MAJOR ARTICLE

# Community Surveillance of Respiratory Viruses Among Families in the Utah Better Identification of Germs-Longitudinal Viral Epidemiology (BIG-LoVE) Study

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**(See the Editorial Commentary by Storch on pages 1225–7.)**

***Background.*** This study: (1) describes the viral etiology of respiratory illness by prospectively collecting weekly symptom diaries and nasal swabs from families for 1 year, (2) analyzed data by reported symptoms, virus, age, and family composition, and (3) evaluated the duration of virus detection.

***Methods.*** Twenty-six households (108 individuals) provided concurrent symptom and nasal swab data for 4166 person-weeks. The FilmArray polymerase chain reaction (PCR) platform (BioFire Diagnostics, LLC) was used to detect 16 respiratory viruses. Viral illnesses were defined as ≥1 consecutive weeks with the same virus detected with symptoms reported in ≥1 week.

***Results.*** Participants reported symptoms in 23% and a virus was detected in 26% of person-weeks. Children younger than 5 years reported symptoms more often and were more likely to have a virus detected than older participants (odds ratio [OR] 2.47, 95% confidence interval [CI], 2.08–2.94 and OR 3.96, 95% CI, 3.35–4.70, respectively). Compared with single person households, individuals living with children experienced 3 additional weeks of virus detection. There were 783 viral detection episodes; 440 (56%) associated with symptoms. Coronaviruses, human metapneumovirus, and influenza A detections were usually symptomatic; bocavirus and rhinovirus detections were often asymptomatic. The mean duration of PCR detection was ≤2 weeks for all viruses and detections of ≥3 weeks occurred in 16% of episodes. Younger children had longer durations of PCR detection.

***Conclusions.*** Viral detection is often asymptomatic and occasionally prolonged, especially for bocavirus and rhinovirus. In clinical settings, the interpretation of positive PCR tests, particularly in young children and those who live with them, may be confounded.

***Keywords.*** infectious diseases; respiratory viruses; rhinovirus; children; PCR.

Respiratory illnesses, often caused by viral infections, are among the most important causes of morbidity and mortality worldwide [1]. Viral infections produce a range of symptoms from mild to life threatening, though some infections can be asymptomatic [2–6]. Associations between viruses and symptoms in different populations remain to be elucidated. Studies of the etiology and epidemiology of respiratory illness conducted in clinical settings may be biased toward identification of more severe infections, while those in community settings should better represent the full spectrum of viral infection.

During the last century, several landmark surveillance studies quantified respiratory illness in US communities. The earliest, conducted in 1921–1924 in Hagerstown, Maryland, captured respiratory illness as

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part of a broader study of acute and chronic illness and did not include testing for viral pathogens [7]. Later studies in Cleveland, Ohio (1948–1957) [8] and in Tecumseh, Michigan (1965–1969) [9, 10] enrolled households prospectively, collected symptoms through diaries, phone calls, and home visits, and obtained samples for serologic and culture-based analyses for viral and bacterial pathogens during illness episodes. The Virus Watch program in New York (1961–1965) enrolled families with young children and collected fecal and respiratory specimens every 2 weeks from index persons within households regardless of symptoms [11]. The Virus Watch study detected viruses from both symptomatic and asymptomatic individuals, though in up to 93% of illness episodes, no virus was isolated [12].

The ability to detect viruses improved with the availability of the polymerase chain reaction (PCR), and many new viruses have been discovered [13–15]. The use of more sensitive methods has led to increased appreciation of asymptomatic viral infections and prolonged shedding.

The objectives of the Utah Better Identification of Germs-Longitudinal Viral Epidemiology (BIG-LoVE) study were to: (1) Describe the epidemiology of respiratory illness and respiratory viral detections by PCR through weekly collection of nasal swabs and symptom diaries from all household members for 1 year, (2) analyze data by reported symptoms, virus, age, and family composition, and (3) evaluate the duration of virus detection.

## METHODS

### Human Subjects Protection

The University of Utah Institutional Review Board approved this study. All participants provided informed consent.

### Study Population and Surveillance Procedures

The Utah BIG-LoVE study was a 52-week prospective investigation of households between August 2009 and August 2010. This period included the second wave of the 2009 H1N1 influenza pandemic [16].

Participants were recruited from the University of Utah campus community. Individuals and families with or without children were eligible. All household members were included. Households that included individuals with immune-compromising conditions were excluded as they have different risks for viral infection and shedding [17].

### Symptom Diaries

One adult in each household was trained and completed all surveys including an initial questionnaire describing the family demographics, health histories, occupation(s), and child care or school participation and all weekly online symptom diaries for each family member on the same day as nasal sample collection throughout the study. The symptom diary documented by the household reporter the occurrence on any day in the past week of: (1) fever, nasal congestion, cough, wheeze, or gastrointestinal symptoms; (2) any missed child-care, school, or work; (3) medical care for respiratory illness; (4) hospitalization for respiratory illness; and (5) influenza immunization. If families failed to report data, a reminder email was sent and the study coordinator contacted the family. Data reported >7 days after the scheduled date were excluded. All survey data were time stamped and archived in the Department of Pediatrics Data Coordinating Center in a HIPAA (Health Insurance Portability and Accountability Act), HITECH (Health Insurance Technology for Economic and Clinical Health), and FISMA (Federal Information Security Management Act) compliant database.

### Nasal Sampling

A weekly anterior nares swab specimen was obtained for all household members regardless of symptoms. A research coordinator instructed participants to self-collect nasal secretions using a flocked swab (Copan Diagnostics, Inc., Murrieta, California) and taught parents how to collect specimens from younger children [18–20]. Self-collection is sensitive for most respiratory viruses [21, 22]. After sampling, swabs were placed in a sterile tube without media for home refrigerator storage until returned to the study coordinator within 1–3 days of collection. Sampling differed from the Food and Drug Administration (FDA) validated nasopharyngeal swab in viral transport media for the FilmArray test.

### Viral Testing

Samples were stored at −80°C prior to testing. We used a developmental version of the FilmArray RP multiplex respiratory virus panel (BioFire Diagnostics, Salt Lake City, Utah) to detect adenovirus, human bocavirus, coronaviruses HKU1, NL63, OC43, and 229E, enterovirus, influenza A (including subtype identification for H1, H3, and A/H1N1pdm09), influenza B, human metapneumovirus, parainfluenza viruses 1–4, respiratory syncytial virus, and rhinovirus [23, 24]. Sample lysis, nucleic acid purification, nested-multiplexed PCR, and amplicon analysis were performed in a closed pouch using the FilmArray instrument; internal controls were included for each sample. For this study, enteroviruses were distinguished from rhinoviruses using separate validated singleplex PCR (BioFire Diagnostics).

### Definitions and Statistical Analyses

Households were characterized by size and the presence of children. The age of participants was determined at enrollment. Analyses were performed for 4 age groups, 0–4, 5–17, 18–39, and 40–59 years, chosen to represent preschool and school aged children and early and mid-adulthood.

We defined several types of episodes (Supplementary Table 1). Data were collected weekly and analyzed as person-weeks. Illness weeks were defined as a week in which symptoms were reported in the symptom diary, regardless of virus detection. Because symptoms and infections can span several weeks, we defined an illness episode as ≥1 consecutive weeks in which symptoms were recorded. Viral detection episodes were defined as ≥1 consecutive weeks in which the same virus was detected and classified as symptomatic or asymptomatic.

Symptoms associated with individual respiratory viruses were compared with the $\chi^2$ or Fisher exact test. The Mann–Whitney *U* test was used to compare continuous variables. Quasi-Poisson and binomial generalized linear models were constructed to determine whether household characteristics were associated with the number and duration of viral detection episodes and the presence or absence of symptoms. Odds ratios (OR) and 95% confidence intervals (95% CI) are presented for all regression analyses. All reported *P*-values are 2-sided. All statistical analyses were performed in R 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

### Description of the Study Cohort

The cohort included 26 households with 105 individuals at initiation. Three infants were born during the study providing a final cohort of 108 individuals ranging in age from 1 day to 57 years (Table 1).

Households included single individuals (N = 4) and families ranging in size from 3 to 8 persons (N = 22, mean 4.2 persons). In 22/26 (85%) households there was at least 1 child, and 12/26 households (46%) included at least 1 child ≤5 years.

### Return of Study Materials

There were 5391 potential person-weeks of observation. Participants submitted 4506 nasal swabs (84%) and returned 4550 symptom diaries (84%). Both were submitted for 4246 weeks (79%). Data were late for 80, leaving 4166 (77%) person-weeks for analysis (Supplementary Table 2).

### Symptom Weeks and Illness Episodes

Overall, participants reported symptoms in 962/4166 (23%) weeks (Supplementary Table 3). Children younger than 5 years were more likely to report symptoms (271/710 [38%] weeks) than older children and adults (691/3457 [20%] weeks; OR 2.47; 95% CI, 2.08–2.94; $P < .0001$) and were more likely to report more severe symptoms such as fever and wheezing.

The 962 weeks with symptoms included 544 distinct illness episodes with symptoms present in a mean of 2.0 consecutive reporting weeks (range 1–23 weeks). Participants experienced a mean of 5.0 (range 1–12) respiratory illness episodes per person per year (pp/py). Children younger than 5 had more illness episodes (mean of 6.1 pp/py) compared with children 5–17 (5.3 pp/py), adults 18–39 (4.6 pp/py), and adults older than 40 (4.1 pp/py) ($P = .02$ for trend). The number of illness episodes was not associated with the size of the household ($P = .6$); however, the presence of children in the household was associated with more illness episodes (OR 2.29, 95% CI, 1.11–5.87; $P = .05$).

Of 544 illness episodes, 324 (60%) had a virus detected in ≥1 weeks. Illness episodes in which a virus was detected were no more likely to be associated with missed school and/or work ($P = .2$) or healthcare visits ($P = .2$) than episodes in which no virus was detected.

**Table 1. Demographic and Clinical Information for the Study Cohort**

| Demographic Variables | N (%) |
|---|---|
| Adults (≥18 y) | 48 (44) |
| 18–39 | 26 (24) |
| 40–59 | 22 (20) |
| Children (<18 y) | 60 (56) |
| 0–4 | 21 (19) |
| 5–17 | 39 (36) |
| Males | 57 (53) |
| Race/ethnicity | |
| White, Non-Hispanic | 88 (81) |
| White Hispanic | 3 (3) |
| Asian | 2 (2) |
| Mixed race | 5 (5) |
| Unreported | 10 (9) |
| Occupation of adults (N = 48) | |
| Healthcare worker | 11 (23) |
| Teacher | 1 (2) |
| Out of home participation of children (N = 60) | |
| Child care | 10 (17) |
| School | 38 (63) |
| Clinical variables | |
| Missed daycare, school, or work for symptoms | 54 (50) |
| Medical care for any symptomatic episode | 32 (30) |
| Emergency department visit for symptomatic episode | 2 (2) |
| Hospital admission | 0 (0) |
| Any influenza immunization | 67 (62) |
| Seasonal injectable | 45 (42) |
| Seasonal inhaled | 16 (15) |
| 2009 H1N1 injectable | 15 (14) |
| 2009 H1N1 inhaled | 21 (19) |

### Viral Detection by Week

A virus was detected in participants during 1064/4166 (26%) person-weeks. Participants reported symptoms in 45% (481/1064).

Age was associated with viral detection. Children younger than 5 were virus positive in 358/710 (50%) of weeks and

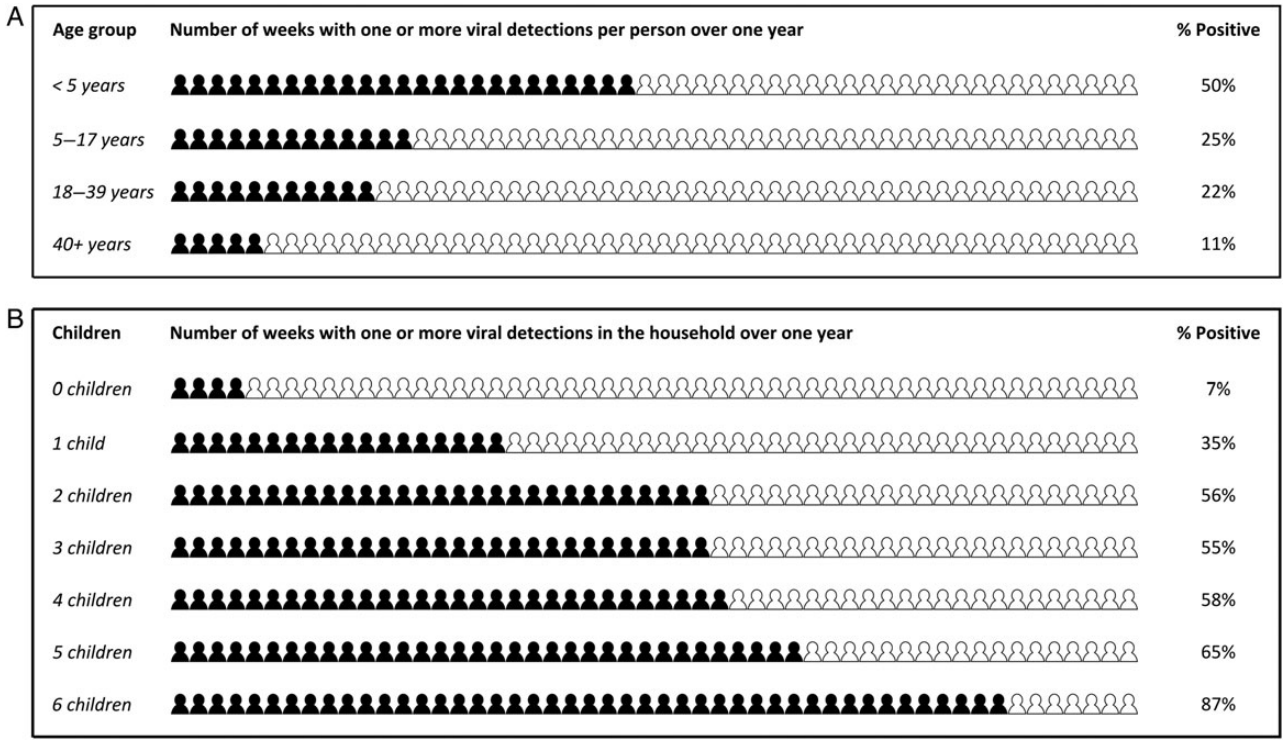


**Figure 1.** *A,* The mean number of weeks with 1 or more viral detections per person during 1 year as a function of age. *B,* The number of weeks with 1 or more viral detections in the household over 1 year stratified by the number of children residing in the household.

children 5–17 years were positive in 402/1597 (25%) of weeks, both significantly more commonly than adults (304/1859 [16%] of weeks; OR 5.20, 95% CI, 4.28–6.33 and OR 1.72, 95% CI, 1.45–2.04, respectively) (Figure 1*A* and Table 2).

Viral detection was more common in larger families (Figure 1*B*). When compared with single person households, individuals living in households with 1or more children experienced 3.09 (95% CI, 1.29–10.07) additional weeks of viral detection per person ($P = .04$).

Rhinovirus was the most commonly detected virus, present in 694 weeks (17%), accounting for 65% of all virus positive weeks. Overall, 100/108 participants (93%) had rhinovirus detected in at least 1 weekly sample. Rhinovirus, bocavirus, and the coronaviruses accounted for 1056 (99%) of the virus positive weeks (Table 2).

The seasonality of viral detection varied (Supplementary Figure 1). Influenza peaked in the fall of 2009, corresponding with the peak of the H1N1 pandemic in Utah [25].

### Virus Positive Illness and Virus Positive Asymptomatic Episodes

There were 783 viral detection episodes (mean 7.3 pp/py); a single virus was detected in 560 (72%). Children younger than 5 years had more viral detection episodes (12.1 pp/py) than school-aged children (7.5 pp/py), adults 18–39 (6.3 pp/py), and adults older than 40 (3.3 pp/py) ($P < .001$ for trend). Larger family size was associated with more virus detection episodes (Supplementary Table 4).

Of 783 viral detection episodes, 440 (56%) were associated with symptoms (Supplementary Table 5). Viral detection episodes were more likely to associated with symptoms among children younger than 5 than among older children and adults (69% vs 50%; OR 2.21, 95% CI, 1.68–2.92; $P < .001$). Symptom frequency varied by virus (Figure 2*A*). Influenza A, human metapneumovirus and the coronaviruses HKU1 and OC43 were most frequently associated with symptoms (76%, 83%, 64%, and 61% of the episodes, respectively). Bocavirus and rhinovirus detection episodes were less often symptomatic (46% and 56%, respectively). Symptomatic bocavirus episodes were more common in children younger than 5 years and in adults 18–39 years (56%) than in older children and adults (14%) ($P < .001$). Rhinovirus episodes were more often symptomatic in children younger than 5 years (67%) than in all other age groups (51%) ($P = .003$).

The mean duration of all viral detection episodes was 1.7 weeks (range 1–12 weeks), with 646 episodes (83%) detected in ≤2 weeks and 137 (17%) in ≥3 weeks (Figure 2*B* and Supplementary Table 6). Viral detection episodes were longer in children younger than 5 years (mean 1.9 weeks) than in other age

**Table 2. Viral Detection Weeks by Age Group and Virus Type**

| Respiratory Virus | 0–4 y (N = 21) 710 wk (%) | 5–17 y (N = 39) 1597 wk (%) | 18–39 y (N = 26) 1004 wk (%) | 40–59 y (N = 22) 855 wk (%) | All Ages (N = 108) 4166 wk (%) |
|---|---|---|---|---|---|
| Any virus[a] | 358 (50) | 402 (25) | 210 (21) | 94 (11) | 1064 (26) |
| Adenovirus | 9 (1) | 3 (0.2) | 2 (0.2) | 0 (0) | 14 (0.3) |
| Bocavirus | 100 (14) | 27 (2) | 74 (7) | 9 (1) | 210 (5) |
| Coronavirus HKU1 | 4 (0.6) | 10 (0.6) | 6 (0.6) | 7 (0.8) | 27 (0.6) |
| Coronavirus NL63 | 0 (0) | 3 (0.2) | 0 (0) | 0 (0) | 3 (0.1) |
| Coronavirus OC43 | 21 (3) | 16 (1) | 12 (1) | 9 (1) | 58 (1) |
| Coronavirus 229E | 18 (3) | 22 (1) | 12 (1) | 12 (1) | 64 (2) |
| Enterovirus | 4 (0.6) | 1 (0.1) | 1 (0.1) | 0 (0) | 6 (0.1) |
| Human metapneumovirus | 8 (1) | 7 (0.4) | 3 (0.3) | 0 (0) | 18 (0.4) |
| Influenza A | 9 (1) | 23 (1) | 7 (1) | 4 (0.5) | 43 (1) |
| Influenza B | 3 (0.4) | 6 (0.4) | 0 (0) | 1 (0.1) | 10 (0.2) |
| Parainfluenza virus 1 | 2 (0.3) | 6 (0.4) | 0 (0) | 3 (0.4) | 11 (0.3) |
| Parainfluenza virus 2 | 0 (0) | 0 (0) | 1 (0.1) | 0 (0) | 1 (0.1) |
| Parainfluenza virus 3 | 3 (0.4) | 4 (0.3) | 1 (0.1) | 0 (0) | 8 (0.2) |
| Parainfluenza virus 4 | 3 (0.4) | 1 (0.1) | 0 (0) | 0 (0) | 4 (0.1) |
| Respiratory syncytial virus | 9 (1) | 11 (0.7) | 4 (0.4) | 2 (0.2) | 26 (0.6) |
| Rhinovirus | 240 (34) | 292 (18) | 112 (11) | 50 (6) | 694 (17) |

[a] More than 1 virus may have been detected during individual weeks.

groups (1.6–1.7 weeks) ($P = .005$). Of 137 episodes ≥3 weeks, most were due to rhinovirus or bocavirus (82%).

## DISCUSSION

These findings from a household-based surveillance study provide a detailed view of respiratory viruses. Participants experienced a mean of 5 respiratory illnesses per year and reported symptoms in 23% of weeks. A virus was detected in more than one quarter of weekly samples. Strikingly, children younger than 5 years had respiratory symptoms in 38% of weeks and a virus detected in 50% of weekly samples. The presence of children in the household was associated with an increased likelihood of viral detection. Rhinovirus was the most commonly detected virus and 93% of the cohort had rhinovirus detected at least once. Obtaining data weekly from symptomatic and asymptomatic individuals provides insights for determining the relevance of viruses detected from nasal samples in clinical settings. A significant proportion (55%) of weekly viral detections and viral detection episodes (44%) were asymptomatic. In 17% of episodes, a virus was detected for ≥3 weeks. These asymptomatic and prolonged detections may confound the interpretation of positive PCR tests for some respiratory viruses in clinical settings.

The Utah BIG-LoVE study extends findings from studies conducted in the 20th century and demonstrates significant differences. The overall rates of respiratory illness of approximately 5 pp/py and the pattern of decreasing rates with increasing age are similar to earlier studies [8]. However, our detection of viruses during approximately 60% of respiratory illnesses is higher than in previous studies. These differences are likely due to enhanced detection of viruses using highly multiplexed PCR. In the 1966 Virus Watch publication, no virus was detected in 86%–93% of illness episodes [12]. A more recent study of households by Monto et al used PCR and detected a virus in 47%–63% of acute respiratory illnesses [26]. Our rate of detection was higher, perhaps because the Monto study tested for fewer viruses than the BIG-LoVE study, and did not test for bocavirus, the second most frequently detected virus in our cohort [26]. The illness episodes in our cohort without a viral etiology may have been due to known or unknown viruses not detected by the FilmArray system, bacterial infections, or noninfectious causes.

Respiratory symptoms were present one quarter of the time. Children younger than 5 were most likely to have symptoms and were more likely to report fever or wheezing than older children or adults, similar to other longitudinal studies [8, 10, 26]. Despite the frequency of symptoms and viral detections, only 30% of participants sought medical care, <2% had contact with an emergency department, and none were hospitalized. Because most symptomatic viral episodes are managed at home, studies performed in hospital settings alone are likely

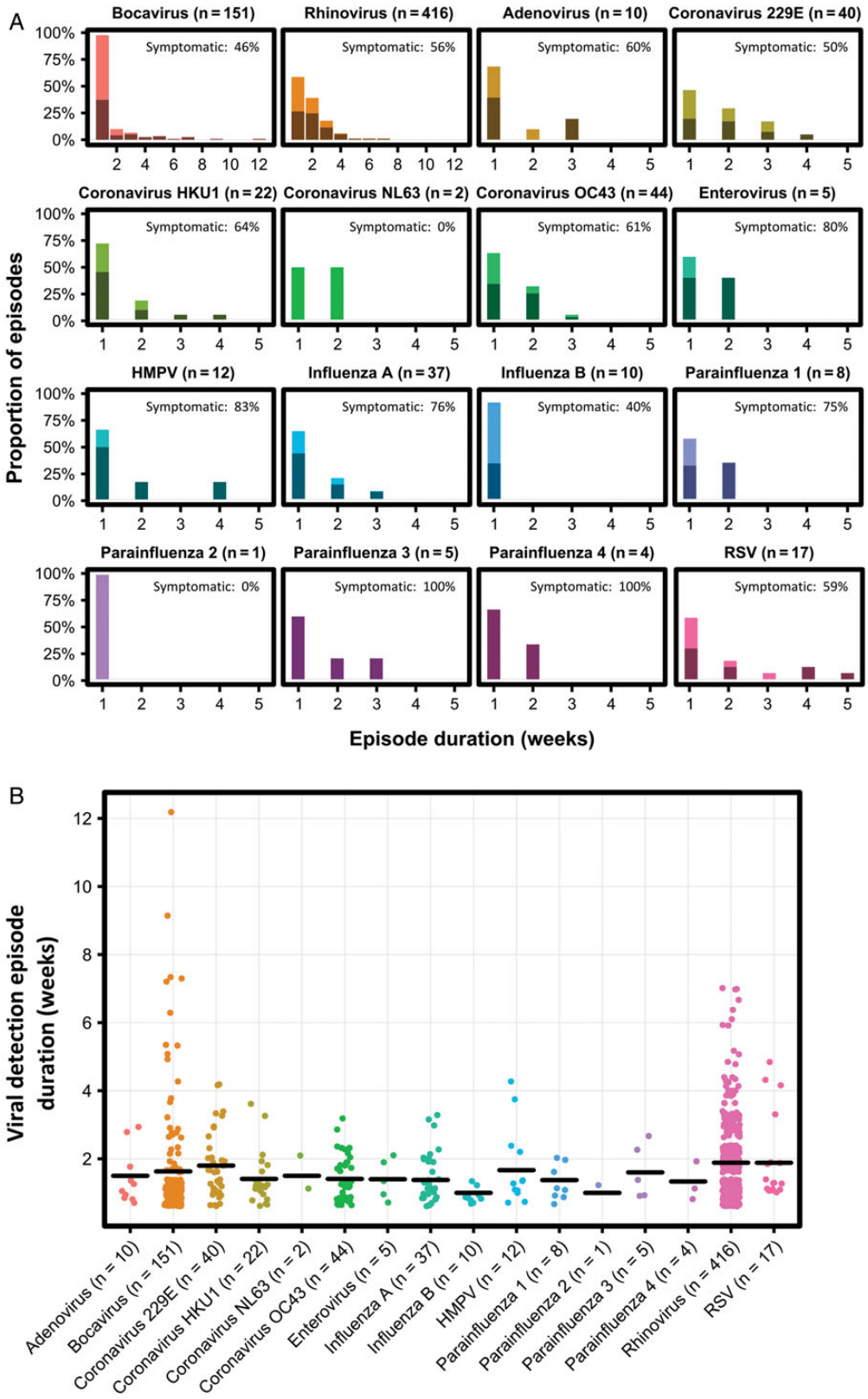


**Figure 2.** The distribution of viral detection episode lengths stratified by virus. *A*, Darker shading indicates symptomatic viral detection episodes and lighter shading indicates asymptomatic viral detection episodes. *B*, Filled circles represent individual viral detection episodes and the solid black lines depict the mean duration for each virus. Note: The horizontal axes for bocavirus and rhinovirus extend from 1 to 12 weeks, whereas for all other respiratory viruses the horizontal axes extend from 1 to 5 weeks. Abbreviations: HMPV, human metapneumovirus; RSV, respiratory syncytial virus.

to give biased views of the overall prevalence and impact of respiratory viral illness.

Viruses were detected in one quarter of weekly samples, regardless of symptoms. Children younger than 5 years had viruses detected in 50% of all weeks tested. Other studies have documented high rates of virus detection in young children with acute respiratory infection [27] and in asymptomatic children [17, 28–30]. Detection of a respiratory virus was more common in adults aged 18–39 than in older adults. This may be partially explained by the fact that many in this age group were parenting young children. Family size was also associated with illness frequency and viral detection, in accord with other studies [8, 26].

As in other longitudinal studies of households, rhinovirus was the most commonly detected virus in the BIG-LoVE households [5, 26]. Rhinovirus detection was ubiquitous, with every household and 93% of all participants positive for rhinovirus at least once during the year. Of the 416 rhinovirus detection episodes, 44% were asymptomatic. Rhinovirus detection was more likely to be asymptomatic with increasing age. Among children younger than 5 years, 67% of rhinovirus detections were associated with symptoms, which was higher than older children and adults (51%) but lower than the 86% recently reported by Peltola [31].

After rhinovirus, bocavirus and the coronaviruses OC43, 229E, and HKU1 were the most commonly detected viruses. Bocavirus is relatively newly described, and the clinical relevance of detection is incompletely understood [32]. Bocavirus has been detected in infants and children with and without respiratory symptoms [27, 33, 34]. In our cohort, bocavirus infections often were asymptomatic; however, this varied with age. Symptomatic bocavirus detections were much more commonly identified among children younger than 5 and adults 18–39 years. Bocavirus is not routinely sought in clinical care and is not reported in the FDA-cleared FilmArray RP panel. We detected coronaviruses, recognized causes of upper and lower respiratory illness including life-threatening infections [14, 15, 35], in all age groups. The majority (56%) of coronavirus episodes were symptomatic, suggesting that coronavirus infection may be an underrecognized cause of respiratory tract infection.

The detection of viruses from asymptomatic individuals may confound the interpretation of PCR-based diagnostic tests in the clinical setting [3, 29]. The BIG-LoVE cohort, with weekly sample collection regardless of symptoms is informative. Most episodes of virus detection were brief with a mean ≤2 weeks. However, the association with symptoms varied by age and virus. Detections of human metapneumovirus, influenza A, and the parainfluenza viruses were strongly associated with symptoms (>75% for all viruses). In the clinical setting, detection of these viruses is likely associated with the illness under evaluation. In contrast, approximately half of the episodes of bocavirus and rhinovirus were asymptomatic, and prolonged asymptomatic detection occurred in 14% and 22% of episodes, respectively. Others have reported prolonged detection of bocavirus of up to 28 days [34]. The mean duration of rhinovirus detection by PCR in 1 study was 10.1 and 11.4 days for immune competent adults and children respectively [17]. Another study demonstrated rhinovirus detection for >30 days in approximately 5% of children younger than one year [36]. Therefore, although bocavirus and rhinoviruses may cause both upper and lower respiratory infection, the association of a single positive test with clinical illness is uncertain, especially in young children or adults exposed to them in the home.

This study has several limitations. First the cohort was drawn from a single university community that may not be generalizable to different geographic or socioeconomic settings. Although additional data from other regions are needed to complement our findings, our results are similar to other longitudinal cohorts. Second, we used self-collected nasal swab specimens, which were stored at home for up to 3 days. This may have resulted in lower detection rates. In spite of this, we were able to detect a virus in 60% of respiratory symptom episodes, which is higher than in other longitudinal studies [8, 10, 26]. Third, in 28% of viral detection episodes, more than 1 virus was detected, limiting our ability to ascribe symptoms to individual viruses. An analysis of dual detection episodes is ongoing. Fourth, we have not completed sequencing of the rhinoviruses. It is possible that longer detection episodes may have included sequential infections with different rhinoviruses [31]. Finally, we did not collect serologic data, which limits our ability to associate viral detections with illness symptoms.

In spite of these limitations, we are able to draw several conclusions. Respiratory viruses are frequently detected in young children and in those who share their households. Viral detection is often asymptomatic and occasionally prolonged, especially for bocavirus and rhinovirus. Therefore, in clinical settings, the interpretation of positive PCR for some viruses, especially in young children and those who live with them may be confounded.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.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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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.

## References

1. World Health Organization. WHO methods and data sources for global causes of death 2000–2011: Technical Paper, **2013**.
2. Shieh WJ, Blau DM, Denison AM, et al. 2009 pandemic influenza A (H1N1): pathology and pathogenesis of 100 fatal cases in the United States. Am J Pathol **2010**; 177:166–75.
3. Jansen RR, Wieringa J, Koekkoek SM, et al. Frequent detection of respiratory viruses without symptoms: toward defining clinically relevant cutoff values. J Clin Microbiol **2011**; 49:2631–6.
4. Loeb M, Singh PK, Fox J, et al. Longitudinal study of influenza molecular viral shedding in Hutterite communities. J Infect Dis **2012**; 206:1078–84.
5. Monto AS. Viral respiratory infections in the community: epidemiology, agents, and interventions. Am J Med **1995**; 99:24S–7.
6. Singleton RJ, Bulkow LR, Miernyk K, et al. Viral respiratory infections in hospitalized and community control children in Alaska. J Med Virol **2010**; 82:1282–90.
7. Sydenstricker E. A study of illness in a general population group, Hagerstown morbidity studies No. 1: the method of study and general results. Public Health Rep **1926**; 41:2063–88.
8. Dingle J, Badger G, Jordan W. Illness in the home: a study of 25,000 illnesses in a group of Cleveland families. Cleveland, OH: The Press of Western Reserve University, **1964**.
9. Monto AS, Napier JA, Metzner HL. The Tecumseh study of respiratory illness. I. Plan of study and observations on syndromes of acute respiratory disease. Am J Epidemiol **1971**; 94:269–79.
10. Monto AS, Ullman BM. Acute respiratory illness in an American community: the Tecumseh study. JAMA **1974**; 227:164–9.
11. Fox J, Elveback L, Spigland I, Frothingham TE, Stevens D, Huger M. The virus watch program: a continuing surveillance of viral infections in metropolitan New York families I. Overall plan, methods of collecting and handling information and a summary report of specimens collected and illnesses observed. Am J Epidemiol **1966**; 83:389–412.
12. Elveback LR, Fox JP, Ketler A, Brandt CD, Wassermann FE, Hall CE. The Virus Watch program: a continuing surveillance of viral infections in metropolitan New York families. 3. Preliminary report on association of infections with disease. Am J Epidemiol **1966**; 83:436–54.
13. van den Hoogen BG, de Jong JC, Groen J, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. Nat Med **2001**; 7:719–24.
14. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med **2012**; 367:1814–20.
15. Poutanen SM, Low DE, Henry B, et al. Identification of severe acute respiratory syndrome in Canada. N Engl J Med **2003**; 348:1995–2005.
16. Update: influenza activity - United States, August 30, 2009–March 27, 2010, and composition of the 2010–11 influenza vaccine. MMWR Morb Mortal Wkly Rep **2010**; 59:423–30.
17. Peltola V, Waris M, Kainulainen L, Kero J, Ruuskanen O. Virus shedding after human rhinovirus infection in children, adults and patients with hypogammaglobulinaemia. Clin Microbiol Infect **2013**; 19:E322–7.
18. Abu-Diab A, Azzeh M, Ghneim R, et al. Comparison between pernasal flocked swabs and nasopharyngeal aspirates for detection of common respiratory viruses in samples from children. J Clin Microbiol **2008**; 46:2414–7.
19. Chan KH, Peiris JS, Lim W, Nicholls JM, Chiu SS. Comparison of nasopharyngeal flocked swabs and aspirates for rapid diagnosis of respiratory viruses in children. J Clin Virol **2008**; 42:65–9.
20. Walsh P, Overmyer CL, Pham K, et al. Comparison of respiratory virus detection rates for infants and toddlers by use of flocked swabs, saline aspirates, and saline aspirates mixed in universal transport medium for room temperature storage and shipping. J Clin Microbiol **2008**; 46:2374–6.
21. Blaschke AJ, Allison MA, Meyers L, et al. Non-invasive sample collection for respiratory virus testing by multiplex PCR. J Clin Virol **2011**; 52:210–4.
22. Lambert SB, Whiley DM, O'Neill NT, et al. Comparing nose-throat swabs and nasopharyngeal aspirates collected from children with symptoms for respiratory virus identification using real-time polymerase chain reaction. Pediatrics **2008**; 122:e615–20.
23. Poritz MA, Blaschke AJ, Byington CL, et al. FilmArray, an automated nested multiplex PCR system for multi-pathogen detection: development and application to respiratory tract infection. PloS One **2011**; 6:e26047.
24. Xu M, Qin X, Astion ML, et al. Implementation of FilmArray respiratory viral panel in a core laboratory improves testing turnaround time and patient care. Am J Clin Pathol **2013**; 139:118–23.
25. Utah Department of Health. 2009 Pandemic Influenza A (H1N1) (Swine Flu) Situation Report & Surveillance Report Archives. Available at: http://pandemicflu.utah.gov/archiveh1n1.htm. Accessed 8 March 2015.
26. Monto AS, Malosh RE, Petrie JG, Thompson MG, Ohmit SE. Frequency of acute respiratory illnesses and circulation of respiratory viruses in households with children over 3 surveillance seasons. J Infect Dis **2014**; 210:1792–9.
27. Martin ET, Fairchok MP, Stednick ZJ, Kuypers J, Englund JA. Epidemiology of multiple respiratory viruses in childcare attendees. J Infect Dis **2013**; 207:982–9.
28. Alper CM, Doyle WJ, Winther B, Hendley JO. Upper respiratory virus detection without parent-reported illness in children is virus-specific. J Clin Virol **2008**; 43:120–2.
29. Jartti T, Jartti L, Peltola V, Waris M, Ruuskanen O. Identification of respiratory viruses in asymptomatic subjects: asymptomatic respiratory viral infections. Pediatr Infect Dis J **2008**; 27:1103–7.
30. Winther B, Hayden FG, Hendley JO. Picornavirus infections in children diagnosed by RT-PCR during longitudinal surveillance with weekly sampling: association with symptomatic illness and effect of season. J Med Virol **2006**; 78:644–50.
31. Peltola V, Waris M, Osterback R, Susi P, Ruuskanen O, Hyypia T. Rhinovirus transmission within families with children: incidence of symptomatic and asymptomatic infections. J Infect Dis **2008**; 197:382–9.
32. Allander T, Tammi MT, Eriksson M, Bjerkner A, Tiveljung-Lindell A, Andersson B. Cloning of a human parvovirus by molecular screening of respiratory tract samples. Proc Natl Acad Sci U S A **2005**; 102:12891–6.
33. Arnold JC. Human bocavirus in children. Pediat Infect Dis J **2010**; 29:557–8.
34. Chonmaitree T, Alvarez-Fernandez P, Jennings K, et al. Symptomatic and asymptomatic respiratory viral infections in the first year of life: association with acute otitis media development. Clin Infect Dis **2015**; 60:1–9.
35. Lau SK, Woo PC, Yip CC, et al. Coronavirus HKU1 and other coronavirus infections in Hong Kong. J Clin Microbiol **2006**; 44:2063–71.
36. Loeffelholz MJ, Trujillo R, Pyles RB, et al. Duration of rhinovirus shedding in the upper respiratory tract in the first year of life. Pediatrics **2014**; 134:1144–50.