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Serial viral infections in infants with recurrent respiratory illnesses

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ABSTRACT: To better understand the viral aetiology of recurrent and prolonged illnesses, nasal secretions were prospectively collected from 285 infants at increased risk of developing asthma. Of these, 27 infants had recurrent (at least five) moderate-to-severe respiratory illnesses (MSIs). The viral aetiology of the 150 MSIs and 86 scheduled visits was analysed by molecular diagnostics. The demographic and clinical data were compared with infants who had 0–4 MSIs.

Frequently ill infants had higher exposure to other children and more wheezing illnesses than less symptomatic children. Viruses were detected in 136 (91%) out of 150 MSIs, 14 (67%) out of 21 mild illnesses and 29 (45%) out of 65 asymptomatic visits. Human rhinovirus was the most common aetiological agent (61, 43 and 35% in MSIs, mild illnesses and asymptomatic visits, respectively). Mixed viral infections were generally associated with more severe illnesses (27, 0 and 5%, respectively). Among the 27 frequently ill infants, only eight (5.3%) out of 150 MSIs were prolonged ($\geqslant$2 weeks duration). Considering all samples, detection of the same virus strain $\geqslant$2 weeks apart was unusual (5.3% of all 244 positive findings).

Human rhinovirus infections occur early, pervasively and repetitively in these high-risk infants. Infants with prolonged or recurrent respiratory illnesses most often have a series of infections rather than persistent infection with one virus strain.

KEYWORDS: Infant, respiratory virus, rhinovirus, virus persistence, virus strain, wheezing

Acute viral infections are a major cause of respiratory morbidity in young children [1]. Approximately 2–3% of all infants are admitted to hospital with bronchiolitis, usually during the seasonal epidemic [2]. Emerging evidence from animal studies indicates that viral infections may be an important environmental stimulus for airway injury and remodelling, resulting in impaired lung function and, potentially, asthma [3].

Recent advances in viral diagnostics have increased the viral detection rate to as high as 95% in infants suffering from respiratory symptoms [4, 5]. The availability of PCR techniques, particularly for human rhinoviruses (HRVs), is one of the main reasons for the improved virus detection rate. Although HRV is principally known as the ''common cold'' virus, it is also found in 41–45% of young wheezing children, second only to respiratory syncytial virus (RSV) [4, 6–9]. Interestingly, HRV-induced wheezing episodes in infancy have been identified as an important predictor of recurrent wheezing in four independent studies [10–13].

Limited data are available on the aetiology and persistence of viruses in children with recurrent respiratory symptoms. HRV appears to be the most prevalent virus detected in this patient group and accounts for 48% of all upper respiratory tract illnesses [1]. Although HRV infections can persist for >1 yr in immunosuppressed patients [14], whether the same HRV strain can persist in children with frequent or prolonged illnesses is unknown [1, 15–17].

In order to better understand the nature and risk factors for recurrent illnesses and wheezing in infancy, two newly developed molecular techniques were used to analyse the viral aetiology of illnesses in children who had family histories of allergic diseases or asthma and experienced frequent moderate-to-severe respiratory illnesses (MSIs) in the first year of life [18, 19]. Three questions were addressed as follows. 1) How do children who suffer from frequent respiratory infections during infancy differ from other children with similar family histories? 2) What is the viral aetiology of their respiratory illnesses during infancy? 3) A subset of infants have

For editorial comments see page 249.
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prolonged or seemingly continuous respiratory illnesses during the winter months: are these prolonged illnesses due to persistent infections or a series of different infections?

METHODS

Study subjects and study design

Originally, 289 subjects were enrolled in the Childhood Origins of ASThma (COAST) study at birth, and 285 were followed prospectively for 12 months. To be eligible for inclusion, each of the COAST children were required to have one or both parents with allergic sensitisation (one or more positive aeroallergen skin tests) and/or history of asthma, as well as having been $\geqslant$37 weeks gestation and otherwise healthy. Details of the study population and design have been described previously [20]. This study was approved by the University of Wisconsin Human Subjects Committee (Madison, WI, USA). Enrolment occurred during the pre-natal period and commenced only after obtaining informed consent from the parents.

During the first year of life, participating families were asked to contact the study centre each time the child had respiratory illnesses. If the illnesses were classified as moderate-to-severe, based on a predefined respiratory symptom score, arrangements were made with the family for study personnel to perform a nasal wash at home or in the clinic. In addition, a nasal wash was performed at each of five scheduled visits (at 2, 4, 6, 9 and 12 months) regardless of whether the child was sick or healthy. In total, 27 (9.3%) children had at least five MSIs during the first year of life, and were classified as children with ''frequent illnesses''. Collectively, the subjects had a total of 150 MSIs and 86 additional scheduled visits (65 visits with no symptoms and 21 visits with mild symptoms) with nasal washes during the first year of life from March 1999 to April 2001.

COAST participants with viral illnesses have been previously analysed for respiratory viruses, and these data have been compared to blood cell cytokine responses [21, 22] and the risk of recurrent wheeze [11]. Furthermore, molecular typing of samples from COAST participants has led to the identification of new HRV strains [19]. The aim of the current study is to identify the pattern and persistence of viral infections and HRV strains in 27 individual infants with frequent MSIs. The demographic and clinical differences between the infants with frequent MSIs and those with fewer respiratory symptoms were also investigated.

Definitions of illnesses and viral infections

An illness was considered moderate-to-severe if a clinical symptom score was $\geqslant$5, and mild if the score was 1–4 (table E1 in the online supplementary material). To be defined as a healthy child, the score had to be zero. The onset day of MSI was considered to be the first day with a score $\geqslant$5. Illness was considered as prolonged if moderate-to-severe symptoms persisted for $\geqslant$2 weeks with the score remaining at $\geqslant$5. Consequently, a new patient evaluation and nasal wash sample was taken every 2 weeks in these prolonged illnesses. The last day of MSI was the final day with a score of $\geqslant$5. If such information was not available, the final day was estimated as occurring halfway between the last day of confirmed MSI and the next follow-up visit day (within 2 weeks) when the child no longer had MSIs. Viral infections were considered persistent or recurrent if they reoccurred $\geqslant$2 weeks apart.

Total immunoglobulin E and allergy tests

Total and allergen-specific immunoglobulin (Ig)E for *Dermatophagoides pteronyssinus, D. farinae, Alternaria alternata*, cat, dog, milk, egg, soy bean and peanut were analysed in all 27 subjects by UniCAP 100^{E} (Pharmacia and Upjohn Diagnostics, Uppsala, Sweden) as described previously [23]. The sensitivity for detection of total IgE was 2 $kU \cdot L^{-1}$. Allergen-specific IgE values $\geqslant$0.35 $kU \cdot L^{-1}$ were considered positive.

Clinical definitions

Sensitisation was defined by a positive allergen-specific IgE test result at 12 months of age. Atopic dermatitis at age 12 months was defined either as a parental report of physician-diagnosed atopic dermatitis during the first year of life or a physician report of atopic dermatitis at physical examination performed at 12 months of age. Wheezing was determined for each illness or outpatient visit by a report from the caregiver or by physical examination, as recorded in the medical record [11].

Microbiology

Diagnostic virology was performed for all nasal samples in the first year of life, whether a child had symptoms or not. Results and methods for viral culture, immunofluorescent antibody staining for RSV and nested PCR for the first year were previously described [11]. Samples of the 27 children with frequent respiratory illnesses were reanalysed with a new multiplex PCR-based assay (Multicode PLx Respiratory Virus Panel; EraGen Biosciences, Madison, WI, USA), which detects the following viruses: HRV, enterovirus (EV), adenovirus (AdV; B, C and E), influenza (A, B), parainfluenza virus (PIV; 1, 2, 3, 4a and 4b), coronavirus (CoV; severe acute respiratory syndrome, OC43, 229E and NL63), RSV (A and B) and human metapneumovirus (hMPV) [18]. Molecular typing of HRV was performed as described previously [19]. For further information, please refer to the online supplementary material. Bacterial aetiology was not studied.

Statistical analysis

No statistical power calculations were performed. The predefined cut-off of more than five MSIs was chosen because it represented the top ~10% of infants with recurrent illnesses. Normality of data distribution was tested using the Kolmogorov–Smirnov test. Skewed data were analysed with Kruskal–Wallis ANOVA. Otherwise, one-way ANOVA or linear regression analysis was used. Dichotomous data were analysed by the Chi-squared test or Fisher's Exact Test (for counts less than five). A nominal p-value of 0.05 was regarded as statistically significant.

RESULTS

Study subjects

A total of 285 children completed the first year of follow-up. Of these, 27 had at least five MSIs, 204 had one to four MSIs and 54 did not have any MSIs during the first year of life (median (interquartile range) 2 (1–3); table 1). Exposure to other children was clearly associated with frequent MSIs. All the children with at least five MSIs either had older siblings or were in day care, compared with 82% of children with one to four MSIs ($p=0.018$)

and 63% of children without MSIs (p=0.0003). The infants with at least five MSIs also differed from the rest of the cohort by having more wheezing illnesses: 85% had wheezed at least once during infancy *versus* 32% in children with one to four MSIs and 2% in the children without MSIs (p<0.0001 for both comparisons). They also had more systemic corticosteroid courses (p<0.0001), antibiotic treatments (p<0.0001) and asymptomatic viral infections (p=0.0058). Children with at least five MSIs were also more likely to have a maternal history of asthma compared with other children (p=0.083). Other demographics and atopic characteristics were comparable.

Of the 150 MSIs in the 27 frequently ill infants, symptoms included cough (9% mild, 29% moderate and 61% severe), rhinorrhea (28% mild and 69% moderate to severe), duration of illness >4 days (59%), wheezing (45%), hoarseness (32%), dyspnoea (10%), retractions (8%), fever (5%) and apnoea (1%). Of the 21 mild illnesses in the same children, symptoms included rhinorrhea (53% mild and 32% moderate to severe), cough (26% mild, 16% moderate and 5% severe), duration of illness >4 days (26%) and fever (11%).

Viral aetiology of MSI and scheduled visits

In the 27 frequently ill infants, a total of 150 MSIs, 21 mild illnesses and 65 healthy visits with nasal wash were recorded during the first year of life (fig. 1). Viral detection rate increased with the severity of illness: 29 (45%) out of 65 in asymptomatic infants, 14 (67%) out of 21 in infants with mild illness and 136 (91%) out of 150 in infants with MSI (p=0.0001 overall; fig. 2). HRV detection rate (including mixed infections) increased with the severity of illness: 23 (35%) out of 65, nine (43%) out of 21 and 91 (61%) out of 150 (p=0.0020 overall) in asymptomatic infants, mild illness and MSI, respectively. Multiple viruses were most often found in infants with MSI (n=39, 27%) and rarely in other infants (asymptomatic: n=3, 5%; mildly symptomatic: n=0, 0%; p=0.0001). Out of the 39 cases with MSI and mixed viral infection, 86 viruses were detected, the most frequent was HRV (n=30), followed by: RSV (n=13); AdV (n=13); PIV (n=8); influenza (n=6); hMPV (n=6); CoV (n=5); and EV (n=5). Only two double HRV infections (two different strains) were found. When viruses were detected in asymptomatic children, an MSI associated with the same viral agent occurred within 2 weeks in four (14%) out of 29 cases.

Viral aetiology of wheezing in frequently ill infants

Of the 27 children with at least five MSIs during infancy, 23 (85%) wheezed with viral infection (table E2 in the online supplementary material). Out of these, 18 (78%) wheezed at

TABLE 1 Patient characteristics

Factor	⩾5 MSIs	1–4 MSIs	0 MSIs	Overall p-value
Subjects	27	207	54	
MSIs during infancy[#]	5 (5–6)	2 (1–3)	0 (0–0)	
Month/yr of birth	Feb 1999 to Apr 2000	Nov 1998 to Apr 2000	Nov 1998 to Mar 2000	
Birth weight kg	3.5±0.6	3.5±0.5	3.6±0.6	0.23
Male	18 (67)	116 (57)	27 (50)	0.35
Wheezed during infancy	23 (85)	65 (32)	1 (2)	<0.0001[+]
Wheezing episodes	3 (1–4)	0 (0–1)	0 (0–0)	<0.0001[+]
⩾1 hospitalisation for wheezing	2/27 (7)	5/204 (2)	0/54 (0)	0.15
⩾1 systemic corticosteroid course	10/27 (37)	18/202 (9)	0/53 (0)	<0.0001[§]
⩾1 antibiotic treatment	26/27 (96)	138/204 (68)	17/54 (31)	<0.0001[f]
Atopic dermatitis during infancy	11 (41)	89 (44)	22 (41)	0.91
Sensitisation at year 1	9 (33)	56/198 (28)	13/53 (25)	0.70
Food	9 (33)	48/198 (24)	10/53 (19)	0.36
Aeroallergen	5 (19)	24/198 (12)	6/53 (11)	0.61
Total IgE at year 1 kU·L^{-1}	17.6 (7.0–31.8)	13.6 (5.2–32.4)	15.5 (5.6–26.8)	0.82
Blood eosinophil count[¶] at year 1 ×10^{9}·L^{-1}	2.0 (1.0–3.5)	2.0 (1.0–4.0)	2.0 (1.0–4.0)	0.95
Breast feeding	9 (33)	64 (31)	18 (33)	0.95
Older sibling or day care	27 (100)	168 (82)	34 (63)	0.0002[##]
Asymptomatic infection per visit	28/60 (47)	20/90 (22)	12/43 (28)	0.0058[¶¶]
Mixed viral infection per illness or asymptomatic visit	36/150 (24)	45/414 (11)	3/187 (2)	<0.0001[++]
Smoke exposure	7 (26)	54 (26)	10 (19)	0.48
Cat at home	9 (33)	62 (30)	13 (24)	0.60
Dog at home	9 (33)	69 (34)	23 (43)	0.47

Data are presented as median (interquartile range), n (%), mean±SD or n positive/N all studied (%), unless otherwise stated. Data analysed using one-way ANOVA, Kruskal-Wallis ANOVA or Chi-squared test. MSI: moderate-to-severe illness; Ig: immunoglobulin. [#]: defined as respiratory symptom score ⩾5; [¶]: 16 infants with ⩾5 MSI, 155 infants with 1–4 MSI, 32 infants without MSI; [+]: ⩾5 *versus* 1–4 MSIs and ⩾5 *versus* 0 MSIs, p<0.0001 for both; [§]: ⩾5 *versus* 1–4 MSIs (p=0.0003), ⩾5 *versus* 0 MSIs (p<0.0001), 0 *versus* 0–4 MSIs (p=0.029); [f]: ⩾5 *versus* 1–4 MSIs (p=0.0012), ⩾5 *versus* 0 MSIs (p<0.0001), 0 *versus* 0–4 MSIs (p<0.0001); [##]: ⩾5 *versus* 1–4 MSIs (p=0.018), ⩾5 *versus* 0 MSIs (p=0.0003); [¶¶]: ⩾5 *versus* 1–4 MSIs (p=0.0030), ⩾5 *versus* 0–4 MSIs (p=0.0030), there were 193 asymptomatic scheduled visits where multiplex PCR-based assay had been carried out; [++]: ⩾5 *versus* 1–4 MSIs (p=0.0001), ⩾5 *versus* 0 MSIs (p<0.0001), 0 *versus* 1–4 MSIs (p=0.0002).

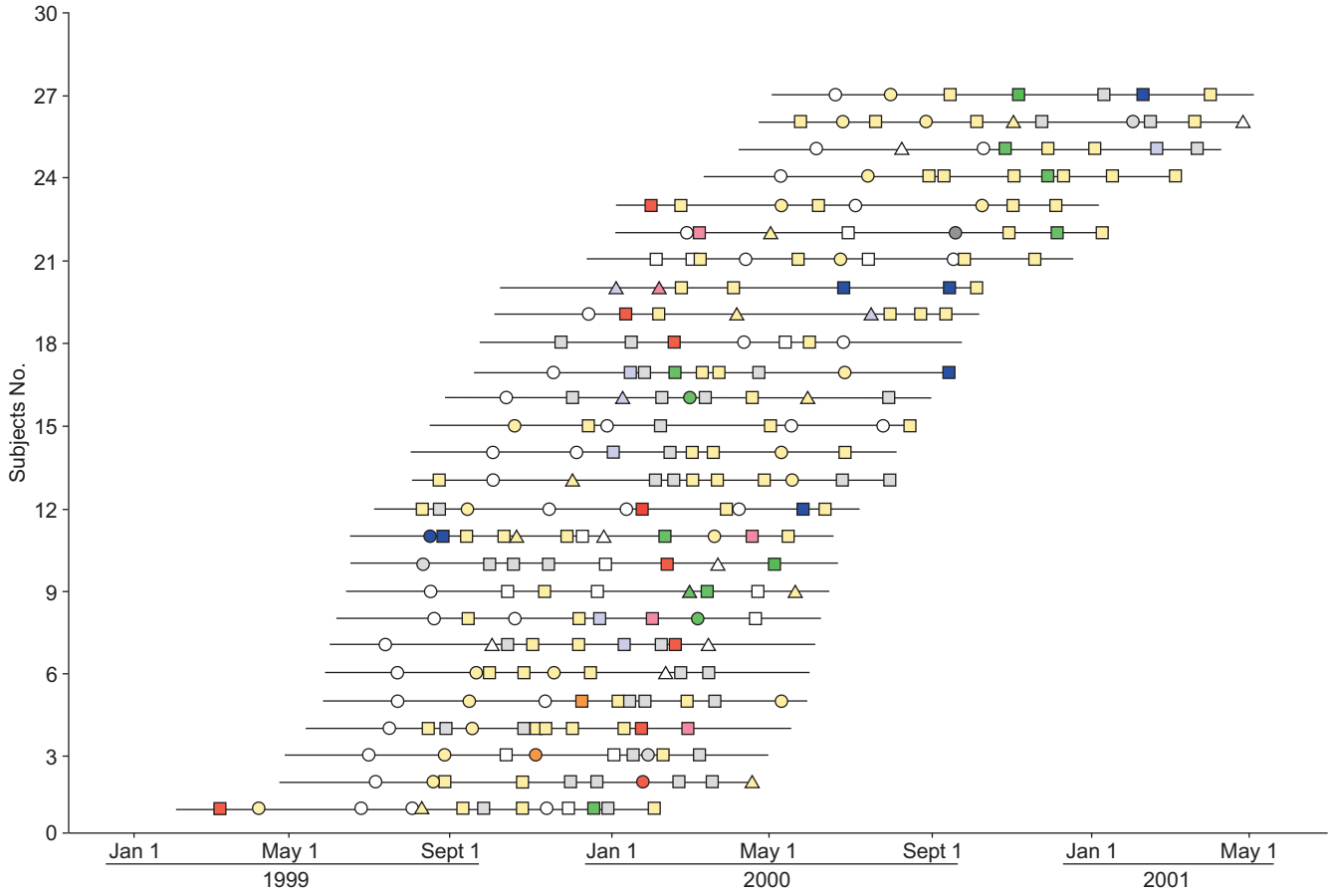

FIGURE 1. Temporal occurrence of viral infections in 27 infants with recurrent moderate-to-severe respiratory illnesses (MSIs) during infancy according to severity of the symptoms. Subjects 1, 5, 7, 9, 10, 15 and 17 also had one MSI each without nasal wash (data not shown). ○: no illness; □: moderate-to-severe illness severity; △: mild illness severity. The viruses detected are as follows: rhinovirus (yellow), respiratory syncytial virus (red), parainfluenza virus (dark blue), coronavirus (green), influenza (pale blue), enterovirus (dark grey), adenovirus (orange), metapneumovirus (dark pink), mixed viruses (light grey) and no virus (white).

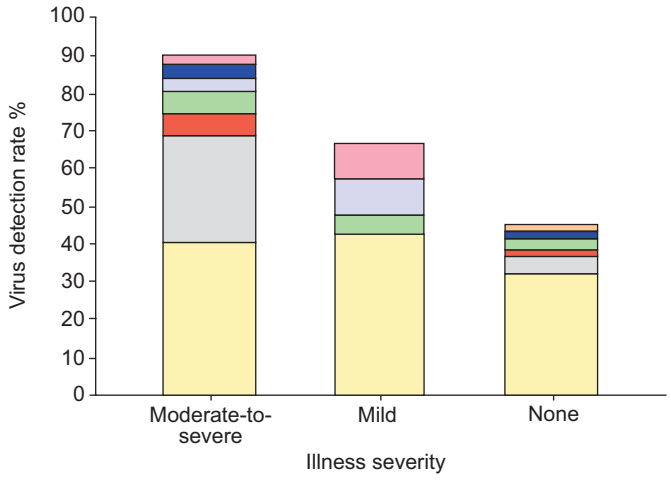

FIGURE 2. Viral findings in 27 infants with recurrent moderate-to-severe respiratory illnesses (MSIs) during infancy according to the severity of symptoms at each visit. Only one subject in the MSIs group had enterovirus. The viruses detected were as follows: human rhinovirus (yellow), mixed virus (grey), respiratory syncytial virus (red), coronavirus (green), influenza (pale blue), parainfluenza virus (dark blue), metapneumovirus (pink), and adenovirus (orange).

least once with HRV, followed by RSV (n=16, 70%) and other viruses. A total of 73 wheezing episodes were recorded in the 27 infants (mean±SD 3.2±1.9 wheezing episodes per child). Of the 68 wheezing episodes with a corresponding nasal wash, virus was detected in 60 (88%) specimens. HRV was the most prevalent agent whether including (n=32, 47%) or excluding (n=17, 25%) multiple viral infections, followed by RSV (total; n=16, 24%; sole agent: n=7, 10%).

Viral findings in prolonged illnesses

The duration of a single MSI was usually <2 weeks (142 (95%) out of 150). Only eight (5.3%) MSIs lasted ⩾2 weeks and were considered prolonged (fig. 3). Only one prolonged MSI was linked to the same viral finding in the consecutive samples taken ⩾2 weeks apart (HRV-12 at both visits 14 days apart, and AdV C only at the second visit).

Recurrent infections

The frequency of recurrent infections was then analysed, defined as the same viral strain occurring in separate clinical illnesses or healthy visits ⩾2 weeks apart in the same infants. Considering all 244 positive viral findings in the 27 frequently ill infants, 13 (5%) viral findings met these criteria and can be

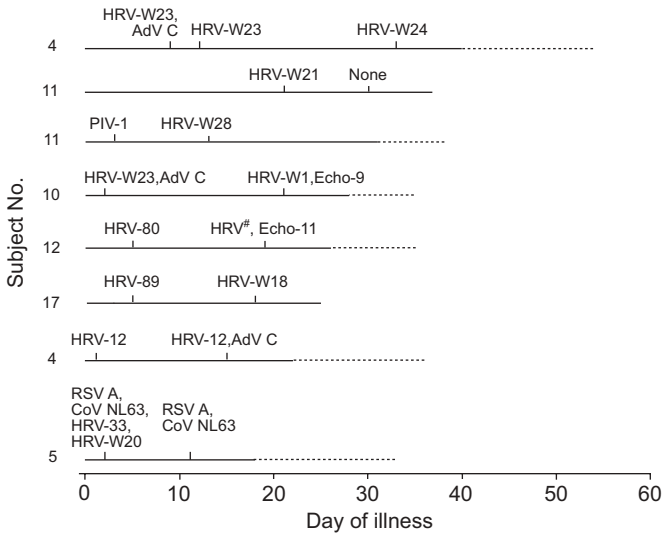

FIGURE 3. Viral findings in several subjects of moderate-to-severe illnesses lasting ⩾2 weeks. Subjects 4 and 11 suffered from moderate-to-severe illness lasting ⩾2 weeks twice. ——: moderate-to-severe symptoms; ·····: the total duration of symptoms. HRV: human rhinovirus; AdV: adenovirus; PIV: parainfluenza virus; Echo: echovirus; RSV: respiratory syncytial virus; CoV: coronavirus. #: no sample was available for molecular typing.

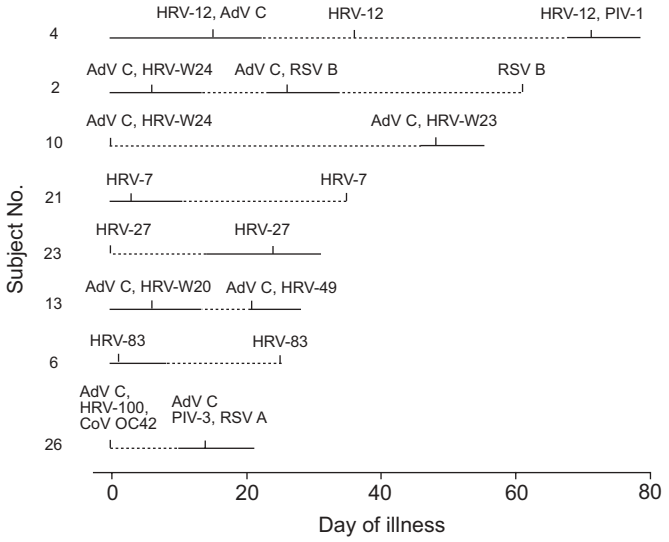

FIGURE 4. Identical viral findings in consecutive nasal wash samples ⩾2 weeks apart relative to illness from several subjects. ——: symptomatic periods; ·····: asymptomatic periods. HRV: human rhinovirus; AdV: adenovirus; PIV: parainfluenza virus; RSV: respiratory syncytial virus; CoV: coronavirus.

considered as recurrent infections with the same or similar viral agents (AdV: n=6; HRV: n=4; RSV: n=1; hMPV: n=1). In total, 12 viruses reoccurred once and one virus reoccurred twice. Consecutive recurrent viral findings are shown in figure 4. Nonconsecutive similar viral findings reoccurred within 83–116 days. Combinations of viruses were common: multiple viruses were detected in over half of the samples associated with persistent or recurrent viral findings.

Comparisons between HRV and other viral infections

HRV infections tended to: occur earliest (mean age at first HRV infection was 4 months compared with ⩾6 months for other viruses); were most frequent (mean 3.6 episodes compared with <1.0 episodes for other viruses); and had similar severity compared with other infections. The first HRV infections occurred before the first RSV infections in 73% of cases (19 out of 26, excluding one case with simultaneous HRV and RSV infection). HRV and RSV infections had comparable severity (mean±SEM symptom score, HRV 8.0±0.3 *versus* RSV 9.1±1.0; mean difference -1.0 (95% confidence interval -2.9–0.7); p=0.23; n=102); after adjusting for or excluding mixed viral infections, the difference remained nonsignificant (p=0.30 or p=0.71, respectively).

DISCUSSION

Understanding the epidemiology and natural history of prolonged and recurrent respiratory viral infections has been hampered by shortcomings associated with traditional viral diagnostics. The present prospective study used molecular viral diagnostics to analyse the aetiology of frequent respiratory infections in a group of infants at increased risk of developing allergies and asthma. The findings demonstrated that HRV was most often associated with MSIs and wheezing during infancy, lending further support to the close association between HRV infections and respiratory morbidity in this age group. In addition, prolonged MSIs occurred infrequently, even in this selected population, and were rarely due to persistent viral infection with the same pathogen. Instead, infants with frequent MSIs typically had a series of infections with different viruses or virus strains.

HRV infections have increasingly been associated with wheezing in infants during the last 10 yrs [4, 6–7, 10, 11, 13]. The HRV detection rates have reached as high as 41–45% of young wheezing children [6, 9]. In the present study of infants with frequent illnesses, 78% of the wheezing infants wheezed at least once with HRV, and this is comparable to the 70% wheezing rate associated with RSV. In addition, HRV was associated with illnesses of comparable severity to other viruses, such as RSV. Finally, molecular analysis revealed that simultaneous infections with more than one HRV strain were rare. When considered collectively with other recent reports [10–13], the current data suggest that the clinical impact of early HRV infections can be similar to that of early RSV infections and forms an important basis for further research.

HRV belong to the Picornaviridae family and, to date, >100 HRV serotypes have been identified by traditional viral culture and serology techniques [24]. In the present study, HRVs were typed by a sensitive molecular assay based on phylogenetic comparisons of their 260-bp variable sequences in the 5′-noncoding regions with homologous sequences of the 101 known serotypes. This molecular typing assay directly identified HRV from the original clinical specimens, and data from this population, in which several new strains that evaded traditional serotyping assays were identified, has been previously reported [19].

Previous studies have suggested that HRV might cause persistent infections, although definitive conclusions were impossible because HRV strains were not identified [15–17].

Despite the high prevalence of HRV positive samples, only one of the prolonged MSIs (fig. 3) and four additional cases of persistent or recurrent infection (fig. 4) were associated with the same HRV in the current study; infections lasting >2 weeks were unusual. Whether prolonged shedding is an indication of immunological anomaly and linked to poorer long-term prognosis remains to be determined. In a previous study of asthmatic and normal adult volunteers, viral shedding was still detectable in 54% of adult subjects 14 days after experimental inoculation with HRV-16 [25]. However, the quantity of virus was quite low at this point, and cold symptoms were generally either gone or resolving. Although the present study design is not optimal for determining the exact duration of illness, sampling during regularly scheduled visits, even when symptoms were absent, reduced the possibility of missing persistent infections. The virus most likely to be persistent in the current study subjects was AdV, which was detected for >2 weeks in six (75%) out of eight cases. However, this DNA virus can be latent and intermittent detection by PCR does not necessarily mean re-infection [26]. With the possible exception of AdV, the present study conclusively demonstrates that recurrent or prolonged illnesses in infants tend to be caused by serial infections rather than prolonged infections with one organism.

Viruses were also detected more often in frequently ill infants when they were asymptomatic (table 1). Nearly half (45%) of the scheduled visits in which no respiratory symptoms were found were associated with positive viral finding. At these healthy visits, HRV was again the most frequently detected virus (35 *versus* ⩽5% for other viruses), which is in agreement with previous reports of 10–41% HRV detection rates in asymptomatic children, with higher rates generally associated with younger age [6, 15, 27]. Interestingly, the frequently ill infants were all exposed to other children at home or day care.

Considering the tremendous sensitivity of PCR-based assays, what does it mean to detect a respiratory virus in an asymptomatic child? Viruses detected in asymptomatic children may represent a low-level infection without associated symptoms, although it is difficult to prove that a young child is totally asymptomatic. In addition, evidence that this may also represent the first sign of a developing clinical illness [15] was found, as 14% of these were linked to MSI associated with the same viral agent within the following 2 weeks. The low proportion of persistent or recurrent viral infections, however, argues against the suggestion that viruses detected by PCR are likely to be residual nucleic acids left over from distant infections. Instead, the current findings suggest that PCR is likely to detect true infections, whether symptoms are present or not. Furthermore, infants with high exposure to other children appear to have more asymptomatic viral infections.

In agreement with a previous study [7], mixed viral infections were linked to more severe respiratory symptoms. Persistent or recurrent infections were also associated with a high prevalence of mixed viral infections. HRV was the virus most often associated with mixed viral infections, as previously reported [5, 7, 8]. Whether mixed infections or higher frequency of asymptomatic infections are primarily due to increased exposure or host factors, such as weak interferon responses, deserves further study. More data is available on HRV infections, and recent studies in humans have linked susceptibility to HRV infections to suboptimal immunological responses of blood or airway cells [10–13, 21, 22, 28–30]. Interestingly, HRV-associated risk for recurrent wheezing remained unchanged after adjusting for exposure to other children and other relevant factors in the COAST study and in an Australian cohort [11, 13].

The present study has some limitations. The study cohort included only infants at high risk for allergies and asthma. Since these children may have increased susceptibility for lower respiratory HRV infections [6], additional studies are needed to determine whether there are any differences in outcomes of a generalised population. Only MSIs and not mild colds were systemically studied. Finally, although the diagnostic virology had a high yield during times of illness, several new viruses have recently been discovered (*e.g.* human bocavirus, CoV HKU1 and respiratory polyomaviruses) and may account for some of the unexplained illnesses.

In conclusion, the current study demonstrates that frequently ill infants at increased risk for chronic allergic diseases and asthma most often have a series of infections with different virus strains rather than persistent infection with one virus. Interestingly, human rhinovirus infections were clearly most often associated with moderate-to-severe respiratory illnesses and wheezing. Thus, the study provides additional evidence that human rhinovirus can produce more than the common cold in high-risk infants and these infections occur early, pervasively and repetitively with different strains.

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