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Timing of First Respiratory Virus Detections in Infants: A Community-Based Birth Cohort Study

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(See the editorial commentary by Storch, on pages 350–2.)

Background. Determining timing of first virus detection episodes (fVDEs) for different respiratory viruses in infants identifies risk periods and informs preventive interventions, including vaccination. We describe the ages and nature of fVDEs in an infant birth cohort and explore factors associated with increased odds of symptomatic fVDEs.

Methods. The Observational Research in Childhood Infectious Diseases (ORChID) study is a community-based birth cohort describing acute respiratory infections in infants until their second birthday. Parents recorded daily symptoms and collected nose swabs weekly, which were batch-tested using polymerase chain reaction assays for 17 respiratory viruses.

Results. One hundred fifty-eight infants participated in ORChID. The median age for fVDEs was 2.9 months for human rhinovirus (HRV) but was ≥13.9 months for other respiratory viruses. Overall, 52% of HRV fVDEs were symptomatic, compared with 57%–83% of other fVDEs. Respiratory syncytial virus and human metapneumovirus fVDEs were more severe than HRV fVDEs. Older age and the winter season were associated with symptomatic episodes.

Conclusions. Infants do not always experience respiratory symptoms with their fVDE. Predominance of early HRV detections highlights the need for timing any intervention early in life. fVDEs from other respiratory viruses most commonly occur when maternal vaccines may no longer provide protection.

Keywords. respiratory viruses; infant; primary infection; human rhinovirus; respiratory syncytial virus; human metapneumovirus; cohort study.

Despite better living conditions, improved nutrition, and greater access to healthcare and vaccine programs, acute respiratory infections (ARIs) remain the most common illness experienced by people of all ages [1]. Viruses are the most frequent cause of ARIs and the highest incidence rates occur during the first 2 years of life where, on average, infants experience 6–8 episodes per annum [2, 3]. While only 3%–5% of all infants are hospitalized for viral ARIs [4], they are responsible for 25% of all hospitalizations in this age group, imposing a major burden and cost to the health system for children [5]. With the overwhelming majority of cases managed solely in the community [3], ARIs in young children also levy considerable additional costs upon families and society [6, 7].

Much of our recent understanding of the epidemiology of viral ARIs in infants relies upon hospital-based studies [8, 9]. These emphasize respiratory syncytial virus (RSV) as the predominant cause of bronchiolitis and the most common reason for infants to be hospitalized in the first year of life [10, 11], and seasonal influenza viruses (INFVs), which also have high hospitalization rates in this age group [11, 12]. Importantly, the highest hospitalization rates for ARIs associated with both viruses are during the first 6 months of life [12–15]. However, hospital-based surveillance systems capture only the most severe illnesses and underestimate the substantial burden of disease within the community caused by these and other respiratory viruses in older infants and young children [16–18]. Indeed, community-based birth cohort studies of infants at high risk of asthma have instead identified human rhinoviruses (HRVs), ahead of RSV and INFVs, as the major upper and lower respiratory pathogens in the first year of life [19]. Moreover, those with HRV-induced wheezing from an early age are also at increased risk of developing asthma, especially if they are already sensitized to aeroallergens [20–22].

Although evidence is limited, first infections with respiratory viruses, particularly those caused by RSV, are thought to be almost always symptomatic [23] and by implication more likely to be brought to medical attention. As a large disease burden may be missed by hospital-based studies, understanding

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community epidemiology is essential when planning effective control measures. Consequently, in light of the aforementioned studies, it is important to determine the timing that different respiratory viruses are first detected in otherwise healthy young infants. This will help identify when risk periods commence and to inform future public health interventions, including maternal and infant immunization strategies for this age group.

Recently, we reported that healthy, term-born infants participating in a community-based birth cohort study had an average of 0.25 (95% confidence interval [CI], 0.18–0.34) respiratory virus detection episodes in the first 28 days of life, of which 72% were HRV, with 45% of these being asymptomatic [24]. In view of this early exposure to respiratory viruses, we now report findings for virus detection during the first 2 years of life by describing the ages at which each of 9 respiratory virus groups, comprising 17 different species and subtypes, were first detected in this birth cohort and in a setting where influenza vaccines are not part of the national infant immunization program. For each of the 9 viruses, we determined the nature of the respiratory symptoms associated with their first detection, including virus shedding characteristics and healthcare use; and whether sociodemographic and seasonal factors were associated with increased odds of developing respiratory symptoms at the time of the first detection episode.

METHODS

Study Population

The Observational Research in Childhood Infectious Diseases (ORChID) project (ClinicalTrials.gov identifier NCT01304914), described in detail elsewhere [25], is an unselected, community-based, birth cohort study conducted in the subtropical city of Brisbane, Australia (population 2.2 million; latitude 27°S; average monthly maximum temperature range, 22°C–33°C; maximum rainfall and humidity in December–February). Recruitment was from antenatal clinics and was progressive over 2 years, which allowed infants born between September 2010 and October 2012 to be enrolled evenly throughout the study period to account for seasonal and year-to-year variation in respiratory virus activity [25]. Consequently, symptom data and nose swab specimen collection spanned >4 years from September 2010 to October 2014. The Children's Health Queensland, Royal Brisbane and Women's Hospital, and the University of Queensland Human Research Ethics Committees approved the study and parents consented antenatally for their infant to participate.

Sociodemographic and Clinical Characteristics

Research staff recorded the parents' sociodemographic, health, pregnancy, and birth details if the infants met the eligibility entry criteria: healthy infants, born at term (36–42 weeks) without congenital abnormalities or underlying chronic disorders [25]. Telephone interviews, conducted quarterly by study staff, were used to collect and update feeding, vaccination, and childcare attendance details throughout the study period. Childcare was categorized as formal (regulated care outside the child's home) or informal (nonregulated care provided by friends or family) [26].

Symptom Data Collection

Parents recorded daily symptoms for their infant on a diary card, which listed predefined respiratory symptoms (nasal congestion or discharge, dry or wet [moist] cough, pneumonia, ear infection [acute otitis media], rattly breathing, shortness of breath, and wheezing). Parents were trained in recognizing respiratory symptoms prior to commencing the study, including distinguishing between a wet and dry cough, and rattly breathing and wheezing or breathlessness, so as to minimize inaccuracy of reporting. Diagnoses of acute otitis media and pneumonia were validated by a doctor's visit and, where appropriate, following review of the hospital emergency department (ED) or admission medical records [3].

Specimen Collection and Laboratory Testing

Parents were taught by trained research staff to collect anterior nose swabs from their infant, beginning around the time of birth and then weekly thereafter. The nose swabs were mailed at ambient temperature to our laboratory by surface mail, where they were stored at −80°C until analysis [27]. The swabs were then batch-tested for 17 respiratory viruses: HRV; RSV-A and RSV-B; parainfluenza viruses 1–3 (PIV-1, PIV-2, PIV-3); INFV-A and INFV-B; human metapneumovirus (HMPV); human coronaviruses (HCoVs) OC43, NL63, 229E, and HKU1; adenovirus (AdV); human polyomaviruses (HPyV) KI and WU; and human bocavirus 1 (HBoV-1) using previously validated real-time polymerase chain reaction (PCR) assays [24, 25, 28]. All virus detections with cycle threshold (Ct) values ≤40 were considered positive. In addition, Ct values were used as semiquantitative markers of viral load as they are inversely proportional to the amount of specific virus nucleic acid present in the specimen [27].

Samples testing positive for HRV were typed by sequencing the variable region of VP4/VP2 genes using a nested PCR assay [29]. If unsuccessful, a 390-nucleotide fragment from the 5′UTR segment was amplified [30] and submitted for DNA sequencing at the Australian Equine Genetics Research Centre (University of Queensland, Brisbane, Australia).

Definitions

- First virus detection episode (fVDE): when a respiratory virus not detected previously was first found in an infant's weekly nasal swab specimen.
- Symptomatic fVDE: when respiratory symptoms were reported within 7 days either side of first detecting the virus of interest in the weekly nasal swab.
- Upper respiratory tract infection (URTI): parent-reported nasal congestion or discharge, dry cough, or doctor-diagnosed acute otitis media [3].

- Lower respiratory tract infection (LRTI): parent-reported rattly breathing, wet (moist) cough, shortness of breath, wheeze, or doctor-diagnosed pneumonia [3].

Symptomatic fVDEs were subcategorized hierarchically as LRTI or URTI episodes, respectively. Additional details for addressing missing swabs and virus codetections are described in the Supplementary Methods.

ARI Burden Diary

Parents were asked to record healthcare-seeking behavior (visits to a family physician, an ED presentation, or a hospital admission) and antibiotic prescriptions in a separate "burden impact diary" [3]. Burden diaries were requested for all LRTIs, acute otitis media, and any URTI resulting in both nasal symptoms (nasal discharge or congestion) and cough. To minimize inconvenience, we did not seek burden diaries for infants with nasal symptoms alone as we reasoned that, under these circumstances, impact would be minor and parents were unlikely to seek medical advice. Both symptom and ARI burden diaries were returned by mail at the end of each month. When reviewing hospital ED presentation or admission notes, the recorded principal diagnosis was accepted as the reason for consultation, irrespective of whether the child had an ARI at the time.

Analysis

Summary statistics are presented as median (25th–75th percentile) for continuous variables and frequency (percentage) for categorical variables. First analyzed separately, HRV, RSV, PIV, INFV, HCoV, and HPyV subtypes and species were then grouped for additional analyses. The time to fVDE and symptomatic fVDE for each virus was calculated using life tables with the day of birth as study entry time. Infants were censored at either the date of the last swab submitted if the next swab was not returned for >30 days, or at 730 days, whichever came first. The association between symptomatic/asymptomatic fVDEs and both the Ct value and length of shedding were compared using a Mann–Whitney test. For clinical characteristics of fVDEs, associations between virus types and symptoms were compared using absolute risk differences for binary outcomes, and median regression for continuous outcomes. In all cases, HRV was the reference virus. The association between potential risk factors (age, sex, season, breastfeeding, childcare attendance, number of children in the household) and symptomatic fVDEs was examined for the 9 respiratory virus groups using logistic regression. Risk factors were categorized as age (0 to <3 months; 3 to <6 months; 6 to <12 months, and 12 to 24 months); sex (male, female); season (winter [June–August], spring [September–November], summer [December–February], fall [March–May]); breastfeeding (exclusively breastfed for ≥4 months, exclusively breastfed for <4 months, or never breastfed); childcare attendance (no childcare, any form of childcare); number of children in the household (no other children, at least 1 other child). Both univariable and multivariable models were constructed. Multivariable models were adjusted for all variables listed above. Data were analyzed using Stata version 12.1 software (StataCorp, Texas).

RESULTS

Cohort Characteristics

Of 891 potential participants approached, 165 (18.5%) eligible infants from 163 families were enrolled, with 7 subsequently excluded for protocol breaches (Supplementary Figure 1). The remaining 158 infants provided 11 192 swabs (68.3% of maximum expected; median, 84.5 [range, 1–104] swabs). Subsequently, 1327 swabs were censored due to a gap of >30 days between successive swabs, as were another 67 swabs submitted after the child's second birthday, leaving 9798 swabs to be included in the full analysis (Supplementary Figures 1 and 2). A further 204 swabs without corresponding symptom data were excluded from the analysis, leaving 9594 swabs describing the association between symptoms and fVDEs. Compared to the general population, study infants were from smaller families of more advantaged backgrounds (Supplementary Table 1).

First Virus Detection Episodes

At least 1 virus was detected in 2542 of 9798 (25.9%) swabs, while codetections of ≥2 viruses were observed in 241 (2.5%) specimens. HRV was the earliest and most commonly detected virus (present in 1964 of 2542 [77.3%] positive swabs). Table 1 and Figure 1 show that HRV-C (found in 98% of infants) and HRV-A (94%) were more frequently detected than HRV-B (56%) by age 2 years and at a younger age (median age of fVDEs was 6.7, 6.1, and 19.6 months for each HRV species, respectively). HRV was detected as early as 2 days of life and, by age 3 months, 50% of the cohort had HRV detected at least once.

Other respiratory viruses were not detected as often in the first 6 months of life (Table 1 and Figure 1). However, by their second birthday, 50%–60% of the cohort had experienced their fVDEs by RSV, PIV-3, and AdV species, and 70%–77% of cohort subjects had HCoV, HPyV KI/WU, and HBoV-1 virus species detected on at least 1 occasion. Influenza virus, PIV-1, and PIV-2 were detected in ≤11% of the cohort.

Nature of First Virus Detection Episodes

While fVDEs for HRV were symptomatic 52% of the time, infections with the other RNA viruses and AdV had symptoms for 69%–83% of these episodes (Tables 2 and 3). fVDEs with other DNA viruses, HBoV-1, and HPyV WU and KI, were symptomatic 57%–66% of the time. Symptomatic fVDEs with RSV and HBoV-1 had significantly lower Ct values (higher viral loads) in their nasal swabs than corresponding asymptomatic fVDEs (Table 2). No such associations were observed with Ct values for the other viruses, and no differences in virus

Table 1. Time to First Detection of Respiratory Viruses Collected From 158 Infants in the First 2 Years of Life in the Observational Research in Childhood Infectious Diseases (ORChID) Birth Cohort

Virus	Virus-Positive Swabs[a] (N = 9798), No. (%)	Age at First Virus Detection, mo[b], Median (25th, 75th Percentile	First Virus Detection Proportions, Cumulative %			
			Age 6 mo	Age 12 mo	Age 18 mo	Age 24 mo
HRV combined[c]	1964 (20.0)	2.9 (1.6, 5.1)	81.1	96.3	99.1	99.1
HRV-A	652 (6.7)	6.7 (3.7, 10.7)	42.4	79.5	92.2	94.4
HRV-B	150 (1.5)	19.6 (7.7, –)	18.9	34.7	45.4	63.0
HRV-C	599 (6.1)	6.1 (3.5, 10.1)	48.8	86.4	98.1	98.1
RSV combined	88[d] (0.9)	19.4 (11.2, –)	8.5	27.7	48.6	58.4
RSV-A	67 (0.7)	– (13.3, –)	7.0	21.6	39.7	46.8
RSV-B	22 (0.2)	– (–, –)	2.4	8.7	14.6	21.7
PIV combined	71 (0.7)	23.2 (12.4, –)	9.4	24.7	37.3	58.2
PIV-1	6 (0.1)	…	0.0	1.8	3.9	6.9
PIV-2	3 (0.0)	…	0.8	0.8	0.8	3.7
PIV-3	62 (0.6)	23.9 (14.2, –)	8.7	22.1	33.9	55.7
INFV combined[e]	11 (0.1)	…	2.2	5.8	8.0	10.9
INFV-A	8 (0.1)	…	0.8	4.4	6.7	8.0
INFV-B	3 (0.0)	…	1.4	1.4	1.4	2.9
HMPV	24 (0.2)	…	0.7	8.6	15.4	21.1
HCoV combined	138 (1.4)	17.2 (9.1, –)	11.5	33.4	52.9	72.2
HCoV-OC43	43 (0.4)	– (19.7, –)	5.3	14.2	20.6	31.6
HCoV-NL63	52 (0.5)	– (16.8, –)	2.9	15.1	27.1	40.2
HCoV- 229E	10 (0.1)	…	2.0	2.0	4.3	7.2
HCoV-HKU1	33 (0.3)	– (22.7, –)	2.0	7.4	18.8	27.2
AdV	95 (1.0)	23.5 (11.0, –)	8.0	28.7	44.9	51.3
HPyV combined	250[f] (2.6)	13.9 (9.3, 23.9)	6.4	39.4	60.6	76.6
HPyV-KI	157 (1.6)	19.2 (10.6, –)	4.8	28.0	46.9	55.0
HPyV-WU	98 (1.0)	– (15.1, –)	1.6	13.5	30.9	48.9
HBoV-1	138 (1.4)	16.0 (9.2, 21.3)	4.7	41.2	63.7	75.4

Abbreviations: AdV, adenovirus; HBoV-1, human bocavirus-1; HCoV, human coronavirus; HMPV, human metapneumovirus; HPyV, human polyomavirus; HRV, human rhinovirus; INFV, influenza virus; PIV, parainfluenza virus; RSV, respiratory syncytial virus.

[a]Includes codetections; infants were censored if a swab was not returned for >30 days.

[b]Age at which 50% (25%, 75%) of the cohort have had their first detection with the virus; a dash in the median (25th percentile, 75th percentile) space reflects <50% (25%, 75%) of children were infected with this virus.

[c]Five hundred sixty-two isolates were not able to be typed, 1 swab extract missing and not sequenced.

[d]Includes 1 RSV-A/RSV-B codetection.

[e]Influenza vaccines are not part of the Australian National Immunization Program; 28 (17.7%) mothers of infants in the ORChID cohort had the influenza vaccine during their pregnancy, and just 7 infants received the influenza vaccine in the first 2 years of life [3].

[f]Includes 5 HPyV-KI/HPyV-WU codetections.

shedding duration were seen between symptomatic and asymptomatic fVDE groups.

Table 3 shows that infants with RSV and HMPV fVDEs had the highest proportions of LRTIs (46.3% and 50.0%, respectively). Compared with HRV, the RSV, PIV, HMPV, HCoV, and AdV fVDEs were significantly more likely to be symptomatic and, for AdV and HPyV, symptomatic fVDEs to last longer. Overall, 128 of 527 (24.3%) fVDEs resulted in medical visits and antibiotics were prescribed in 63 (49.2%) of these illness episodes. Compared with HRV, those with RSV, PIV, HMPV, HCoV, AdV, and HBoV-1 symptomatic fVDEs were significantly more likely to seek medical advice and for those with RSV, INFV, AdV, HPyV, and HBoV-1 to receive antibiotics. While family physician consultations were common, infants were infrequently taken to the ED or hospitalized, and there were no deaths in the cohort.

Because virus codetections may confound individual virus contributions to ARI symptoms, analyses of Ct values, shedding duration, and clinical characteristics were repeated for single only fVDEs (Supplementary Tables 2 and 3). Overall, these gave similar results, although DNA rather than RNA virus fVDEs were significantly more likely to have virus codetections (risk ratio, 2.15 [95% CI, 1.62–2.78]). A separate analysis found that single fVDEs with DNA viruses were consistently less likely to be symptomatic than corresponding fVDEs when other viruses were also present, reaching statistical significance for HPyV-KI and HBoV-1 (Supplementary Table 4).

Factors Associated With Symptomatic First Virus Detection Episodes

After adjusting for potentially confounding variables, characteristics associated with symptomatic fVDEs included the winter season, as opposed to summer for HRV and spring and

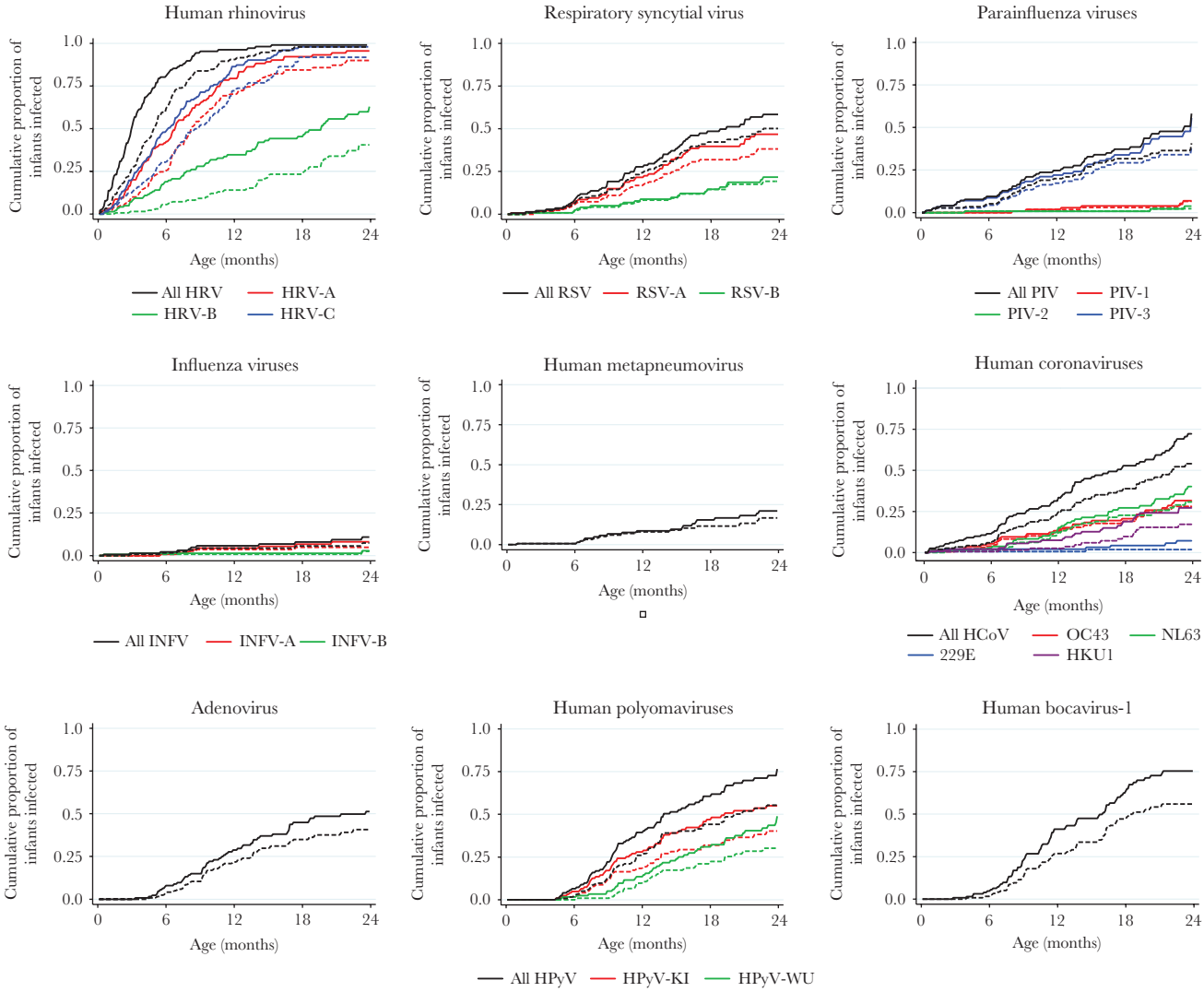

Figure 1. Time to first respiratory virus detection episode by virus and subtype/species. Solid line represents all censored first detections for that respiratory virus or virus subtype; dashed lines represent all censored symptomatic first detections; Abbreviations: HCoV, human coronavirus; HPyV, human polyomavirus; HRV, human rhinovirus; INFV, influenza virus; PIV, parainfluenza virus; RSV, respiratory syncytial virus.

summer for HPyV, whereas age between 6 and <12 months was identified for PIV-3. No sociodemographic or seasonal factors were identified for symptomatic fVDEs for the other respiratory viruses (Supplementary Table 5).

DISCUSSION

In this community cohort of healthy Australian children, we detected respiratory viruses early in life, with HRV playing a dominant role from birth, and other viruses detected generally after 6 months of age. Although only about half of the HRV fVDEs were associated with respiratory symptoms, 70%–83% of fVDEs with other respiratory RNA viruses were symptomatic. While 57%–69% of fVDEs with AdV, HPyV KI/WU, and HBoV-1 DNA viruses had symptoms, this decreased to 43%–59% when these were the sole detected agents. High viral loads for RSV and HBoV-1 were associated with symptoms, but shedding duration was independent of symptom status. Overall, RSV and HMPV fVDEs were most likely to be associated with LRTIs and to result in medical visits where antibiotics were commonly prescribed, irrespective of the virus or viruses detected around the time of presentation. The winter season was an independent risk factor for symptomatic HRV and HPyV fVDEs, and age >6 months was a risk factor for symptomatic PIV fVDEs. No risk factors were identified for other common viruses.

First respiratory virus infections are believed to be almost invariably symptomatic and, in the case of RSV, to result in more severe disease because of the infant's immature immune system and small airways, with reinfections thought to have a lower risk of illness [23, 31]. Our data show that during their fVDEs, infants do not always experience respiratory symptoms.

Table 2. Number of Symptomatic and Asymptomatic First Respiratory Virus Detection Episodes, Virus-Specific Median Cycle Threshold Values, and Median Duration of Virus Shedding, in the First 2 Years of Life in 152 Infants Participating in the Observational Research in Childhood Infectious Diseases (ORChID) Birth Cohort (n = 9594 Swabs)

		First Respiratory Virus Detection Episodes							
		Symptomatic Episodes			Asymptomatic Episodes				
Virus (No.)	Infants With Single Positive Swab, %[a]	Infants, No.	Median Ct Value (Range)	Median Virus Shedding, wk[a] (Range)	Infants, No.	Median Ct Value (Range)	Median Virus Shedding, wk[a] (Range)	*P* Value[b]	*P* Value[c]
HRV (130)	47.7	68	29.2 (18.8–39.8)	1.5 (1–9)	62	29.2 (20.6–39.1)	2 (1–11)	.5	.4
RSV (54)	83.3	42	29.3 (22.3–37.3)	1 (1–3)	12	36.0 (27.4–39.6)	1 (1–3)	**.003**	.5
PIV (52)	94.2	37	31.0 (22.0–38.5)	1 (1–2)	15	31.4 (26.0–38.3)	1 (1–1)	.3	.3
INFV (11)	100.0	8	31.9 (29.5–38.2)	1 (1–1)	3	30.2 (29.6–30.3)	1 (1–1)	.2	NC
HMPV (18)	83.3	15	33.7 (23.8–39.2)	1 (1–2)	3	34.4 (34.0–35.5)	1 (1–1)	.5	.4
HCoV (67)	74.6	47	29.3 (21.5–38.9)	1 (1–3)	20	28.8 (21.4–38.5)	1 (1–2)	.8	.06
AdV (52)	76.9	36	31.3 (18.6–39.4)	1 (1–7)	16	33.6 (24.4–39.1)	1 (1–2)	.7	.05
HPyV (70)	37.1	40	27.5 (19.0–39.1)	2.5 (1–7)	30	32.2 (18.4–39.3)	2 (1–5)	.1	.2
HBoV-1 (73)	56.2	48	28.0 (16.9–38.4)	2 (1–4)	25	31.6 (18.1–38.9)	1 (1–4)	**.001**	.3

Abbreviations: AdV, adenovirus; Ct, cycle threshold; HBoV-1, human bocavirus-1; HCoV, human coronavirus; HMPV, human metapneumovirus; HPyV, human polyomavirus; HRV, human rhinovirus; INFV, influenza virus; NC, not calculable; PIV, parainfluenza virus; RSV, respiratory syncytial virus.

[a]Nasal swabs collected weekly by parents.

[b]Mann–Whitney test comparing median Ct values for the 2 groups.

[c]Mann–Whitney test comparing median shedding duration for the 2 groups.

The cumulative proportion of infants in our cohort with fVDEs from viruses other than HRV increased steadily after age 6 months. The delayed appearance of these other viruses may be from the protective effects of maternal antibodies and reduced exposure, as attendance at childcare centers is less common in this age group [3, 32].

Our findings differ from the Houston Family study, which, relying heavily upon serology, reported that 68% of infants had RSV by age 12 months and virtually all were infected by their second birthday. However, studies from Asia, Europe, and Latin America observed RSV seroprevalence rates of 36%–70% by age 2 years [33–37], whereas in Kenya a birth cohort project similar in design to the Houston study found that 73% had RSV by 2 years of age [38]. These results are more in keeping with our own, and possible explanations for our lower incidence of RSV fVDEs during the first 2 years of life than in the Houston study include variations in intensity and duration of seasonal exposure [39], fewer subjects with older siblings to introduce RSV into the household [38, 40], and relying upon PCR rather than serology to detect the virus.

Hospital-based studies are skewed toward those with the most severe infections and represent <5% of the infant population [4]. Whereas RSV predominates in hospitalized infants aged <6 months with LRTIs, HRV is the most common virus detected in older infants and children admitted with wheezing illnesses, which are often recurrent and associated with a subsequent increased risk of asthma [20–22, 41]. In contrast, community-based studies like our own find symptomatic fVDEs with HRV occurring by age 4–6 months, and with RSV and other viruses appearing on average beyond this age [19, 38, 42]. Viruses such as RSV, PIV, INFV, and HMPV are more likely than other viruses to be associated with respiratory symptoms [9] and, consequently, although less commonly exposed to these viruses than HRV at a young age, it is thought that young infants hospitalized with more severe disease have preexisting smaller airways, have immature immune systems, and/or are lacking protective maternal antibodies [43, 44]. As these infants become older and their airways grow and immune systems mature, the symptoms of infections by these other viruses lessen [31, 38].

While wheezing illnesses following early exposure to HRV are associated with a greater likelihood of developing asthma in high-risk cohorts [20–22], the role of early asymptomatic HRV infections has received less attention. A recent report suggested that HRV detection in the first 4 weeks of life, even if asymptomatic, may help program immune memory with an exaggerated T-helper 2 (rather than T-helper 1) mucosal immune response and impaired antiviral responses [45]. This suggests a potential pathway for the later development of asthma and allergic sensitization in susceptible individuals. If true, interventions seeking to reduce HRV infections in high-risk infants will need to be introduced early. Although maternal vaccines to protect infants from early respiratory virus infections is an active area of research, especially for RSV and influenza viruses [32], our study emphasizes the predominance of early HRV detections, the long-term effects of which remain uncertain in healthy infants. It also highlights that for many in our study population, their first infection from non-HRV viruses occurs at an age when maternal vaccines may no longer be protective [32].

Table 3. Clinical Characteristics of the First Respiratory Virus Detection Episodes in the First 2 Years of Life in 152 Infants Participating in the Observational Research in Childhood Infectious Diseases (ORChID) Birth Cohort (n = 9594 Swabs)

Virus[a]	No. of Infants	ARI Episodes, URTI/ LRTI[b], %	Risk Difference for ARI Episodes, % (95% CI)	Median ARI Symptom Duration, d (IQR)	Median Difference of ARI Episode Duration, d (95% CI)[c]	Medical Visits FP/ED/ Hospitalized[d,e], %	Risk Difference for Medical Visits, % (95% CI)	Antibiotics After Any Medical Visit[e], %	Risk Difference for Antibiotics, % (95% CI)
HRV	130	46.2/6.2	0.0 (ref)	5.5 (3–10)	0.0 (ref)	13.1/0.0/0.8	0.0 (ref)	23.5	0.0 (ref)
RSV	54	31.5/46.3	**25.5 (11.4 to 39.5)**	9 (7–11)	1.8 (–0.2 to 6.2)	37.0/5.6/1.9	**24.0 (9.8 to 38.1)**	55.0	**34.4 (4.4 to 64.4)**
PIV	52	50.0/21.2	**18.8 (3.8 to 33.9)**	9 (4–14)	1.8 (–0.4 to 6.4)	26.9/1.0/0.0	**15.8 (2.2 to 29.4)**	35.7	12.2 (–20.0 to 44.4)
INFV	11	54.5/18.2	20.4 (–7.3 to 48.1)	11 (7–16.5)	1.9 (–0.2 to 12.2)	36.4/0.0/0.0	23.3 (–5.7 to 52.3)	75.0	**51.5 (4.5 to 98.5)**
HMPV	18	33.3/50.0	**31.0 (11.8 to 50.2)**	9 (6–11)	1.3 (–1.7 to 7.7)	33.3/5.6/0.0	**20.3 (1.7 to 25.9)**	33.3	9.8 (–33.0 to 52.6)
HCoV	67	46.3/23.9	**17.8 (3.9 to 31.8)**	9 (3–13)	1.9 (–0.1 to 6.1)	25.4/4.4/0.0	**13.8 (1.7 to 25.9)**	50.0	26.5 (–4.2 to 57.1)
AdV	52	44.2/25.0	**16.9 (1.7 to 32.1)**	10 (5–13.5)	**2.9 (1.6 to 8.4)**	32.7/0.0/0.0	**19.6 (5.6 to 33.6)**	58.8	**35.3 (4.4 to 66.2)**
HPyV	70	41.4/15.7	4.8 (–9.7 to 19.3)	11 (4–17.5)	**3.0 (1.7 to 8.3)**	15.7/0.0/0.0	4.1 (–6.5 to 14.6)	66.6	**43.1 (9.7 to 76.6)**
HBoV-1	73	50.7/15.1	13.4 (–0.4 to 27.3)	9 (5–14)	1.9 (–0.1 to 8.0)	26.0/2.7/0.0	**13.0 (1.3 to 24.6)**	57.9	**34.4 (4.4 to 64.4)**

Abbreviations: AdV, adenovirus; ARI, acute respiratory infection; CI, confidence interval; ED, emergency department; FP, family physician; HBoV-1, human bocavirus-1; HCoV, human coronavirus; HMPV, human metapneumovirus; HPyV, human polyomavirus; HRV, human rhinovirus; INFV, influenza virus; IQR, interquartile range; LRTI, lower respiratory tract infection; PIV, parainfluenza virus; ref, reference; RSV, respiratory syncytial virus; URTI, upper respiratory tract infection.

[a]Detected in nasal swabs collected weekly by parents.

[b]Mutually exclusive hierarchical classification of ARI episodes (LRTI > URTI).

[c]Median difference of ARI episode duration calculated by quantile regression technique.

[d]Medical visits were not mutually exclusive categories as an infant may have had >1 medical encounter in different settings during a single ARI episode.

[e]Medical visits and antibiotic information were derived from the ARI burden diary triggered in 223 of 233 (95.7%) eligible recorded ARI episodes.

The fVDEs by DNA viruses were significantly more likely than RNA viruses to have additional viruses codetected during this episode. In part, this might be explained by most HRV fVDEs occurring during the first 6 months of life where other viruses were detected uncommonly. When sole fVDEs by these DNA viruses were examined, they were found to be similar to HRV fVDEs in that about 50% of episodes were associated with symptoms, although symptomatic episodes with HPyV and HBoV-1 were significantly more prolonged than those associated with HRV. These findings indicate that, while common, these viruses often cause mild or no ARI symptoms, even after an fVDE [9, 46, 47]. Interestingly, HBoV-1 viral load was associated with the presence of ARI symptoms, a metric along with HBoV-1 capsid messenger RNA that has been reported previously to be associated with disease severity [47].

The ORChID cohort spanned multiple seasons, and its strengths include the comprehensive surveillance provided by regular weekly nasal swab collections and daily symptom diary recordings by parents. The return rate of 68% of expected swab is noteworthy given the project's intensive and prolonged nature. Potential limitations include parents missing very mild symptoms. However, we minimized reporting inaccuracy by training parents on symptom recognition and diary completion before they commenced the study and included only doctor-diagnosed episodes of otitis media and pneumonia [3]. This study design has been used successfully before where parents were trained to recognize respiratory symptoms [48]. Another limitation is parents having a suboptimal nasal swabbing technique [28]. However, sensitive molecular detection methods combined with mailed parent-collected nasal swabs provide comparable results with nasopharyngeal swabs collected by health professionals [27, 48, 49]. For logistical reasons, we did not include other respiratory viruses, such as INFV-C or PIV-4, in our assays, although 17 viruses still provide a comprehensive survey of early-life exposures. Additionally, 29% of HRV-positive specimens were unable to be typed, mainly due to low viral loads, a finding comparable with other community-based cohort studies [50]. We may have underestimated virus shedding duration because of missing swabs or swabs being collected only weekly. Similarly, ascribing symptoms to viruses when swab collection was not always done weekly or if other viruses were detected during the fVDE could compromise accuracy, although subanalyses of sole fVDEs were reassuring. It is also likely that we were unable to identify risk factors associated with symptomatic non-HRV fVDEs because of a lack of power, as numbers for some subcategories were small. As is common with cohort studies, our families were from more advantaged backgrounds, but our findings for infections rates, such as RSV, approximate recent studies [23, 37, 38] and provide an insight into respiratory viruses affecting infants from a developed country in a subtropical, urban setting.

In conclusion, respiratory viruses are detected early in life, with HRV playing a dominant role from birth. The onset of fVDEs for other respiratory viruses increased after age 6 months, with RSV and HMPV having the more severe symptoms, but identifiable sociodemographic and seasonal factors were not consistently associated with symptomatic fVDEs in our cohort. Whether early fVDEs, particularly from HRV, are important or preventable and have adverse long-term effects on some individuals warrants further study.

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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Potential conflicts of interest. After completion of data collection for this study, M. D. N. became a full-time employee of GlaxoSmithKline. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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