Parainfluenza Virus Infection in an Australian Community-based Birth Cohort

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ABSTRACT

In a community-based birth cohort of 158 Australian infants followed to age 2-years the incidence rate of human parainfluenza virus (HPIV) was 0.42 (95%CI=0.33,0.54) episodes per child-year with episodes occurring year-round, peaking in the spring season. HPIV3 was the dominant sub-type. Overall, 41% of detections were asymptomatic; only 32% of HPIV episodes led to healthcare contact with one hospitalization.

INTRODUCTION

Acute respiratory infection (ARI) is a common cause of morbidity and mortality in young children, placing a considerable burden on the healthcare system and the child's family. In their first 2-years of life, Australian children experience an average of 13 discrete ARI episodes and 5-months of respiratory symptoms.[1]

ARI in early life can be associated with infection from the human parainfluenza virus (HPIV), an enveloped single-stranded RNA virus of the *Paramyxoviridae* family, which has four subtypes: HPIV1-4. Both upper and lower respiratory illnesses are attributed to HPIV with the most severe being laryngotracheobronchitis (croup), bronchiolitis, and pneumonia. To date, there is no licensed HPIV specific antiviral drug or vaccine for either the treatment or prevention of HPIV. However, DAS181, a sialidase fusion protein that enzymatically cleaves viral receptors from epithelial cell surfaces, has proven to be well tolerated in phase 2 clinical trials in HPIV-associated lower respiratory infection (LRI) in immunocompromised patients and is the focus of ongoing research.[2]

Contemporary pediatric HPIV literature focuses predominantly on hospital-based cases. However, to fully quantify the population-level burden of HPIV among children, community-based population studies are essential. An Australian birth-cohort, the Observational Research in Childhood Infectious Diseases (ORChID) study, has shown there are approximately 44 new HPIV episodes per 100 child-years, that 25% of children had an HPIV infection within the first-year of life, and that the median age at first detection was 23-months.[3,4] The aim of this study was to use ORChID data to further quantify new HPIV detections by subtype and investigate associations between subtypes and health-seeking behavior in children aged <2-years.

METHODS

The ORChID study (clinicaltrials.gov: NCT01304914), which is described in detail elsewhere,[5] prospectively recruited healthy term infants born in Brisbane, Australia, between September 2010 and October 2012 and followed them until their second birthday. Parents consented for their child's participation shortly after birth. Participants exited the study when they stopped returning diaries and swabs, or when the child had their second birthday. The Children's Health Queensland (HREC/10/QRCH/16), the Royal Brisbane and Women's Hospital (HREC/10/QRBW125), and The University of Queensland (2010000820) Human Research Ethics Committees approved the study.

Parents of recruited children completed a daily tick-box respiratory symptoms diary, for which they received training from the research team. These diaries were used to identify ARI episodes. An ARI was categorized as an upper respiratory infection (URI) when the child had nasal congestion or discharge, dry cough, or physician-diagnosed acute otitis media (AOM) and as an LRI if the child had a combination of any of the following: rattle-like breathing, moist

cough, shortness of breath, wheeze, or physician-diagnosed pneumonia. Three or more symptom-free days demarcated new ARI episodes. Parents kept illness-burden diaries to capture healthcare-seeking behavior, such as a visit to their family physician or hospital, when ARI symptomatology met a defined threshold (all LRI, AOM, and URI with dry cough plus nasal symptoms).[5] Emergency Department (ED) and hospital records of ORChID participants were reviewed at the end of the study.

Every week parents collected anterior nasal swab specimens and surface-mailed them to the study laboratory (received at a median of 3-days [interquartile range=2,4] after collection), where they were stored at -80^{0}C degrees.[3] A study by the same research team has shown parent-returned nasal swabs have similar pathogen detection rates compared with health-care worker collected swabs.[6] Swabs were batch tested for 17 viruses (including HPIV virus subtypes HPIV1-3) by previously validated real-time polymerase chain reaction (PCR) assays.[5] Endogenous retrovirus-3 (ERV-3), a marker of human genomic DNA, assessed swab quality. ERV-3 cycle threshold (Ct) values >38 identified lower-quality swabs, which were excluded from incidence calculations to avoid underestimating incidence rates.[3] A new HPIV detection was defined as detection of an HPIV virus subtype by PCR for the first time, or if previously positive for the same HPIV subtype after two consecutive negative swabs for the virus, or after 30-days from the last positive swab. Virus detection was classified as symptomatic if a new virus detection occurred when ARI symptoms were present 7-days before or after a new virus detection episode.[3]

Parents of participants provided demographic, social, and health information (including pregnancy and birth details), childcare attendance, and feeding-related information at enrolment and throughout the study. The period from birth to the time of solid food or formula

food introduction determined the duration of exclusive breastfeeding. Formal childcare was defined as outside home care from a regulated childcare service, while informal care comprised non-regulated care by relatives, friends or neighbors.

Analysis

The incidence rate of single new HPIV episodes, and associations between pre-defined risk factors (age, sex, mode of delivery, gestational age, season, family history of asthma or eczema, maternal exposure to tobacco smoke, number of children in the household, maternal education status, mode of feeding, and type of childcare attendance) and HPIV episodes were calculated using mixed-effects Poisson regression models with child included as a random effect. Multivariable models were adjusted for age, season, family history, number of children in the household, mode of feeding, and childcare attendance. Models included child-year-at-risk as an offset. All analyses were conducted using Stata statistical software v16 (StataCorp, College Station, TX, USA).

RESULTS

One-hundred and fifty-eight children returned 11,126 swabs, and 154 provided 87,547 symptom diary-days of observation (78% of expected observation days; Figure, Supplemental Digital Content 1). This included 10,811 swabs matched to 82,036 diary-days from 154 children, and 8,101 higher-quality swabs from 157 children. Participant characteristics are displayed in the Table, Supplemental Digital Content 2. There were 81 HPIV positive swabs, of which 77 were incident episodes. Twenty-five percent of episodes were co-detected with another virus (Table, Supplemental Digital Content 3). Just 59% of HPIV episodes were associated with ARI symptoms with the remaining 41% of episodes being asymptomatic. (Table, Supplemental Digital Content 4). The median (interquartile range) Ct value for 45

swabs linked to symptoms was 31.3 (28.9,33.2), whereas for the 32 swabs linked to no symptoms the equivalent figures were 31.3 (29.9,34.3); median difference=0.0, (95% confidence interval [CI]=-1.9,1.9), suggesting these latter swabs represented true asymptomatic infections.

The overall incidence of HPIV in the first 2-years of life was 0.42 episodes/child-year (95%CI=0.33,0.54). The incidence in the 1st and 2nd year was 0.30 (95%CI=0.20,0.44) and 0.57 (95%CI=0.35,0.91) episodes/child-year respectively. The overall incidence rate for symptomatic HPIV infections was 0.25 (95%CI=0.18,0.34) per child-year. HPIV incidence was highest in the Spring season (Table, Supplementary Digital Content 5).

HPIV-3 was more prevalent (69 detections, 65 incident-episodes) than HPIV-1 (8 detections and incident-episodes) and HPIV-2 (4 detections and incident-episodes). Overall, 95% of incident-episodes shed HPIV for 1-week with the rest shedding the virus for up to 2-weeks.

Of the 77 incident episodes, 73 were linked to symptom diaries and all 38 expected parent-completed illness-burden diaries relating to symptomatic ARI episodes were returned (Table). Overall, 32% of all HPIV episodes (54% of ARI episodes) led to healthcare contact of any kind, including 49% treated by the family physician only. There were four hospital presentations, of which one child was admitted with croup. Another with croup was managed as an outpatient. Notably, 57% of children seeking healthcare were prescribed antibiotics, in just two (15%) cases this was for AOM and none received a diagnosis of pneumonia. Neither symptom occurrence nor healthcare-seeking behavior were associated with co-detections (Table, Supplementary Digital Content 6).

DISCUSSION

In the Australian community-based ORChID birth cohort, healthy children averaged 0.42 HPIV infections (0.25 symptomatic) per child-year during the first 2-years of life. Thirty-two percent of all episodes, and 54% of symptomatic episodes, resulted in a visit to a healthcare professional. Antibiotics were prescribed in almost 60% of physician visits for this viral infection, highlighting the ongoing challenge of promoting antimicrobial stewardship in pediatric practice. New HPIV detections were most common in the spring season. While some existing studies have suggested a spring peak for HPIV, they primarily sourced data from hospital-based studies, concentrated on specific HPIV subtypes, and were not based on data from the first 2-years of life. Nevertheless, studies from the United States, and Australia also suggest an HPIV3 detection surge during the spring season,[7,8] while a recent systematic review involving studies from 83 sites globally, reported HPIV epidemics occurred in Spring and early Summer months in both the northern and southern hemispheres.[9]

A strength of ORChID is that it is one of the first longitudinal prospective community-focused birth cohort studies to estimate the burden of HPIV using high-density sampling and advanced molecular technology in an unselected healthy community-based cohort. Since there are relatively few contemporary population-based data on viral ARI burden at the community level,[10] these findings serve as preliminary direct community-based evidence in the context of HPIV. Study limitations include diary symptoms not being validated by healthcare professionals other than for AOM and pneumonia. Despite sensitive PCR assays, suboptimal swabbing techniques may have missed virus detections. However, these are the only practical methods for conducting such longitudinal community cohort studies. We did not test nasal swabs for HPIV4; therefore, our burden estimates do not include HPIV4 data. Due to the low

absolute number of HPIV-1 and 2 infections, effect estimates are imprecise with wide confidence intervals. Also, while croup is strongly associated with HPIV-1 and 2 infections, we could not report croup incidences as our symptom diaries were not constructed to capture these episodes. Nevertheless, most should have been identified by illness-burden diaries and ED/hospital chart reviews. Finally, ORChID participants were mainly from urban and more advantaged families. Consequently, the generalizability of results to children from rural or disadvantaged backgrounds is uncertain.

Currently, when HPIV vaccines are still undergoing clinical trials, the seasonal findings of our study might help in improving the HPIV surveillance and epidemic prediction during early childhood, which will assist with health service planning and public health prevention and control strategies.

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Table: Healthcare-seeking behavior by acute respiratory infection category and HPIV subtype (10,811 swabs, 82,036 days)

	Any healthcare contact (n, %)	Any family physician visits (n, %)	Family physician visit only (n, %)	Other healthcare professional (n, %)	ED presentation without admission (n, %)	Hospital admission ‡ (n, %)	Antibiotics (n, %)
HPIV combined (n=73)*							
ARI (n=43)	23 (53.5)	21 (48.8)	17 (39.5)	2 (4.7)	3 (7.0)	1 (2.3)	13 (30.2)
URI (n=26)	11 (42.3)	11 (42.3)	10 (38.5)	1 (3.8)	0 (0.0)	0 (0.0)	5 (19.2)
LRI (n=17)	12 (70.6)	10 (58.8)	7 (41.2)	1 (5.6)	3 (17.7)	1 (5.6)	8 (47.1)
HPIV-1 (n=8)							
ARI (n=6)	2 (33.3)	2 (33.3)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)
URI (n=4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
LRI (n=2)	2 (100.0)	2 (100.0)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)
HPIV-2 (n=4)							
ARI (n=3)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)
URI (n=2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
LRI (n=1)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
HPIV-3 (n=61)							
ARI (n=34)	20 (58.8)	19 (55.9)	15 (44.1)	2 (5.9)	2 (5.9)	1 (2.9)	12 (35.3)
URI (n=20)	11 (55.0)	11 (55.0)	10 (50.0)	1 (5.0)	0 (0.0)	0 (0.0)	5 (25.0)
LRI (n=14)	9 (64.3)	8 (57.1)	5 (35.7)	1 (7.1)	2 (14.3)	1 (7.1)	7 (50.0)

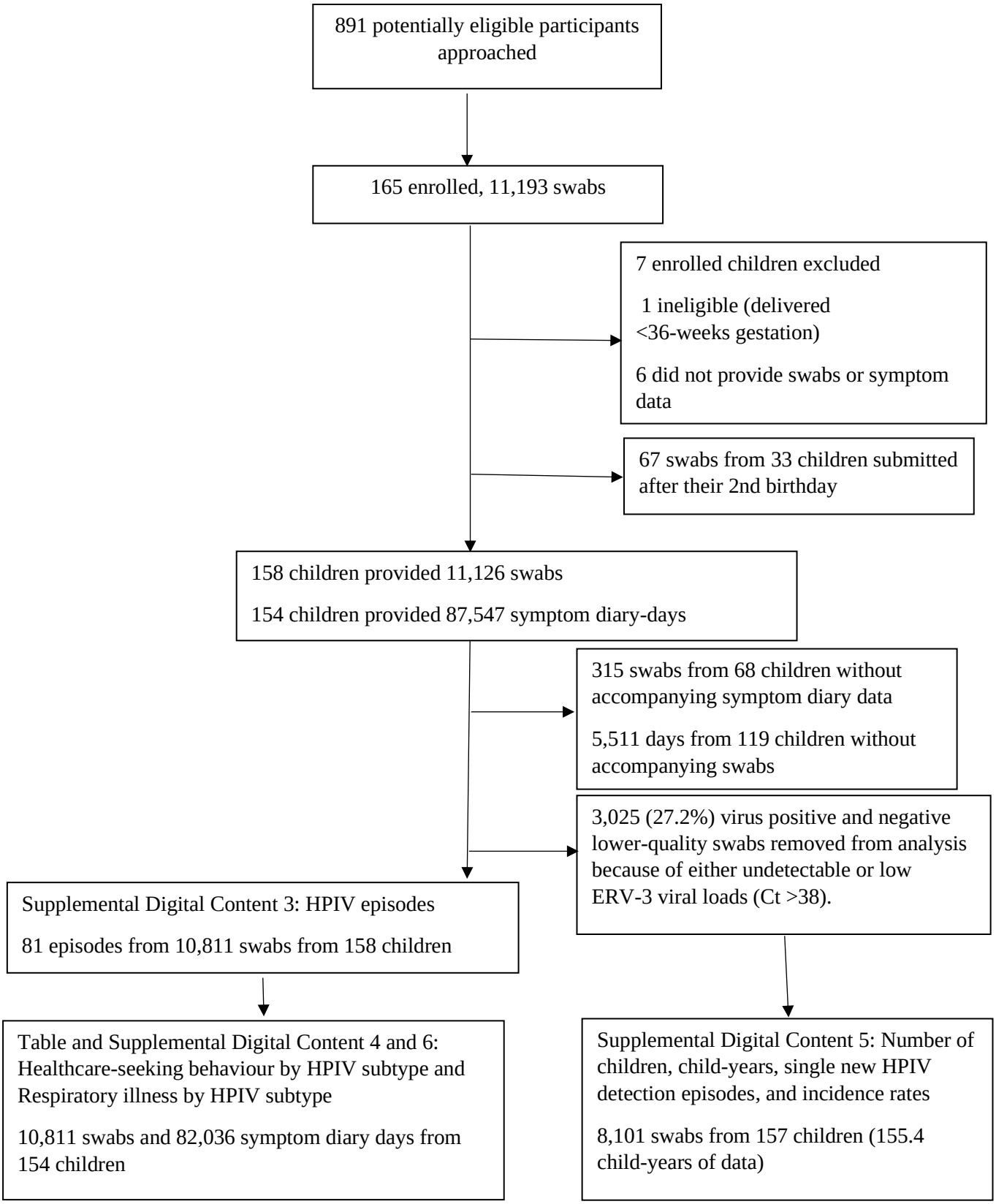
Abbreviations: AOM: acute otitis media; ARI: acute respiratory infection; ED: emergency department; HPIV: human parainfluenza virus; LRI: lower respiratory infection; URI: upper respiratory infection.

Healthcare use data and antibiotic information from illness-burden diary. On 38 occasions ARI symptomatology met the pre-defined threshold (all LRI, AOM, and URI with dry cough plus nasal symptoms) and burden diaries were returned. On five occasions isolated symptomatic episodes (runny nose, n=4; dry cough, n=1) without healthcare contact did not require an illness-burden diary return.

* 73 incident HPIV episodes, with ARI symptoms recorded for 43 episodes.

‡ The primary diagnosis for the hospitalized child was “Croup”.

Figure, Supplemental Digital Content 1: Flow chart of nasal swabs and symptom diaries from children in the Observational Research in Childhood Infectious Diseases study



Table, Supplemental Digital Content 2: Characteristics of the ORChID cohort (N=158)

	Total
	N (%)
Gender (Male)	75 (47.5)
Season of birth	
Summer	42 (26.6)
Fall	30 (19.0)
Winter	43 (27.2)
Spring	43 (27.2)
Vaginal delivery	107 (67.7)
Gestational age at birth	
36-38 weeks	36 (22.8)
39-41 weeks	122 (77.2)
Family history	
Either parent has asthma/eczema	80 (50.6)
Mother smoked during pregnancy (n=156)	5 (3.2)
Household smoke exposure at birth (n=156)	19 (12.1)
Older sibling(s) at birth	52 (32.9)
Maternal education status (n=157)	
Tertiary	99 (63.1)
Diploma/certificate	38 (24.2)
Secondary school	15 (9.6)
Primary school	5 (3.2)
Mode of feeding (n=153)	
Exclusive BF beyond age 4-months	87 (56.5)
Childcare attendance at 6-months* (n=133)	
No childcare	102 (76.7)
Informal childcare only	14 (10.5)
Formal and/ or informal childcare	17 (12.8)
Childcare attendance at 12-months* (n=116)	
No childcare	44 (37.9)
Informal childcare only	21 (18.1)
Formal and/ or informal childcare	51 (44.0)
Childcare attendance at 18-months* (n=108)	
No childcare	16 (14.8)
Informal childcare only	23 (21.3)
Formal and/ or informal childcare	69 (63.9)
Childcare attendance at 24-months* (n=103)	
No childcare	17 (16.5)
Informal childcare only	18 (17.5)
Formal and/ or informal childcare	68 (66.0)

Abbreviations: BF: breastfeeding SD: standard deviation.
*Formal childcare was defined as outside homecare from a regulated childcare service, while informal care comprised non-regulated care by relatives, friends or neighbors.

Table, Supplemental Digital Content 3: Co-detection of HPIV with at least one other virus (n=81 swabs)

			ARI symptoms*					
			None		URI		LRI	
	N	%	N	%	N	%	N	%
No co-detection	56	69.1	22	40.7	21	39.9	11	20.4
Human rhinovirus	18	22.2	5	31.3	5	31.3	6	37.5
Human coronavirus†	3	3.7	2	66.7	0	0.0	1	33.3
Human polyomavirus WU/KI	3	3.7	2	66.7	1	33.3	0	0.0
Human bocavirus-1	2	2.5	1	50.0	0	0.0	1	50.0
Human metapneumovirus	1	1.2	0	0.0	1	100.0	0	0.0

*77 HPIV swabs matched with symptom diary data.
Viruses tested that had no co-detections with HPIV identified were adenovirus, influenza virus, and respiratory syncytial virus.
Abbreviations: ARI: acute respiratory infection; HPIV: human parainfluenza virus; LRI: lower respiratory infection; URI: upper respiratory infection. †includes alpha-coronaviruses 229E and NL63 and lineage A beta-coronaviruses HKU1 and OC43.

Table, Supplemental Digital Content 4: Association of HPIV subtypes with respiratory illness (10,811 swabs, 82,036 days)

	Total episodes N	Asymptomatic episodes n, %	ARI n, %	URI n, %	LRI n, %
HPIV combined	73	30 (41.1)	43 (58.9)	26 (35.6)	17 (23.3)
HPIV-1	8	2 (25.0)	6 (75.0)	4 (50.0)	2 (25.0)
HPIV-2	4	1 (25.0)	3 (75.0)	2 (50.0)	1 (25.0)
HPIV-3	61	27 (44.3)	34 (55.7)	20 (32.8)	14 (23.0)

Abbreviations: ARI: acute respiratory infection; LRI: lower respiratory infection; HPIV: human parainfluenza virus; URI: upper respiratory infection.
81 HPIV-positive swabs (77 episodes) in total, of which 77 HPIV-positive swabs (73 episodes) were linked to symptom diaries.

Table, Supplemental Digital Content 5: Number of children, child-years, single new HPIV detection episodes, and incidence rates in children in the Observational Research in Childhood Infectious Diseases cohort (n=8101 swabs).

Risk factor	Number of children	Child-years observation	New HPIV episodes	Incidence rate per child-year (95% CI)	Incidence Rate Ratio (95% CI)	Incidence Rate Ratio (95% CI)
					Unadjusted	Adjusted*
Age (months)						
0-<3	157	22.6	5	0.18 (0.07-0.48)	0.5 (0.2-1.0)	0.6 (0.2-1.5)
3-<6	144	21.7	4	0.18 (0.07-0.49)	0.4 (0.2-1.0)	0.6 (0.2-1.5)
6-<12	136	41.2	17	0.42 (0.26-0.67)	0.7 (0.4-1.1)	0.8 (0.4-1.4)
12-<24	120	69.8	40	0.58 (0.43-0.80)	Reference	Reference
Sex						
Male	75	69.3	33	0.49 (0.35-0.68)	Reference	Reference
Female	82	86.1	33	0.38 (0.27-0.53)	0.8 (0.5-1.2)	0.8 (0.5-1.2)
Season of birth						
Summer	42	45.3	23	0.52 (0.34-0.78)	Reference	Reference
Fall	30	29.5	9	0.31 (0.16-0.59)	0.8 (0.4-1.5)	0.9 (0.4-1.8)
Winter	43	39.2	21	0.52 (0.34-0.81)	1.1 (0.6-2.0)	1.1 (0.6-2.1)
Spring	42	41.4	13	0.32 (0.18-0.55)	0.8 (0.4-1.5)	0.8 (0.4-1.5)
Type of delivery						
Vaginal	107	103.5	47	0.45 (0.34-0.60)	Reference	Reference
Caesarean	50	51.8	19	0.37 (0.24-0.58)	0.9 (0.5-1.4)	0.9 (0.5-1.4)
Gestational age at birth						
36-38 weeks	35	32.3	8	0.25 (0.12-0.50)	0.6 (0.3-1.1)	0.6 (0.3-1.2)
39-41 weeks	122	123.1	58	0.47 (0.36-0.61)	Reference	Reference
Season of acquisition						
Summer	145	34.7	12	0.35 (0.20-0.62)	Reference	Reference
Fall	146	38.1	6	0.16 (0.07-0.35)	0.5 (0.2-1.2)	0.5 (0.2-1.1)
Winter	141	43.1	13	0.30 (0.18-0.52)	0.7 (0.4-1.6)	0.7 (0.3-1.5)
Spring	141	39.4	35	0.89 (0.63-1.25)	**2.7 (1.5-4.9)**	**2.6 (1.4-4.8)**
Family history						
Neither parent has asthma/eczema	79	71.6	35	0.50 (0.36-0.69)	Reference	Reference
Either parent has asthma/eczema	78	83.7	31	0.36 (0.25-0.52)	0.8 (0.5-1.2)	0.8 (0.5-1.2)
Tobacco smoke exposure (n=155)						

No exposure	136	137.8	63	0.46 (0.36-0.59)	Reference	Reference
Other householder smokes	19	16.3	3	0.19 (0.06-1.57)	0.5 (0.2-1.3)	0.4 (0.1-1.1)
Household size at birth						
No older children in household	102	101.4	41	0.40 (0.29-0.55)	Reference	Reference
More than one child in household	55	54.0	25	0.47 (0.32-0.70)	1.0 (0.6-1.6)	1.0 (0.6-1.6)
Maternal education status (n=156)						
University/higher university degree	99	102.8	42	0.41 (0.30-0.55)	Reference	Reference
No university degree	57	52.5	24	0.46 (0.31-0.69)	0.9 (0.5-1.4)	0.9 (0.5-1.4)
Mode of feeding (n=153)						
Exclusive BF beyond age 4-months	86	85.85	43	0.50 (0.37-0.68)	Reference	Reference
Non-exclusive BF by age ≤4-months	67	69.77	34	0.49 (0.35-0.68)	0.97 (0.62-1.53)	0.92 (0.58-1.44)
Childcare attendance[†]						
No childcare	156	78.8	24	0.30 (0.20-0.45)	Reference	Reference
Informal childcare only	42	19.1	9	0.48 (0.25-0.91)	1.5 (0.7-3.0)	1.1 (0.5-2.4)
Formal and/or informal childcare	89	57.4	33	0.59 (0.42-0.82)	**1.9 (1.2-3.0)**	1.4 (0.8-2.7)

Abbreviations: BF: breast feeding; CI: confidence interval; HPIV: human parainfluenza virus.
For incidence calculations there were 66 incident HPIV episodes; 7 episodes were removed due to lower-quality swabs.
An additional 11 lower-quality HPIV-positive swabs were included when calculating associations between variables of interest and HPIV detections.
* Multivariable regression adjusted for age, sex, childcare attendance and season of acquisition.
[†] Formal childcare was defined as outside homecare from a regulated childcare service, while informal care comprised non-regulated care by relatives, friends or neighbors

Table, Supplemental Digital Content 6: Healthcare-seeking behavior by acute respiratory infection category and detection status (10,811 swabs, 82,036 days)

	Any healthcare contact (n, %)	Any family physician visits (n, %)	Family physician visit only (n, %)	Other healthcare professional (n, %)	ED presentation without admission (n, %)	Hospital admission ‡ (n, %)	Antibiotics (n, %)
HPIV combined (n=73)*							
ARI (n=43)	23 (53.5)	21 (48.8)	17 (39.5)	2 (4.7)	3 (7.0)	1 (2.3)	13 (30.2)
URI (n=26)	11 (42.3)	11 (42.3)	10 (38.5)	1 (3.8)	0 (0.0)	0 (0.0)	5 (19.2)
LRI (n=17)	12 (70.6)	10 (58.8)	7 (41.2)	1 (5.6)	3 (17.7)	1 (5.6)	8 (47.1)
Single detection (n=53)							
ARI (n=33)	16 (48.5)	15 (45.5)	12 (36.4)	1 (3.0)	2 (6.1)	1 (3.0)	8 (24.2)
URI (n=22)	9 (40.9)	9 (40.9)	8 (36.4)	1 (4.5)	0 (0.0)	0 (0.0)	4 (18.2)
LRI (n=11)	7 (63.6)	6 (54.5)	4 (36.4)	0 (0.0)	2 (18.2)	1 (9.1)	4 (36.4)
Co-detection (n=20)							
ARI (n=10)	7 (70.0)	6 (60.0)	5 (50.0)	1 (10.0)	1 (10.0)	0 (0.0)	5 (50.0)
URI (n=4)	2 (50.0)	2 (50.0)	2 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)
LRI (n=6)	5 (83.3)	4 (66.7)	3 (50.0)	1 (16.7)	1 (16.7)	0 (0.0)	4 (66.7)

Abbreviations: AOM: acute otitis media; ARI: acute respiratory infection; ED: emergency department; HPIV: human parainfluenza virus; LRI: lower respiratory infection; URI: upper respiratory infection.

Healthcare use and antibiotic information from illness-burden diary. On 38 occasions ARI symptomatology met the pre-defined threshold (all LRI, AOM, and URI with dry cough plus nasal symptoms) and burden diaries were returned. On five occasions isolated symptomatic episodes (runny nose, n=4; dry cough, n=1) without healthcare contact did not require an illness-burden diary return.

* 73 incident HPIV episodes, with ARI symptoms recorded for 43 episodes.

‡ The primary diagnosis for the hospitalized child was “Croup”.