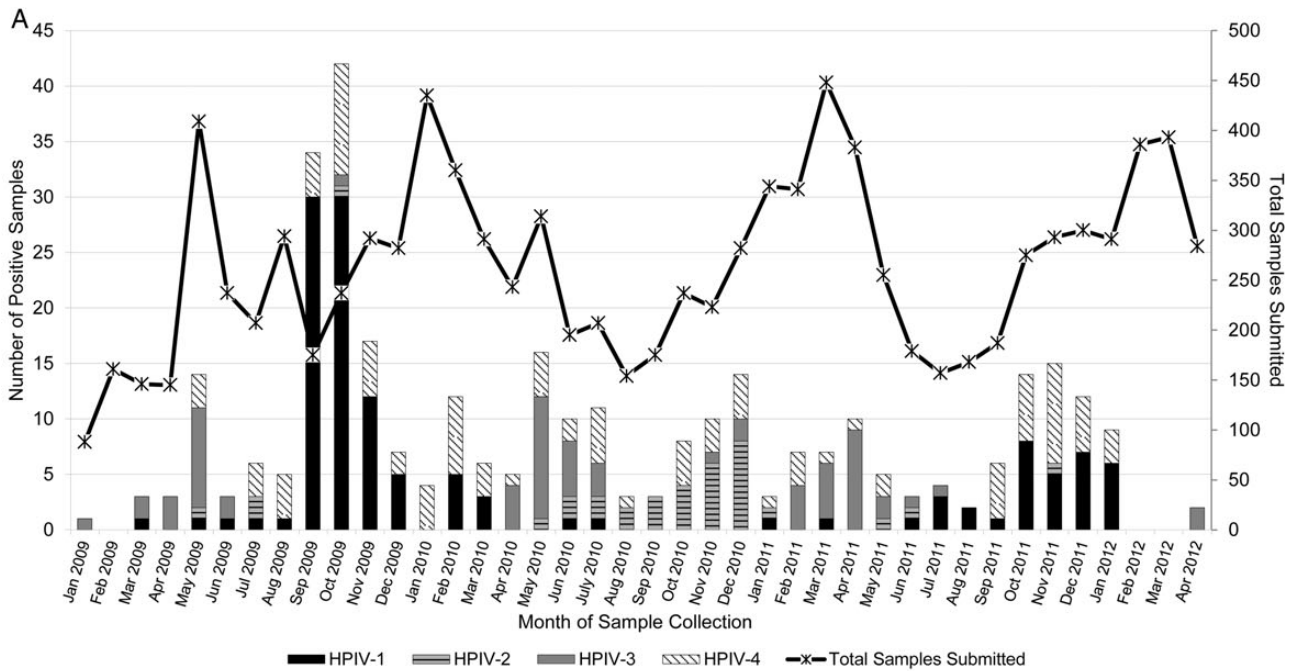
## RESULTS

### Epidemiology

From January 2009 to April 2012, 22 913 specimens were tested. Of these, 11 380 were tested by DFA, with 471 (4.1%) positive for HPIV. These specimens were excluded because the type of HPIV could not be determined. RVP was performed on 11 533 specimens, of which 752 (6.5%) were positive for HPIV-1–4. Prior to applying exclusion criteria, 231 of these specimens were positive for HPIV-1, 93 for HPIV-2, 154 for HPIV-3, and 263 for HPIV-4. During this same time frame, 65% of samples submitted were positive for at least 1 respiratory virus, including 6.9% that were positive for RSV and 6.8% that were positive for influenza. Fifty-five percent of patients with HPIV-4 detected by RVP had concurrent viral infections. Of patients positive for HPIV-4, 27% had rhinovirus, 20% had  $\geq 2$  viral coinfections, 5% had RSV, 3% had adenovirus, and  $<3\%$  had coronavirus, human metapneumovirus, influenza, or an additional HPIV type. After elimination of specimens with viral or bacterial coinfections and those without available clinical data, 316 HPIV-positive specimens were included in the final analysis. Of these, 123 (33%) were singly positive for HPIV-1, 33 (10%) for HPIV-2, 61 (19%) for HPIV-3, and 99 (31%) for HPIV-4. The number of singly positive samples for each HPIV type by month is shown in Figure 1A. The epidemiology curve for single infection with HPIV types 1–4 by month is shown in Figure 1B.

### Demographics

Demographic information for children with HPIV-1–4 is summarized in Table 1. Patients with HPIV-4 had similar ages of presentation, sex distribution, daycare attendance rates, and



**Figure 1.** A, Number of samples positive for human parainfluenza virus types 1–4 (HPIV-1–4) by month during the study period. B, Percentage of samples positive for HPIV-1–4 per month during the study period.

**Table 1. Demographics and Underlying Medical Conditions of Patients With Human Parainfluenza Virus Types 1–4**

Characteristic or Condition	HPIV-1 (n = 123)	HPIV-2 (n = 33)	HPIV-3 (n = 61)	HPIV-4 (n = 99)	P Value
<b>Demographics</b>					
Male sex	65 (52.9)	19 (57.6)	30 (49.2)	59 (59.6)	.57
Age, y, mean	3.3	4.9	3.1	4.1	.08
Daycare or school attendance	42 (34.2)	11 (33.3)	14 (23.0)	43 (43.4)	.07
Sick contacts	55 (44.7)	6 (18.2)	18 (29.5)	35 (35.4)	<b>.02</b>
Underlying medical conditions	64 (52.0)	17 (51.5)	46 (75.4)	61 (61.6)	<b>.02</b>
Prematurity (<37 wk)	18 (14.6)	6 (18.2)	13 (21.3)	12 (12.1)	.44
Asthma	18 (14.6)	7 (21.2)	3 (4.9)	13 (13.1)	.12
Pulmonary <sup>a</sup>	18 (14.6)	9 (27.3)	23 (37.7)	25 (25.3)	<b>.01</b>
Cardiac	13 (10.6)	3 (9.1)	14 (23.0)	11 (11.1)	.08
Immunocompromised	11 (8.9)	1 (3.0)	13 (21.3)	11 (11.1)	<b>.03</b>
Neurologic	17 (13.8)	9 (27.3)	19 (31.2)	20 (20.2)	<b>.04</b>

Data are presented as No. (%) unless otherwise specified. Categorical data comparison using Fisher exact test or  $\chi^2$  test. Continuous variable analysis using 1-way analysis of variance, Wilcoxon rank-sum test, or Kuskal-Wallis test. Bolded text highlights characteristics that are statistically significant ( $P < .05$ ).

Abbreviation: HPIV, human parainfluenza virus.

<sup>a</sup> Underlying pulmonary condition excluding asthma.

prevalence of underlying medical conditions as patients with HPIV-1–3. The mean age of patients ranged from 3.1 to 4.9 years. Compared to children with HPIV-4 (35.2%), HPIV-2 (18.2%), and HPIV-3 (29.5%), children with HPIV-1 (44.7%) were more likely to have sick contact exposure ( $P = .02$ ). More than 50% of all patients had underlying medical conditions. Children with HPIV-4 (61.6%), HPIV-1 (52.0%), and HPIV-2 (51.5%) were less likely to have underlying medical conditions including pulmonary conditions, immunocompromise, and neurologic conditions than children with HPIV-3 (75.2%) ( $P = .02$ ). There were no differences in underlying prematurity, cardiac conditions, or asthma between the 4 groups.

### Clinical Characteristics

Clinical characteristics, laboratory studies, and radiographic findings are displayed in Table 2. HPIV-4 was the only group in which no patient had stridor. Decreased oral intake was least likely in patients with HPIV-4 (20.2%) compared to HPIV-1 (42.5%), HPIV-2 (30.3%), and HPIV-3 (32.8%) ( $P < .01$ ). Among patients with HPIV-4, 9.1% had otitis media, compared to none of the patients with HPIV-1–2 and 4.9% of patients with HPIV-3 ( $P < .01$ ). Hypoxia was more common in HPIV-4 (51.5%) and HPIV-3 (50.8%) compared to HPIV-1 (20.3%) and HPIV-2 (33.3%) ( $P < .01$ ). Seizure, otitis media, rash, red eyes, and hypoxia were rare among patients with HPIV-1. There were no differences in fever, pharyngitis, vomiting, diarrhea, cough, congestion, or lymphadenopathy among the 4 groups.

Patients with HPIV-4 had similar numbers of chest radiographs (CXRs) obtained and CXRs with airways disease or lower respiratory tract infection, including pneumonia, identified as patients with HPIV-2 and HPIV-3. CXRs were least

likely to be obtained or be abnormal for patients with HPIV-1. Patients with HPIV-4 had higher white blood cell counts (11.5–1000 cells/ $\mu$ L) than patients with HPIV-1 (7.8–1000 cells/ $\mu$ L), HPIV-2 (9.8–1000 cells/ $\mu$ L), or HPIV-3 (7.7–1000 cells/ $\mu$ L) ( $P = .01$ ). Erythrocyte sedimentation rate, C-reactive protein (CRP), and platelet count did not vary significantly among groups.

### Hospital Course

Comparative information on hospital course is displayed in Table 3. More than half of samples collected were from hospitalized patients. Median length of admission ranged from 3 to 5 days ( $P = .33$ ). Median duration of fever was 1.5–4.0 days ( $P = .17$ ). Patients with HPIV-4 presented most similar to HPIV-3, with similarly high rates of admission for hypoxia. Patients with HPIV-4 (9.8%) and HPIV-3 (10.1%) also had higher rates of admission for neurologic problems such as seizure or altered mental status compared to patients with HPIV-1 (0.8%) or HPIV-2 (6.1%) ( $P < .01$ ). Of patients admitted to the pediatric intensive care unit (ICU), patients with HPIV-4 (3 days), HPIV-1 (2 days), and HPIV-2 (2 days) had shorter lengths of stay than patients with HPIV-3 (6 days) ( $P = .01$ ). Compared to patients with HPIV-4 (26.3%) and HPIV-2 (24.2%), patients with HPIV-3 (36.1%) were more likely to be discharged home on oxygen, whereas patients with HPIV-1 (6.5%) were least likely to be discharged home on oxygen ( $P < .01$ ). Patients with HPIV-4 (74.8%), HPIV-2 (81.8%), and HPIV-3 (70.5%) were more likely to require hospital admission than patients with HPIV-1 (39%) ( $P < .01$ ). Patients with HPIV-4 (35.4%), HPIV-2 (48.5%), and HPIV-3 (27.9%) were also more likely to require ICU admission than patients with HPIV-1 (19.5%) ( $P < .01$ ). In addition to lower

**Table 2. Clinical Characteristics of Patients With Human Parainfluenza Virus Types 1–4**

Characteristic	HPIV-1 (n = 123)	HPIV-2 (n = 33)	HPIV-3 (n = 61)	HPIV-4 (n = 99)	P Value
History and physical exam					
Fever (>38.0°C)	103 (83.7)	28 (84.9)	42 (68.9)	73 (73.7)	.06
Congestion	85 (69.1)	22 (66.7)	39 (63.9)	69 (69.7)	.88
Cough	100 (81.3)	24 (72.7)	47 (77.1)	66 (66.7)	.09
Stridor	29 (23.6)	8 (24.2)	4 (6.6)	0 (0)	<b>&lt;.01</b>
Pharyngitis	5 (4.1)	5 (15.2)	3 (4.9)	6 (6.1)	.12
Work of breathing	57 (46.3)	22 (66.7)	25 (41.0)	41 (41.4)	.07
Cyanosis	4 (3.3)	2 (6.1)	10 (16.4)	5 (5.1)	<b>&lt;.01</b>
Crackles	10 (8.1)	3 (9.1)	13 (21.3)	16 (16.2)	.06
Wheeze	8 (6.5)	2 (6.1)	7 (11.5)	16 (16.2)	.10
Emesis	30 (24.4)	5 (15.2)	14 (23.0)	23 (23.2)	.73
Diarrhea	15 (12.2)	5 (15.2)	4 (6.6)	11 (11.1)	.58
Decreased oral intake	51 (41.5)	10 (30.3)	20 (32.8)	20 (20.2)	<b>&lt;.01</b>
Red eyes	4 (3.3)	6 (18.2)	5 (8.2)	6 (6.1)	<b>.02</b>
Rash	10 (8.1)	4 (12.1)	13 (21.3)	8 (8.1)	<b>.04</b>
Seizure	4 (3.3)	4 (12.1)	7 (11.5)	13 (13.1)	<b>.05</b>
Otitis media	0 (0)	0 (0)	3 (4.9)	9 (9.1)	<b>&lt;.01</b>
Lymphadenopathy	5 (4.0)	3 (9.1)	7 (11.5)	5 (5.1)	.21
Hypoxia (oxygen saturation <90%)	25 (20.3)	11 (33.3)	31 (50.8)	51 (51.5)	<b>&lt;.01</b>
Radiographic findings					
CXR obtained	53 (43.1)	24 (72.7)	43 (70.5)	68 (68.7)	<b>&lt;.01</b>
Airway disease or atelectasis	28 (22.8)	14 (42.4)	28 (45.9)	43 (43.4)	<b>&lt;.01</b>
Lower respiratory tract infection <sup>a</sup>	15 (12.2)	5 (15.2)	14 (23.0)	18 (18.2)	.29
Laboratory studies, median					
White blood cell count, per 1000/μL	7.8	9.8	7.7	11.5	<b>.01</b>
Platelet count, per 1000/μL	271	243	278	309	.37
C-reactive protein, mg/dL	0.6	0.75	3.3	3.1	.49
Erythrocyte sedimentation rate, mm/h	10.5	18	13	20	.24

Data are presented as No. (%) unless otherwise specified.

Categorical data comparison using Fisher exact test or  $\chi^2$  test. Continuous variable analysis using 1-way analysis of variance, Wilcoxon rank-sum test, or Kuskal-Wallis test. Bolded text highlights characteristics that are statistically significant ( $P < .05$ ).

Abbreviations: CXR, chest radiograph; HPIV, human parainfluenza virus.

<sup>a</sup> Lower respiratory tract infection including consolidation, effusion, and empyema.

hospital and ICU admission rates patients with HPIV-4 (19.2%), HPIV-1 (3.3%), and HPIV-3 (16.4%) had lower rates of intubation compared to patients with HPIV-2 (27.3%) ( $P < .01$ ).

Medications administered varied among HPIV types. No patients with HPIV-4 received racemic epinephrine. Patients with HPIV-4 (18.2%), HPIV-1 (33.3%), and HPIV-3 (18.0%) were less likely to receive corticosteroids than children with HPIV-2 (54.6%) ( $P < .01$ ). Children with HPIV-4 (0%), HPIV-1 (15.5%), and HPIV-3 (8.2%) were also less likely to receive racemic epinephrine than children with HPIV-2 (30.3%) ( $P < .01$ ). Antibiotic use was high among all groups, although patients with HPIV-4 (51.5%), HPIV-1 (27.2%), and HPIV-3 (55.7%) were less likely to receive antibiotics than patients with HPIV-2 (72.7%) ( $P < .01$ ).

There were 5 total deaths (1.6%). All-cause mortality did not differ statistically between the 4 HPIV types. Three patients

died as a result of sudden cardiac arrest with respiratory specimens positive for HPIV-1, HPIV-2, and HPIV-4, respectively. One patient with HPIV-2 died from respiratory failure, and 1 patient with HPIV-4 died from status epilepticus with intraventricular hemorrhage. All deceased patients had underlying medical conditions.

## DISCUSSION

Previous studies have implicated HPIV-4 as a cause of upper and lower respiratory tract infections in children, but have not definitively demonstrated its epidemiology secondary to limited sample sizes [12, 18]. Our study shows year-round prevalence of HPIV-4 with peaks in the autumn of odd-numbered years. Our study also demonstrates that parainfluenza viruses are common respiratory pathogens in children. The rate of

**Table 3. Hospital Course and Management of Patients With Human Parainfluenza Virus Types 1–4**

Characteristic	HPIV-1 (n = 123)	HPIV-2 (n = 33)	HPIV-3 (n = 61)	HPIV-4 (n = 99)	<i>P</i> Value
Hospital admission	48 (39.0)	27 (81.8)	43 (70.5)	74 (74.8)	<b>&lt;.01</b>
Respiratory admission	39 (31.7)	20 (60.6)	22 (36.1)	44 (44.4)	<b>.05</b>
Neurologic admission	1 (0.8)	2 (6.1)	6 (9.8)	10 (10.1)	<b>&lt;.01</b>
Median length of stay, d	3	4	5	3	.33
Median duration of fever, d	2	4	1.5	3.5	.17
Discharged home on oxygen	8 (6.5)	8 (24.2)	22 (36.1)	26 (26.3)	<b>&lt;.01</b>
Pediatric ICU admission	24 (19.5)	16 (48.5)	17 (27.9)	35 (35.4)	<b>&lt;.01</b>
Median length of critical care, d	2	2	6	3	<b>.01</b>
Intubated	4 (3.3)	9 (27.3)	10 (16.4)	19 (19.2)	<b>&lt;.01</b>
Medications administered					
Corticosteroids	41 (33.3)	18 (54.6)	11 (18.0)	18 (18.2)	<b>&lt;.01</b>
Racemic epinephrine	19 (15.5)	10 (30.3)	5 (8.2)	0 (0)	<b>&lt;.01</b>
Albuterol	20 (16.3)	7 (21.2)	14 (23.0)	26 (26.3)	.33
Antibiotics	34 (27.6)	24 (72.7)	34 (55.7)	51 (51.5)	<b>&lt;.01</b>
Mortality					
Deceased	1 (1.2)	2 (6.1)	0 (0.0)	2 (2.0)	.12

Data are presented as No. (%) unless otherwise specified. Categorical data comparison using Fisher exact test or  $\chi^2$  test. Continuous variable analysis using 1-way analysis of variance, Wilcoxon rank-sum test, or Kuskal-Wallis test. Bolded text highlights characteristics that are statistically significant ( $P < .05$ ).

Abbreviations: HPIV, human parainfluenza virus; ICU, intensive care unit.

parainfluenza virus detection was similar to both influenza and RSV during the study period. The rate of viral coinfection with HPIV-4 was high. Rhinovirus was the most frequently encountered coinfection, likely because rhinovirus was the most prevalent virus during the study period. The number of samples with  $\geq 3$  viruses detected was higher than previous studies have reported [12].

Clinical characteristics of patients in our study varied widely among parainfluenza types. Previous studies on HPIV-4 have reached varying conclusions about its clinical relevance. Some reports suggest that HPIV-4 has minimal clinical impact, whereas others find associations with significant illnesses [7, 11, 12, 14]. Most of these studies have had small sample sizes, did not exclude patients with concurrent viral infections, did not use sensitive detection methods, or relied on laboratory-developed PCRs that may have different performance characteristics [10, 12, 14–16]. Due to the large number of patients included in our study without any known coinfections, we were able to ascertain several clinical features of the virus. HPIV-4 was the only HPIV that did not cause croup. HPIV-4, along with HPIV-3, was

associated with hypoxia, lower respiratory tract infections, abnormal radiographic findings, abnormal lung findings, and neurologic presentation. This is well demonstrated in the literature for HPIV-3 and has been suggested for HPIV-4, although minimal data are available [7, 11–16]. In agreement with other studies, we found an association of HPIV-1–4 with febrile seizures in otherwise healthy children [19]. CRP was mildly elevated for both HPIV-3 and -4. Elevated CRP has been reported with HPIV infection, although not for specific HPIV types [3]. There was an increased incidence of otitis media in HPIV-4; however, numbers were low. Patients with HPIV-4 had similar admission rates and mortality as those with HPIV-1–3.

Previous studies have reported a biennial autumn peak of HPIV-1 occurring during odd-numbered years, which our study confirms [1, 2, 4, 9, 18, 20]. HPIV-2 had a biannual distribution over the study period. A longer study period would be needed to further characterize this distribution. HPIV-2 has previously been suggested to have biennial, annual, or biannual peaks, with most studies limited by sample size [2, 12, 18]. HPIV-3 also showed biannual peaks. Previous studies have reported that HPIV-3 tends to peak annually in spring; however, in years when HPIV-1 is low, HPIV-3 may show an extended season or have an additional autumn peak [18, 20, 21]. We were able to appreciate this relationship between HPIV-1 and HPIV-3. The autumn of 2009 represented an exceptionally high peak of HPIV likely secondary to increased testing during the 2009 influenza A(H1N1) outbreak.

The median age of our HPIV-infected patients was higher than has previously been reported in the literature [1–3, 8, 9, 11–13]. Previous studies have shown the age of patients with HPIV-1–3 to be between 6 months and 2 years, whereas our median patient age ranged from 3 to 5 years. This difference may be attributable to the large numbers of our patients who were hospitalized or a difference in the predisposition of children with underlying medical conditions to acquiring HPIV at an older age, as a higher proportion of our patients had underlying medical conditions (51%–75%) compared with previous reports, or may reflect strain variation [22].

HPIV-1 and HPIV-2 were most commonly associated with croup, whereas only a few patients with HPIV-3 had croup. These findings are consistent with previous studies of HPIV-1–3 [2, 3, 6, 8, 13, 21]. Among the 4 HPIV groups, patients with HPIV-1 presented with the least severe clinical disease as evidenced by the lowest likelihood of requiring hospital admission, ICU admission, intubation, having a CXR obtained, or being prescribed antibiotics.

Patients with HPIV-3 presented with the most severe clinical disease as evidenced by prolonged duration of hospitalization (5 days), prolonged ICU stay (6 days), and the highest proportion of patients discharged home on oxygen. This is in agreement with previous studies, which have demonstrated increased severity of HPIV-3 infection, particularly lower respiratory tract

infections, in young or immunocompromised children, compared to HPIV-1 and -2. One possible explanation for this increased severity might be lower serologic protective immunity from maternal or postnatal exposure to HPIV-3 [18, 23]. The patients in our HPIV-3 group also had significantly more underlying medical conditions, which could also account for the above findings.

The low level of HPIV-2 seen in our patient population is consistent with global epidemiologic data [1, 3, 9, 12, 18]. Our patients with HPIV-2 had a higher severity of illness than has previously been reported, demonstrated by increased intubations, hospital admissions, and critical care admissions compared to other HPIV types. This may be secondary to viral virulence, as HPIV-2 has been historically difficult to study given low prevalence, or may be secondary to sampling bias as more patients with HPIV-2 were sampled in the inpatient setting compared to other HPIV types.

Antibiotic use was high (27%–72%) among all HPIV types. It is unclear if this represents medical complexity of the patients, severity of illness, or unclear diagnosis at the time of admission. Overuse of antibiotics with viral illnesses remains a significant problem in the pediatric population. Use of rapid and sensitive diagnostic testing such as PCR for respiratory viruses has the potential to limit additional diagnostic studies and decrease the use of antibiotics in children. Previous studies have suggested that for children without underlying medical conditions, rapid testing for viral respiratory pathogens does not change diagnostic testing, admission rates, length of stay, or antibiotic use [24–27]. However, many of these tests were not rapid enough to impact clinical care, and rapid diagnostic testing, such as rapid PCR, may be more useful in directing diagnostic testing and treatment in medically complex patients, although its role has not been fully explored.

There are several limitations to this study. The study was performed at a large tertiary care children's hospital, most likely selecting the more seriously ill patients with HPIV infections. Underlying medical conditions are also likely higher in this population compared to the general population. Clinicians' decision to test for viral infection and, at the beginning of our study, the initial use of DFA as opposed to RVP in non-critical care settings may cause selection bias toward children with increased severity of symptoms. Therefore, our data do not necessarily reflect the overall burden of HPIV respiratory disease in the general pediatric population. Additionally, the availability of RVP results may have influenced clinicians' medical decision making with regards to diagnostic testing, treatment, and disposition. We also acknowledge that the presence of viral RNA in a respiratory specimen does not always reflect the cause of current symptoms. It is possible that some patients had a positive RVP result due to prolonged shedding from a prior unrelated infection or asymptomatic carriage of a virus with signs and symptoms due to another disease process or infectious agent [28–30]. By excluding

patients with bacterial and viral coinfections from the study, we limited this effect as much as possible.

In summary, HPIV infections cause significant morbidity and burden of hospitalization in pediatric patients. This study presents the first large-scale description of HPIV-4 clinical and epidemiologic features in children. Clinical presentation and severity of HPIV-4 infections most closely resembled those of HPIV-3 infections; however, HPIV-4 did not have the same predisposition for patients with underlying medical conditions as HPIV-3. HPIV-4 was the only HPIV type not associated with croup. HPIV-4 was detected year round, with peaks in the autumn of odd-numbered years. HPIV-4 is a common and underappreciated respiratory pathogen capable of causing considerable morbidity in pediatric patients.

## Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (<http://jid.oxfordjournals.org/>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

## Notes

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