Rhinovirus Infections in Children: A Retrospective and Prospective Hospital-Based Study

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To analyze clinical characteristics and prevalence of rhinovirus infections in children in the hospital, we reviewed a retrospective dataset from a 20-year period, and conducted a short-term prospective study. Records of children and adolescents treated at our hospital during 1987–2006 with a documented rhinovirus infection were reviewed and compared with patients with other respiratory virus infections. Prospective study included all children ≥1 month of age admitted to pediatric infectious disease ward during an autumn period. Rhinoviruses were detected by reverse transcription-PCR and/or culture, and sequence analysis was used for virus typing. In the retrospective study, the median age of 580 children with rhinovirus infection was 1.9 years (interquartile range, 1.0–4.3 years), and 27% had an underlying medical condition. Eighty-four children (16% of in-patients) were treated at pediatric intensive care unit. Twenty-one children (4%) had a hospital-acquired rhinovirus infection. In the prospective study, rhinoviruses were detected in 28% of 163 hospital episodes. Acute wheezing illness was diagnosed in 61% of children with rhinovirus and in 31% of children with respiratory syncytial virus, enterovirus, or no study virus ($P < 0.001$). One-half of sequence-analyzed rhinovirus strains belonged to the newly identified C group. In conclusion, rhinovirus infections are a frequent cause of pediatric hospitalizations, and they are common also at the intensive care unit. Acute wheezing is the most frequent manifestation in hospital setting, but the range of clinical presentations is wide. Group C rhinoviruses may account for a large part of rhinovirus hospitalizations. *J. Med. Virol. 81:1831–1838, 2009.* © 2009 Wiley-Liss, Inc.

KEY WORDS: rhinovirus; respiratory virus; respiratory tract infection; wheezing illness; pneumonia

INTRODUCTION

Rhinoviruses are the most common cause of respiratory infections in the community [Monto et al., 1987; Vesa et al., 2001], but their effect on hospitalization of children has not been fully established. In recent studies, rhinoviruses have been found as or more frequently as respiratory syncytial virus (RSV) in children hospitalized with wheezing illnesses (bronchiolitis, wheezy bronchitis, or asthma) [Rawlinson et al., 2003; Jartti et al., 2004; Lemanske et al., 2005; Jacques et al., 2006; Kusel et al., 2006]. Rhinoviruses have been common also in studies of children hospitalized with pneumonia, other acute respiratory infections, or febrile diseases [Juvén et al., 2000; Tsolia et al., 2004; Miller et al., 2007; Lahti et al., 2009]. However, their role as primary pathogens, co-pathogens with other microbes, or as innocent bystanders is not always clear.

Specific diagnosis of rhinovirus infections is not routinely obtained in hospitals. Conventional virus culture is labor-intensive, it has poor sensitivity for rhinoviruses, and results are not rapidly available. A major improvement has been the development of reverse transcription (RT)-PCR, that enables rapid and sensitive detection of rhinoviruses from respiratory specimens [Hyypiä et al., 1998]. Although vaccines or antiviral drugs against rhinoviruses are currently not available, specific diagnosis of rhinovirus infection may be helpful for estimation of prognosis, choosing adequate supportive care, and in prevention of hospital infections. Regarding prognosis, rhinovirus-induced wheezing in early childhood is a major risk factor for subsequent

recurrent wheezing or persistent asthma [Kotaniemi-Syrjänen et al., 2003; Lemanske et al., 2005; Lehtinen et al., 2007; Jackson et al., 2008].

To characterize rhinovirus infections in children in the hospital, we reviewed clinical findings of 580 children with rhinovirus infections during 1987–2006, and compared them to those of 3,697 children infected with other respiratory viruses. In addition, we performed a prospective study of rhinoviruses, enteroviruses, and RSV in all children ≥1 month of age admitted to pediatric infectious disease ward during a 61-day period in autumn. We compared clinical characteristics of rhinovirus-positive children with those of other study children.

METHODS

Patients

Retrospective study population. Rhinovirus infections were analyzed in children and adolescents treated at the Department of Pediatrics, Turku University Hospital (Turku, Finland), during the 20-year period 1987–2006. This is the only tertiary care hospital in southwestern Finland and serves a population of 690,000, including 120,000 individuals <16 years of age (2006 census data). Most children are referred to the hospital by primary care givers. Children who had rhinovirus, detected by viral culture or RT-PCR, were identified from the files of the Department of Virology, University of Turku. The medical records of these children were reviewed to collect demographic, clinical, and laboratory data. Rhinovirus infection was defined as hospital-acquired if virus was detected 7 or more days after admittance and no respiratory symptoms were documented at admittance. Multiple hospitalizations were regarded as independent in the analysis.

We compared the demographic and clinical data from rhinovirus infections with corresponding data from other respiratory virus infections confirmed by antigen test at the Department of Pediatrics, Turku University Hospital during 1980–1999. Influenza A and B virus infections in this population have been published previously [Peltola et al., 2003], whereas data of RSV, adenovirus, and parainfluenza virus types 1, 2, and 3 infections are previously unpublished.

Prospective study population. A prospective study was conducted in children ≥1 month of age, admitted for any reason to pediatric infectious disease ward in the Turku University Hospital during a 61-day period in September–November 2005, when rhinovirus prevalence in the community was high. Data from the prospective study were not included in the retrospective dataset. Presence and duration of respiratory symptoms (rhinorrhea, nasal congestion, cough, sore throat) and fever were collected on a questionnaire. Hospital course, discharge diagnoses, and laboratory data were obtained from the medical records. Acute wheezing illnesses were diagnosed as bronchiolitis in children <1 year of age and wheezy bronchitis at ≥1 year of age, and asthma was

diagnosed based on recurrent wheezing (≥3 attacks). Multiple hospitalizations were regarded as independent in the analysis. Parents of participating children gave their written informed consent. The study protocol was approved by the Ethics Committee of the Hospital District of the South-Western Finland.

Virologic Analysis

Nearly all samples in the retrospective study were taken from the upper respiratory tract (97%), in the majority of cases by nasopharyngeal aspiration. All samples in the prospective study were nasal swab specimens.

Rhinoviruses were detected by culture and/or RT-PCR. Use of rhinovirus RT-PCR increased and that of virus culture decreased during the study period of 1987–2006. HeLa Ohio-Salisbury and human foreskin fibroblast cells were used for virus culture at 33°C as described by Hyypiä et al. [1998]. RT-PCR was performed with conserved picornavirus primers allowing differentiation of human rhinovirus amplicons by size or using hybridization probes [Halonen et al., 1995; Hyypiä et al., 1998; Lönnrot et al., 1999].

In the prospective study, the specimens were analyzed using a multiplex real-time RT-PCR for rhinoviruses, enteroviruses, and RSV [Peltola et al., 2008]. Rhinovirus RT-PCR amplification was carried out with conserved picornavirus primers amplifying a 120 bp fragment from the 5′ noncoding region of the genome [Lönnrot et al., 1999]. Positive amplicons were identified as rhinoviruses, enteroviruses, or RSV based on the melting temperatures. Dilutions of human rhinovirus type 16 RNA from purified virions with a spectrophotometrically determined copy number were used as a standard in quantitative RT-PCR.

Rhinovirus isolates were further differentiated by sequence analysis of 397 bp long amplicons from the 5′ noncoding region [Peltola et al., 2008]. Sequences were considered to represent the same genotype if there was a >98% homology. They were typed to A, B, and C groups according to the nearest strain (≥90% homology) in Genbank by BLAST.

Influenza A and B viruses, parainfluenza virus types 1–3, adenoviruses, and RSV were detected by indirect immunofluorescence in 1980–1981, by indirect enzyme immunoassay in 1982–1986, and by time-resolved fluoroimmunoassay from 1987 through 1999 [Hierholzer et al., 1987; Arstila and Halonen, 1988; Waris et al., 1988; Nikkari et al., 1989].

Statistical Analysis

Children with rhinovirus infection were compared with other study children using the Mann–Whitney test for continuous data and χ^2 test for categorical data. One-way ANOVA followed by Bonferroni test was used to compare ages of children with different virus infections in the retrospective study. The association of age with rhinovirus copy numbers in nasal swab samples was analyzed using Spearman's rho. $P < 0.05$ was considered

to be significant. Statistical analyses were done using SPSS for Windows, version 14.0 (SPSS).

RESULTS

Retrospective Study

Virology. Rhinoviruses were detected in 580 children by virus culture (215 children, 37%) and/or RT-PCR (421 children, 73%). Another virus was identified in 55 children (9%); most commonly RSV (n = 19), adenovirus (n = 10), parainfluenza virus type 1 (n = 5), or rotavirus (n = 5). Three viruses were simultaneously present in samples from three children.

Demographic and clinical characteristics. The median age of rhinovirus-positive children was 1.9 years with interquartile range (IQR) of 1.0–4.3 years (Table I). The median age and IQR of children with other respiratory viruses from 1980 to 1999 were as follows: RSV, 0.6 (0.3–1.5) years ($P < 0.001$, compared with rhinovirus); adenovirus, 1.8 (1.0–4.5) years ($P = 1.000$); parainfluenza virus type 1, 1.5 (0.9–3.4) years ($P = 0.408$); parainfluenza virus type 2, 1.4 (0.9–2.9) years ($P = 0.621$); parainfluenza virus type 3, 1.2 (0.5–2.1) years ($P < 0.001$); influenza A virus, 2.0 (0.9–4.8) years ($P = 1.000$); and influenza B virus, 4.2 (1.1–8.8) years ($P < 0.001$). Male sex was overrepresented in children with a rhinovirus infection (338 boys, 58%) and in those with another respiratory virus infection (2,116 boys, 57%). One-fourth of children with a rhinovirus infection had a chronic illness or another underlying condition (Table I).

Clinical manifestations. Most rhinovirus findings were from hospitalized children (91%) (Table II). Children presented at the hospital after median of 3 days of symptoms (IQR, 2–7 days, n = 540). Twenty-one cases (4%) fulfilled our criteria for a hospital-acquired rhinovirus infection.

TABLE I. Demographic and Clinical Characteristics of 580 Children With Rhinovirus Infection at the Department of Pediatrics, Turku University Hospital in 1987–2006

Characteristics	No. of children	%
Age, years		
0–<1	149	26
1–<2	150	26
2–<4	126	22
4–<9	85	15
9–18	70	12
Sex		
Male	338	58
Female	242	42
Underlying condition	156	27
Immunosuppression[a]	55	9
Asthma	39	7
Neurological	24	4
Other[b]	38	7

[a]Treatment of malignancy, 50 children; other cause, 5 children.
[b]Includes prematurity (<37 weeks gestation), cardiac disease, cystic fibrosis, diabetes mellitus, and gastrointestinal, renal, hematologic, rheumatologic, and pulmonary diseases excluding asthma.

TABLE II. Examinations at Presentation to Hospital and Treatment of 580 Children With a Rhinovirus Infection at the Department of Pediatrics, Turku University Hospital

	No. of children	%
WBC count ($\times 10^9$ cells/L)[a]		
0–3.9	8	2
4.0–14.9	227	62
15.0–52.0	130	36
Serum CRP (mg/L)[b]		
0–19	188	53
20–39	48	14
40–79	41	12
80–366	75	21
Blood bacterial culture	226	39
Positive[c]	9	2
Cerebrospinal fluid examination	50	9
Positive[d]	3	1
Hospitalization		
Outpatients	55	9
Inpatients	525	91
Antibiotic treatment	341	65
Intensive care unit	84	16
Ventilator treatment	19	4
Length of stay (days)		
1–2	287	55
3–4	100	19
≥5	138	26

[a]n = 365.
[b]n = 352.
[c]Excluding findings interpreted as contamination.
[d]Includes two cases of bacterial meningitis (one also blood culture positive) and one enterovirus meningitis.

At presentation, elevated values in white blood cell count (WBC) or serum C-reactive protein (CRP) were common. WBC was ≥15.0×10^9 cells/L in 36% of children and serum CRP was ≥40 mg/L in 33% of children. Chest radiography was done in 312 children (54%). Based on the frequency of collected blood and cerebrospinal fluid bacterial cultures (Table II), invasive bacterial infection was often suspected. However, invasive bacterial infection was confirmed only in 11 children (2%). *Mycoplasma pneumoniae* infection was confirmed in nine children (2%) concomitantly with rhinovirus infection, *Bordetella pertussis* in six children (1%), and *Chlamydia pneumoniae* in one child. Two-thirds of hospitalized children were treated with antibiotics for documented or suspected bacterial co-infections. Of rhinovirus findings in hospitalized children, 16% were from children admitted to pediatric intensive care unit. Median length of stay in the hospital was 2 days (IQR, 1–5 days).

Major clinical findings were identified from the discharge diagnoses and clinical notes in the medical records, and children with a rhinovirus infection were compared with those with another respiratory virus infection (Table III). Wheezy bronchitis and pneumonia were more common in children with rhinovirus infection than in those with another respiratory virus infection ($P < 0.01$). In children with other than rhinovirus infections, RSV was associated with bronchiolitis, adenovirus with tonsillitis, parainfluenza virus types 1 and 2 with laryngitis, and influenza A and B viruses with high fever.

TABLE III. Major Clinical Findings in Children With a Laboratory-Confirmed Viral Respiratory Infection at Turku University Hospital

Finding	Rhinovirus, % (n = 580)	RSV, % (n = 1655)	Adenovirus, % (n = 902)	PIV 1, % (n = 94)	PIV 2, % (n = 49)	PIV 3, % (n = 315)	IAV, % (n = 544)	IBV, % (n = 139)	Other than rhinovirus combined, % (n = 3697)
Wheezy bronchitis	**22**	12	2	2	4	8	6	6	8
Pneumonia	**18**	16	8	9	6	14	9	8	12
Otitis media	23	**59**	24	27	20	30	26	19	40
ARI	14	32	37	27	22	50	44	**53**	37
Bronchiolitis	3	**34**	1	2	10	5	1	1	16
Laryngitis	2	2	1	37	**53**	10	5	4	5
Tonsillitis	2	0	**30**	1	0	2	5	4	8
Fever without a focus	2	1	5	**10**	0	2	1	2	2
Febrile convulsion	1	2	7	4	0	5	**12**	9	5
Fever ≥38°C	44	63	81	77	76	63	**94**	89	73

RSV, respiratory syncytial virus, PIV, parainfluenza virus, IAV, influenza A virus, IBV, influenza B virus, ARI, nonspecified acute respiratory infection.
Highest percentage in each row is bolded.
Rhinovirus infections are from 1987 to 2006, and other respiratory virus infections are from 1980 to 1999.

Prospective Study

Study population. There were 221 eligible children at the ward during the study period. Parents of 179 children were contacted by the study personnel and 163 children (74% of all eligible) were enrolled after informed consent. After exclusion of seven illness episodes because of problems with the specimen or inconclusive result of virologic diagnosis, 163 separate hospital stays of 156 children were included in the analysis.

Rhinovirus detection, typing, and quantitation. Of 163 hospitalizations by study children, RT-PCR was positive for rhinoviruses in 46 (28%), enteroviruses in 22 (13%), and RSV in 20 episodes (12%) (Table IV). One child was co-infected with RSV and enterovirus. Thus, multiplex RT-PCR for these three viruses was positive in 53% of all hospitalization episodes. When culture was attempted in 43 rhinovirus RT-PCR positive samples, 22 of them were positive according to cytopathic effect

and RT-PCR of culture medium, while 3 exhibited cytopathic effect only, and 2 were positive only by RT-PCR. None of five samples from asymptomatic children, and 22 of 38 samples from children with respiratory symptoms (58%) were rhinovirus culture positive by cytopathic effect and RT-PCR of medium.

The median copy number of the rhinovirus genome in quantitative RT-PCR of nasal swab samples was 6.43 $\log^{10}$ copies/sample (SD, 1.21 $\log^{10}$ copies/sample) in children with respiratory symptoms and 4.49 $\log^{10}$ copies/sample (SD, 1.37 $\log^{10}$ copies/sample) in those without symptoms ($P = 0.005$, Mann–Whitney test). Rhinovirus copy numbers were inversely correlated with age, being highest in children younger than 2 years of age (Spearman's rho, 0.310, $P = 0.039$) (Fig. 1). Copy numbers did not differ between males and females.

A 397 bp long amplicon from the 5′ noncoding region was successfully amplified and sequenced from 28 (61%) of the rhinovirus RT-PCR positive samples. They rep-

TABLE IV. Demographic and Clinical Characteristics in the Prospective Study Population of Children ≥1 Month of Age Admitted for Any Reason to Pediatric Infectious Disease Ward

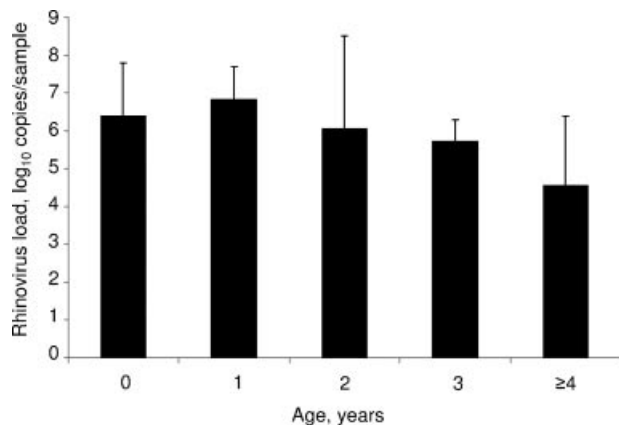| Characteristics	Virus detection by RT-PCR				
	Rhinoviruses, % (n = 46)	Enteroviruses, % (n = 21)	RSV, % (n = 20[a])	Negative, % (n = 76)	Enteroviruses, RSV, or negative, % (n = 117)
Age, years					
0–<1	28	14	45	20	23
1–<2	35	33	20	16	20
2–<4	17	33	30	18	23
4–<9	17	14	5	22	18
9–15	2	5	0	24	16
Sex					
Male	80	57	65	57	58
Female	20	43	35	43	42
Respiratory symptoms					
Yes	85	100	100	74	83
No	15	0	0	26	17

[a]Includes one co-infection with enterovirus.

Fig. 1. Median ($\pm$SD) rhinovirus copy numbers in nasal swab samples in relation to the age of children. $P = 0.039$ for correlation between age and copy numbers using Spearman's rho.

resented 16 different genotypes; 4 genotypes (7 samples) belonged to subgroup A and major receptor group, 2 genotypes (4 samples) to subgroup A and minor receptor group, 2 genotypes (2 samples) to subgroup B, and 8 genotypes (14 samples) to subgroup C. Of the different genotypes, 10 were detected only once and 6 were detected in 2–5 different individuals.

Demographic and clinical characteristics. The median age of children with rhinovirus infection was 1.7 years (IQR, 0.7–3.4 years), compared with 2.3 years (IQR, 1.0–5.2) in those with enterovirus or RSV infection, or no study virus ($P = 0.036$) (Table IV). Higher percentage of children with rhinovirus infection were male (80%, $P = 0.007$). We found no statistically significant difference in day care attendance of children younger than 5 years of age (n = 116): 24% of children with rhinovirus infection and 35% of those without it attended a day care center ($P = 0.23$). Respiratory symptoms were present on the day of nasal swab sampling in 39 (85%) children with rhinovirus infection, in 41 (100%) children

with enterovirus or RSV infection, and in 56 (74%) children with no study virus ($P = 0.77$ for comparison between rhinovirus-positive and other study children). The median age was 1.5 years in symptomatic and 5.3 years in asymptomatic rhinovirus-positive children ($P = 0.003$, Mann–Whitney test).

Clinical manifestations. Discharge diagnosis of asthma was associated with rhinovirus infection ($P = 0.006$) (Table V). In total, an acute wheezing illness (bronchiolitis, wheezy bronchitis, or asthma) was diagnosed in 28 (61%) of the 46 children with a rhinovirus infection and in 36 (31%) of the 117 children with another study virus, or no study virus ($P < 0.001$). Urinary tract infection was diagnosed in 7% of children with rhinovirus, but other infections with a focus outside the respiratory tract were documented rarely or not at all.

DISCUSSION

The first part of this study reports a large, hospital-based data collection from rhinovirus-positive children. Rhinovirus infections occurred most frequently in young children: one-half of all cases were in those younger than 2 years of age. Clinical findings in children with different respiratory viruses overlapped substantially, but certain manifestations were typical for specific viral etiology. Wheezy bronchitis and pneumonia were common discharge diagnoses in children with rhinovirus infection, which is in accordance with other studies [Juvén et al., 2000; Tsolia et al., 2004; Calvo et al., 2007; Cheuk et al., 2007; Miller et al., 2007]. Documented co-infections with other microbes were relatively uncommon, suggesting that rhinovirus infection was the primary cause of hospitalization in most cases. It should be noted, however, that more recently identified respiratory viruses such as human metapneumovirus, human coronaviruses NL63 and HKU1, and human bocavirus were not studied.

TABLE V. Common Discharge Diagnoses, in the Prospective Study Population of Children $\geq$1 Month of Age Admitted for Any Reason to Pediatric Infectious Disease Ward

	Virus detection by RT-PCR				
Diagnosis	Rhinoviruses, % (n = 46)	Enteroviruses, % (n = 21)	RSV, % (n = 20[a])	Negative, % (n = 76)	Enteroviruses, RSV, or negative, % (n = 117)
Asthma	26	24	15	4	9
Bronchiolitis	22	10	40	7	13
Otitis media	15	14	35	12	16
Wheezy bronchitis	13	24	10	4	9
Pneumonia	9	24	30	21	23
Sepsis	9	10	5	7	7
Urinary tract infection	7	5	0	5	4
Laryngitis	4	0	5	5	4
ARI	4	10	5	8	8
Gastroenteritis	0	0	5	7	5
Tonsillitis	0	5	0	8	6

ARI, nonspecified acute respiratory infection.
[a]Includes one co-infection with enterovirus.

This dataset is of sufficient size to reveal associations of rhinovirus infections with rare and severe disease manifestations, it involves a long study period to level off epidemiologic variations, and sampling for rhinovirus detection was not limited by any predetermined criteria. Moreover, efficient methods were used for the identification of the study viruses. Potential bias in patient selection is a limitation of the dataset, because samples for virus detection were not taken systematically from all patients. Furthermore, the dataset includes viral findings from previous clinical studies of children with pneumonia [Juvén et al., 2000], wheezing illness [Jartti et al., 2004], and leukemia [Koskenvuo et al., 2008]. These data were included in the present study in spite of the fact that they potentially bias the dataset towards these diseases, because their exclusion would have caused an opposite effect. Comparison dataset of children with other respiratory viruses was partly from different time period than that for rhinoviruses, but we do not consider that as a substantial cause of bias in comparisons of clinical picture.

Few previous studies have reported rhinoviruses from pediatric or neonatal intensive care units [Valenti et al., 1982; Verboon-Maciolek et al., 2005; Daubin et al., 2006; Richard et al., 2008]. In the present study, rhinoviruses were common in children at pediatric intensive care unit, and 19 rhinovirus-positive children needed ventilator therapy. Six cases were documented at neonatal intensive care unit. Blood and cerebrospinal fluid cultures and chest X-rays were done in a large proportion of children with rhinovirus infection. WBCs and serum CRP levels were increased often, which is not the case in children with influenza or RSV [Peltola et al., 2003, 2006a]. These findings suggest that rhinovirus infections may be severe or they associate with severe bacterial infections. Invasive bacterial infections were, however, rarely confirmed by blood or cerebrospinal fluid cultures. Looking the other way around, previously healthy children with invasive pneumococcal infection during autumn, and children with leukemia and documented bacterial sepsis, may be often positive for rhinoviruses or other respiratory viruses [Peltola et al., 2006b; Koskenvuo et al., 2007].

The frequency of hospital-acquired rhinovirus infection is currently not known. The risk of acquiring respiratory viruses from hospital roommates without direct contact was estimated to be low in an older study using viral culture [Wenzel et al., 1977]. By using PCR methods, rhinoviruses have been detected from filtered office air samples, suggesting risk of air-borne transmission in poorly ventilated indoor environments [Myatt et al., 2004]. Hospital-acquired rhinovirus infections were identified sporadically in the present study, but a separate study designed for this purpose would be needed to assess their impact.

Because of the above-mentioned limitations of our retrospective study, we performed a short-term prospective study in ≥1-month-old children, including also asymptomatic children. This study revealed the high impact of rhinoviruses at pediatric infectious

disease ward during autumn: 28% of all children were positive for rhinoviruses by RT-PCR, and rhinoviruses were cultured in 63% of these children. Age distribution of children in the prospective study was similar to that in the retrospective study. Major role of rhinoviruses in acute wheezing illnesses was confirmed.

We detected rhinoviruses in 7 (26%) of 27 children with no respiratory symptoms at the time of sampling by RT-PCR, but none of them had positive rhinovirus culture. Similarly, in other studies rhinoviruses have been detected by RT-PCR in 15–30% and by culture in 0–5% of individuals with no respiratory symptoms [Jartti et al., 2008a]. Nevertheless, 85% of rhinovirus-positive children in the present study had respiratory symptoms, and other than respiratory infections were recorded as discharge diagnosis rarely. Viral copy numbers were lower in asymptomatic than symptomatic children. These findings suggest that in most rhinovirus positive cases with respiratory symptoms, rhinovirus infection was the likely cause of hospitalization. Asymptomatic rhinovirus findings were from older children, and viral loads were highest in the youngest children. This is in accordance with our previous study of rhinoviruses in families, where asymptomatic infections occurred in school-aged children and adults as a result of transmission from symptomatic young children [Peltola et al., 2008]. Studies with repetitive sampling show that PCR-positivity for specific rhinovirus types is of relatively brief duration [Peltola et al., 2008; Jartti et al., 2008b].

Recently, new human rhinovirus types have been identified by sequencing of RT-PCR products. Many of these viruses have not been cultivable and they cluster into a separate genetic group (suggestively, C) that is different from human rhinoviruses A and B [Arden et al., 2006; Lamson et al., 2006; Lee et al., 2007]. In our study, half of the strains belonged to the C group according to sequence analysis of the 5′ noncoding region. Notably, analysis of this region allows grouping of strains by the species level, but not determination of virus types, which would have needed sequencing of the capsid regions. Number of study children was too low for comparison of clinical manifestations between rhinovirus groups. There is limited earlier evidence that clinical associations, such as the frequency of pneumonia, may differ between the newly identified rhinoviruses and the previously identified ones [Renwick et al., 2007], but further study would be needed to determine the clinical impact of group C rhinoviruses.

In conclusion, this study suggests that the effect of rhinovirus infections on hospitalizations of young children is larger than previously recognized, and rhinovirus should be routinely included in viral diagnostic tests of hospitalized children. The clinical manifestations of rhinovirus infections overlap substantially with those of other respiratory virus infections. These results highlight the need for development of specific prevention and treatment modalities for rhinovirus infections.

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