

# Population-based Surveillance for Medically Attended Human Parainfluenza Viruses From the Influenza Incidence Surveillance Project, 2010–2014

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**Background:** Parainfluenza viruses (PIV) have been shown to contribute substantially to pediatric hospitalizations in the United States. However, to date, there has been no systematic surveillance to estimate the burden among pediatric outpatients.

**Methods:** From August 2010 through July 2014, outpatient health care providers with enumerated patient populations in 13 states and jurisdictions participating in the Influenza Incidence Surveillance Project conducted surveillance of patients with influenza-like illness (ILI). Respiratory specimens were collected from the first 10 ILI patients each week with demographic and clinical data. Specimens were tested for multiple respiratory viruses, including PIV1–4, using reverse transcriptase–polymerase chain reaction assays. Cumulative incidence was calculated using provider patient population size as the denominator.

**Results:** PIVs 1–3 were detected in 8.0% of 7716 ILI-related outpatient specimens: 30% were PIV1, 26% PIV2 and 44% PIV3. PIV circulation varied noticeably by year and type, with PIV3 predominating in 2010–2011 (incidence 110 per 100,000 children), PIV1 in 2011–2012 (89 per 100,000), dual predominance of PIV2 and PIV3 (88 and 131 per 100,000) in 2012–2013 and PIV3 (100 per 100,000) in 2013–2014. The highest incidence of PIV detections was among patients aged <5 years (259–1307 per 100,000). The median age at detection for PIV3 (3.4 years) was significantly lower than the median ages for PIV1 (4.5 years) and PIV2 (7.0 years;  $P < 0.05$ ).

**Conclusions:** PIVs 1–3 comprise a substantial amount of medically attended pediatric ILI, particularly among children aged <5 years. Distinct seasonal circulation patterns as well as significant differences in rates by age were observed between PIV types.

**Key Words:** parainfluenza virus, population-based, surveillance, epidemiology, children

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Parainfluenza viruses (PIVs) are a known cause of respiratory illness in children and contribute substantially to ambulatory

care visits and hospitalizations in the United States, with rates of hospitalization estimated at 1.02 per 1000 among children aged <5 years.<sup>1</sup> The 4 distinct types of PIV are associated with specific clinical presentations, causing a spectrum of respiratory illness. PIVs 1 and 2 are the leading cause of croup in young children, and PIV1 is isolated in most cases of croup. Infection with PIV3, often considered the most clinically severe of the PIVs, can lead to lower respiratory tract disease, bronchiolitis and pneumonia.<sup>2–5</sup> Together, PIVs are second only to respiratory syncytial virus as a cause of hospitalization for respiratory tract illness (RTI) in young children.<sup>6</sup>

Outpatient and community studies have demonstrated the considerable impact of PIVs on pediatric respiratory disease outside the hospital setting; however, little has been published since the widespread use of more sensitive molecular laboratory methods. Studies published in the 1990s demonstrated that PIVs were responsible for 64%–65% of croup, 18%–45% of viral upper RTI and 22%–38% of viral lower RTI in children,<sup>2,7</sup> and most children will experience infection with each PIV type by the time they reach 5 years of age.<sup>8</sup> Despite the substantial contribution of PIVs to respiratory illness, to date, there has been no systematic domestic surveillance to ascertain the population-based burden among pediatric outpatients.

The Influenza Incidence Surveillance Project (IISP) provides a unique opportunity to assess the age-specific burden of PIVs in outpatient practice across multiple years and a broad geographic range in the United States. Since 2010, the IISP has monitored the year-round incidence of influenza-like illness (ILI) and associated incidence of respiratory viruses, including PIVs 1–4, in a network of outpatient clinics across 13 US states and jurisdictions. Using IISP data from 2010 to 2014, we describe the seasonality and age-specific burden of PIVs in the IISP, which will help to improve understanding of these viruses in the outpatient setting and support efforts for the prevention and treatment of PIV-associated illness.

## MATERIALS AND METHODS

### Influenza Incidence Surveillance Project and Parainfluenza Virus Surveillance

Detailed methodology for the IISP has been published previously.<sup>9,10</sup> Briefly, surveillance was conducted year-round, with surveillance years defined from August to July. We included data from 12 state and local health departments (sites) from August 2010 to July 2013 and from 5 sites from August 2013 to July 2014 as follows: Florida, Los Angeles County, Minnesota (MN) and Wisconsin (WI) from 2010 to 2014; Iowa, New Jersey, New York City, North Dakota, Oregon, Philadelphia and Virginia from 2010 to 2013; Utah (UT) from 2010 to 2011; and Texas from 2011 to 2014. The IISP conducted nonresearch, public health surveillance.

Participating public health departments, or sites, recruited ≈5 small to moderate sized outpatient healthcare providers (HCPs) with enumerated patient populations to report weekly age-specific counts of ILI and all-cause patient visits. Among patients aged ≥2 years, ILI was defined as fever with cough or sore throat; among patients aged <2 years, fever with ≥1 of the following respiratory symptoms: cough, sore throat, nasal congestion or rhinorrhea.

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Respiratory specimens (nasal, nasopharyngeal or oropharyngeal) were collected from the first 10 ILI patients each week along with demographic and clinical data; the sampling of up to 10 ILI patients each week ensured that a large proportion of all ILI patients would be sampled, given the small clinic size of HCPs.

Specimens were tested using molecular-based respiratory virus panels chosen by the participating laboratories: Los Angeles County, New Jersey, New York City, North Dakota, Texas and Virginia used Luminex xTAG respiratory virus panel (Luminex Diagnostics, Toronto, Canada); Florida, Iowa, MN, Oregon and Philadelphia used the virus-specific reverse transcriptase–polymerase chain reaction assay developed by Centers for Disease Control and Prevention<sup>11</sup>; UT and WI used ResPlex II v2.0 (Qiagen, Venlo, The Netherlands). PIVs 1–3 were included in the respiratory virus panels at all health departments; PIV4 was included in the testing panel in MN, UT and WI. Information regarding proficiency testing was published previously.<sup>10</sup>

### Data Analysis

Analysis was limited to children aged <18 years who met the ILI case definition, presented for care within 7 days of illness onset and were tested for PIV. Parainfluenza virus 4 detections were insufficient for analyses beyond overall proportions.

To identify PIV seasons, we calculated the weekly percent contribution or the percent of the entire surveillance year's PIV positives that were detected each week. Onset of a season was defined as the first of 3 consecutive weeks with  $\geq 2\%$  of the specimens contributing to the total yearly detections; the conclusion of a season was defined as the last of 3 consecutive weeks with  $\geq 2\%$  contribution. At least 4 consecutive weeks of  $\geq 2\%$  contribution were required to be determined as a season.

The proportion of ILI patients who tested positive for each PIV type each week, or the weekly percent positive, was multiplied by the weekly count of ILI patients to extrapolate the number of PIV-associated ILI visits. Incidence estimates were then calculated per 100,000 children, using the weekly patient population size as the denominator. Incidence estimates for individual weeks were summed by surveillance year to generate the cumulative incidence for each year and age group. Bootstrapping methods were used to calculate 95% confidence intervals of PIV rates.<sup>9,10</sup>

Differences in seasonality between PIV types were demonstrated by plotting the 3-week moving average of the extrapolated detection totals for each week for the 4 surveillance years; the 3-week moving average was centered on the week reported and was used to better visualize the seasonal trends of each PIV.

To evaluate the frequency of symptoms included in the ILI case definition (fever, cough and sore throat) across the parainfluenza virus types, we used a subset of IISP data collected among sites that systematically conducted surveillance for more broadly defined acute respiratory illness (ARI). Patients with ARI were defined as having at least 2 respiratory symptoms, including fever, cough, sore throat, nasal congestion and rhinorrhea. These patients were inclusive of ILI, and sites followed the same methodology as previously described for ILI surveillance. Data from the following sites participating in ARI surveillance was included: MN and WI from 2010 to 2014; Iowa from 2010 to 2013; New Jersey and New York City from 2010 to 2012; and Florida, Los Angeles County, North Dakota, UT and Virginia from 2010 to 2011. All other symptoms were evaluated using data from ILI surveillance conducted by all sites in all years.

Demographic characteristics and symptoms were compared between PIV-positive and PIV-negative cases and across PIV types using the  $\chi^2$  test for association. A *P* value of <0.05 was considered statistically significant. Relative risk and 95% CIs for PIV

detections by age group were calculated using the 5–17-year age group as the reference. Analyses were conducted using SAS Version 9.3 (SAS Institute Inc., Cary, NC).

## RESULTS

From August 2010 to July 2014, a total of 114 HCPs participated in IISP, ranging from 30–74 per year. Participating HCPs were primary care clinics (90%), urgent care (9%) and student health (1%) facilities. The clinics were split between rural (27%), suburban (32%) and urban (41%) locations, and 57% of the HCPs were identified as private organizations. The distribution of ages in the surveillance population was similar to the US population; 25% of the population was pediatric compared with 24% in the United States, with the following age distribution: 2% <12 months (US 1%), 2% 12–24 months (US 1%), 4% 2–4 years (US 4%) and 16% 5–17 years (US 17%).

### PIVs Within the IISP Population

Among 560,941 pediatric outpatient visits, 19,277 (3.4%) were reported as ILI. Specimens were collected from 7716 (40%) children and tested for PIV 1–3; the distribution of PIV 1–3 detections by type are shown in Table 1. Among 2552 (33%) children tested for all 4 PIV types, 229 (9.0%) tested positive for at least one PIV, including 62 (2.4%) PIV1, 57 (2.2%) PIV2, 98 (3.8%) PIV3 and 12 (0.5%) PIV4. The distribution of virus types among all detections was 27% PIV1, 25% PIV2, 43% PIV3 and 5% PIV4. At least one additional respiratory virus was detected in 19% of 619 children positive for PIV 1–3: most commonly, rhinovirus/enterovirus (49%), adenovirus (23%), coronavirus (18%) and influenza (11%). Parainfluenza virus co-detections were identified in 5 children (0.8%), including 1 PIV1/PIV2, 1 PIV3/PIV4, 1 PIV2/PIV3 and 2 PIV1/PIV3. Across all years, 63% of ILI patients negative for PIV 1–3 tested positive for at least one respiratory virus (data not shown).

### Parainfluenza Virus Seasonality

During the 4 surveillance years, PIV1 and PIV2 were most frequently detected in the fall and winter (Fig. 1). The PIV1 season generally lasted from October to January, with onset occurring between August 28 and October 29 and offset between January 1 and March 17; the PIV2 season began between 16 September and 23 October, but demonstrated a wide offset range between November 27 and March 13 (Fig. 2). Detection of PIV1 was significantly increased in odd-numbered years compared with even-numbered years (relative risk 6.1, 95% CI: 4.4–8.6), with a peak percent positive of 29% in elevated seasons. Conversely, PIV2 detections were significantly higher in even-numbered years as compared with odd years (odds ratio 2.4, 95% CI: 1.6–3.6) with a peak between 14% and 22% positive. PIV3 demonstrated an annual spring with an onset between February 3 and April 13 and offset between April 21 and July 22 (Fig. 1), and peak percent positive between 17% and 33%. The percent of ILI patients with PIV3 detected was significantly lower in odd-numbered years compared with even-numbered years, when circulation of PIV1 was elevated (*P* < 0.05). During the 2012–2013 surveillance year, 2 time periods met PIV3 season criteria, including 14 weeks from September to December 2012 and 12 weeks from February to April 2013; detections occurring during January and February did not meet season criteria (Fig. 2). Circulation patterns of PIV1, 2 and 3 were evaluated by geographic region and found to be consistent across the United States.

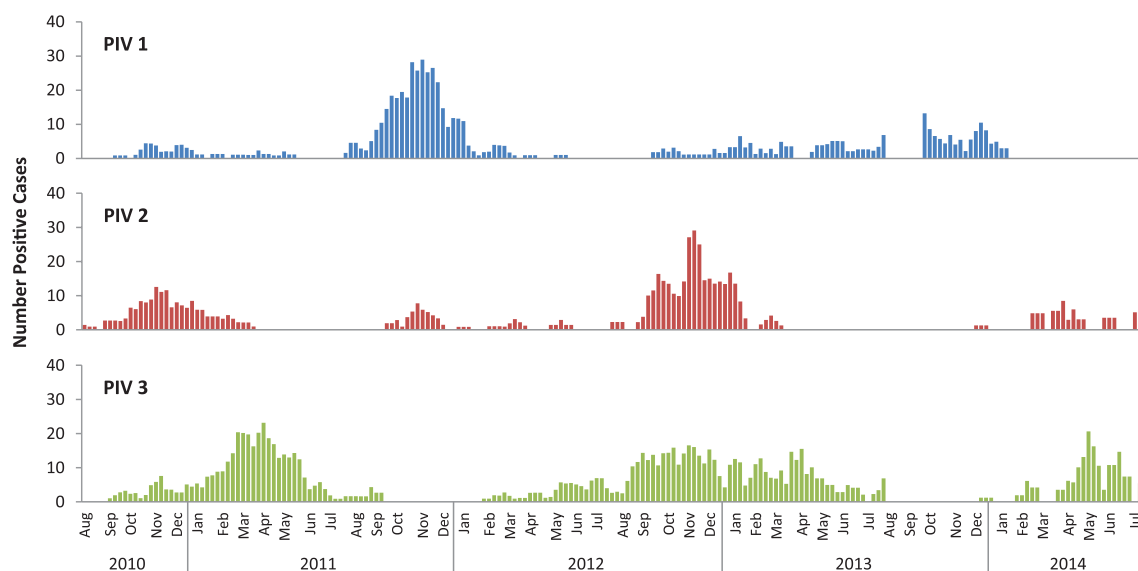
### Burden of PIVs by Surveillance Year

The incidence of parainfluenza virus-associated ILI visits varied significantly by surveillance year and virus type (see Table,

**TABLE 1.** Distribution by Age Group and Surveillance Year of Pediatric Outpatients With ILI Tested for PIV 1–3, August 2010 to July 2014

	Patients Tested for PIV	PIV Positive (1–3)	PIV Negative	P Value	Parainfluenza Detections			P Value
					PIV-1	PIV-2	PIV-3	
Age group	7716 (100.0)	619 (8.0)	7097 (92.0)	<0.0001	185 (29.7)	162 (26.0)	276 (44.3)	<0.0001
<1 year	734 (9.5)	64 (10.3)	670 (9.4)	<0.0001	17 (9.2)	7 (4.3)	40 (14.5)	<0.0001
1–<2 years	980 (12.7)	105 (17.0)	875 (12.3)		24 (13.0)	6 (3.7)	76 (27.5)	
2–4 years	1932 (25.1)	221 (35.7)	1711 (24.1)		75 (40.5)	43 (26.5)	105 (38.0)	
5–17 years	4067 (52.7)	229 (37.0)	3838 (54.1)		69 (37.3)	106 (65.4)	55 (19.9)	
Median age (years)	6.2	4.7	6.3	<0.0001	4.5	7.0	3.4	<0.0001
Season								
2010–11	2658 (34.5)	187 (7.0)	2471 (93.0)	0.078	20 (10.7)	54 (28.9)	116 (62.0)	<0.0001
2011–12	1950 (25.3)	169 (8.7)	1781 (91.3)		114 (67.5)	22 (13.0)	33 (19.5)	
2012–13	2405 (31.2)	211 (8.8)	2194 (91.2)		24 (11.4)	79 (37.4)	109 (51.7)	
2013–14	703 (9.1)	52 (7.4)	649 (92.6)		27 (51.9)	7 (13.5)	18 (34.6)	
Comparison of age distribution across PIV-positive, PIV types and PIV-negative patients		Odds ratio (95% CI) for a pediatric ILI patient in the <1, 1–2 or 2–4 age group to have a positive PIV test, compared with the 5–17 year age group						
<1 year		1.6 (1.2–2.0)			1.4 (0.8–2.3)	0.4 (0.2–0.8)	4 (2.7–6.0)	
1–<2 years		1.9 (1.6–2.4)			1.4 (0.9–2.3)	0.2 (0.1–0.5)	5.7 (4.1–8.1)	
2–4 years		2 (1.7–2.4)			2.3 (1.7–3.2)	0.9 (0.6–1.2)	4 (2.9–5.5)	
5–17 years		REF			REF	REF	REF	

REF indicates referent category.



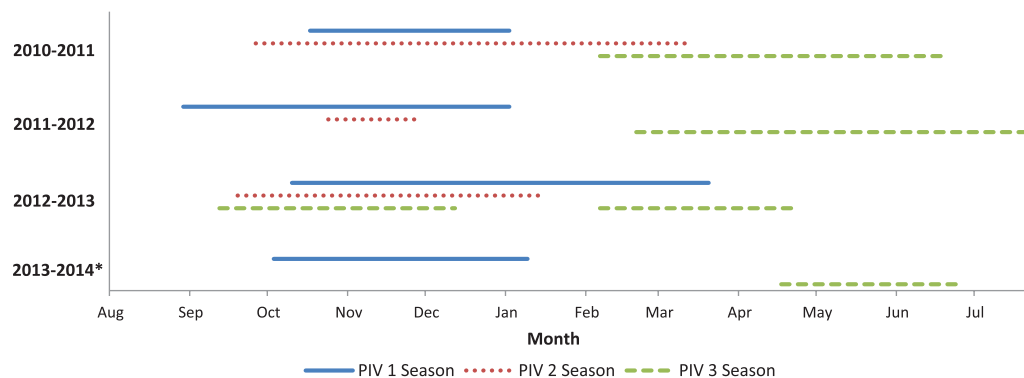
**FIGURE 1.** The extrapolated\* weekly number (3-week average) of PIV-associated ILI visits among pediatric outpatients, August 2010 through July 2014. \*Extrapolated counts of PIV-associated ILI visits were calculated as the weekly proportion of PIV-positive ILI visits multiplied by the weekly count of ILI visits. [full color online](#)

Supplemental Digital Content 1, <http://links.lww.com/INF/C419>, which provides incidence of parainfluenza virus-associated ILI by surveillance year and age group). In 2010–2011, PIV3 predominated (110 per 100,000 children), while PIV1 predominated in 2011–2012 (89 per 100,000 children). The 2012–2013 surveillance year was characterized by dual-predominance of PIV2 and PIV3 (88 and 131 per 100,000 children, respectively), and in 2013–2014, PIV3 predominated (100 per 100,000 children). A particularly high burden of PIV was observed in 2012–2013, indicated by an incidence of PIV-associated visits of 251 per 100,000 children and age-specific incidence ranging from 367 to 1307 per 100,000 children.

### Burden of PIVs by Age

Children with any PIV detection were significantly younger than PIV-negative children (median age 4.7 vs. 6.3 years, respectively;  $P < 0.05$ ). Sixty-three percent of PIV 1–3 detections were in children aged <5 years, and age varied significantly between each of the PIV types. Parainfluenza virus 3 affected significantly younger children than PIV1 or PIV2 (median age = 3.3 years;  $P < 0.05$ ), while PIV2 affected older children than the other PIV types (median age = 7.1 years;  $P < 0.05$ ; Table 1).

Figure 3 demonstrates the variation in cumulative incidence of PIV types by age group and surveillance year. The burden of PIV3 tended to be highest among children aged 1 to <2 years in



**FIGURE 2.** Seasonal circulation of PIV 1–3 detections across 12 months, by surveillance year, August 2010 through July 2014. \*A PIV2 season was not detected during the 2013–2014 surveillance year. [full color online](#)



**FIGURE 3.** Comparison by surveillance year of age-specific cumulative incidence estimates of PIV 1–3-associated outpatient visits per 100,000 children, August 2010 through July 2014. [full color online](#)

all years (range by season 222–868 per 100,000 children). During biennial years of elevated circulation, the incidence of PIV1-associated and PIV2-associated visits was greatest in children aged 2 to 4 years (388 and 273 per 100,000 children for PIV1 in 2011–2012 and 2013–2014; 193 and 412 per 100,000 children for PIV2 in 2010–2011 and 2012–2013). In general, PIV3 affected children aged <2 years more frequently than PIV1 or PIV2 with the exception of 2011–2012 when PIV1 overwhelmingly

predominated (Fig. 3 and Table, Supplemental Digital Content 1, <http://links.lww.com/INF/C419>).

### Comparative Symptomatology of PIVs

Among children presenting with more broadly defined ARI, 79% (282/355) of PIV-positive children met ILI case criteria, which did not vary significantly by PIV type or age group (see Table, Supplemental Digital Content 2, <http://links.lww.com/INF/C420>, which provides symptomatology of PIV-associated ILI and ARI). Children with ARI and any PIV detection were more likely to have cough (91%) and fever (80%) compared with PIV-negative ARI children ( $P < 0.05$ ). PIV2 was detected more frequently among children with sore throat (71%) than were PIV1 (55%) or PIV3 (35%;  $P < 0.05$ ). Among children presenting with ILI, myalgia and chills were reported significantly more frequently among PIV-negative ILI patients as compared with PIV-positive ILI patients ( $P < 0.05$ ). Children with ILI and PIV3 were 1.7 times as likely to report rhinorrhea compared with those with PIV1 or PIV2 (95% CI: 1.4–2.0).

### DISCUSSION

PIVs represented a substantial burden of respiratory illnesses among children in IISP, accounting for 9% of all ILI-related pediatric outpatient visits overall and up to 33% of visits at season peak. Consistent annual spring PIV3 and biennial fall PIV1 and PIV2 epidemics were observed across 4 years, yielding an ILI visit incidence range by season of 130–251 visits per 100,000 children. The incidence of PIV-associated visits was highest among children aged <5 years, and we also observed substantial variation by age for PIV types.

Each PIV type demonstrated unique and distinct seasonal circulation patterns, consistent with previous studies.<sup>6,7,12</sup> PIVs 1 and 2 in the IISP circulated annually in the fall but caused alternating biennial epidemics, with substantial seasons of PIV1 in odd years and PIV2 in even years. Annual spring epidemics of PIV3 were observed, but PIV3 circulation was significantly reduced during odd years of elevated PIV1 circulation. Prior studies have attributed this inverse pattern of activity to viral interference and cross-protection of PIV1 and PIV3 antibodies, producing consistent PIV seasonality.<sup>3,5,7,12,13</sup> Patterns of PIV2 circulation were varied, and we were unable to identify any season onset during 2013–2014. Seasonality findings for PIV2 have varied over the last half century and include reports of annual, biannual or biennial seasonality in either even or odd years, or irregular activity,<sup>1,3,6,14–17</sup> and may be explained by evolving seasonality, regional variability, difficulties in virus isolation or sample size limitations.<sup>2,7,12,18,19</sup> Consistent with

previous studies, PIV4 was too infrequently detected to identify any circulation patterns or associated epidemiologic trends, but comprised 5% of all PIV detections.<sup>12,14</sup>

PIVs contribute substantially to the burden of medically attended ILI in children, accounting for 9% of ILI-related pediatric outpatient visits and 12% among children aged <5 years. Comparable estimates from 2 recent studies were found,<sup>20,21</sup> though our estimates were higher than many other estimates of non-hospitalized PIV which used more broadly defined case definitions, less sensitive testing methods or included adults.<sup>2,8,13</sup> Corresponding cumulative incidence estimates from IISP suggest that PIVs are detected among pediatric outpatients aged <5 years at a rate of 259–1307 visits per 100,000 children, compared with estimates of 180–2740 per 100,000 children for influenza virus.<sup>9,10</sup> Trends in the detection of PIV among pediatric outpatients are consistent with previous estimates among children with acute respiratory and/or febrile illnesses<sup>7</sup>; however, population-based rates of PIV outpatient visits among children are unique to IISP.

PIVs were shown to have a substantial burden among children aged <5 years, and variation in detection by age was observed between PIV types. In particular, PIV3 affected younger children than either PIV1 or PIV2 and was significantly more likely to be detected in children aged <2 years than those aged ≥2 years. These observed age patterns have been well-established.<sup>2,4,7,22</sup> PIV3 has been shown to have the lowest median age among respiratory viruses<sup>14</sup> and infects most children by age 2, with high rates of reinfection among the very young, while PIV1 and PIV2 each infect most children by age 5.<sup>2,4,6,8,13</sup> Detections of PIV in very young children may be attributable to less mixing among preschool aged children, which may lead to a build-up of immunologically susceptible children and seasonal epidemics among the very young.<sup>13</sup> This analysis supports previous findings that viral co-detections are frequent among young PIV-positive children, with estimates around 20%.<sup>22,23</sup> High rates of co-detection may be attributable to immature immune systems and prolonged viral shedding in the very young; however, whether co-detections lead to increased severity among outpatients is unclear.<sup>23</sup>

Analysis of symptom data demonstrated that fever and cough were associated with PIV positivity among patients presenting with ARI. Although cough is reported consistently in PIV cases,<sup>24</sup> the presence of fever among PIV-positive patients presenting with symptoms of RTI varies widely in the literature, with estimates between 33% and 80%.<sup>2,5,22</sup> The difference in fever presentation across PIV studies may be attributable to differences in study populations, but most analyses assess clinical diagnoses rather than symptomatology.

The IISP is a well-established respiratory virus surveillance network; however, this analysis was nevertheless subject to limitations. The IISP reflects ILI in the outpatient setting; thus, our analysis does not capture PIV patients with non-ILI presentation. However, we found that among a limited number of sites conducting surveillance including all ARI patients, 79% of the PIV-positive patients reported ILI symptoms within the 7 days before the clinical visit. As a more sensitive case definition, we expect that surveillance of ARI patients would have produced greater numbers of PIV cases than ILI surveillance; however because of decreased specificity, the percent positivity of PIV among ARI patients would be lower than among ILI patients. Surveillance for PIVs was reduced in the 2013–2014 surveillance year from 12 to 5 participating health departments, leading to decreased PIV detections for that year; although PIV data from 2013 to 2014 was consistent with previous surveillance years, the analysis may have been subject to bias related to decreased specimen collection and testing. Finally, although all sites used sensitive and specific reverse

transcriptase–polymerase chain reaction assays for PIV detection, small differences between the assays may have resulted in minor differences in PIV detection.

It is well-established that PIVs contribute substantially to ILI morbidity and hospitalization among children, being second only to respiratory syncytial virus in hospitalizations because of respiratory tract infections among children aged <5 years.<sup>2,3,6,16,25</sup> Here we use population-based surveillance data to calculate the incidence of ILI visits and demonstrate the appreciable contribution of PIVs to respiratory illness among children in the outpatient setting. Although PIVs are the leading cause of croup and contribute substantially to rates of upper and lower respiratory tract disease among children, there are currently no available antivirals or vaccines to treat PIV infection. Because PIV infections may be clinically indistinguishable from other ILI etiologies, it is important that surveillance be conducted to provide a resource to inform clinicians of viral circulation. We demonstrated the consistent seasonality and high-risk age groups which may help outpatient providers to better identify the etiology of PIV-related illness. Furthermore, population-based estimates of the incidence of PIV-associated outpatient ILI visits improve our understanding of the circulation and burden of PIV and support efforts for the prevention and treatment of infections, including the development of a PIV vaccine for very young children.

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