Rhinovirus Infections in the First 2 Years of Life

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abstract

BACKGROUND AND OBJECTIVES: Rhinoviruses frequently cause respiratory infections in young children. We aimed to establish the burden of acute respiratory infections caused by rhinovirus during the first 2 years of life.

METHODS: In this prospective birth cohort study, we followed 923 children for acute respiratory infections from birth to 2 years of age. Data on respiratory infections were collected by daily symptom diaries, study clinic visits, and from electronic registries. Respiratory viruses were detected by reverse transcription-polymerase chain reaction and antigen assays during respiratory infections and at the age of 2, 13, and 24 months. The rates of rhinovirus infections and associated morbidities were determined.

RESULTS: We documented 8847 episodes of acute respiratory infections, with an annual rate of 5.9 per child (95% confidence interval [CI], 5.7–6.1). Rhinovirus was detected in 59% of acute respiratory infections analyzed for viruses. Rhinovirus was associated with 50% of acute otitis media episodes, 41% of wheezing illnesses, 49% of antibiotic treatments, and 48% of outpatient office visits for acute respiratory infections. The estimated mean annual rate of rhinovirus infections was 3.5 per child (95% CI, 3.3–3.6), 47 per 100 children (95% CI, 42–52) for rhinovirus-associated acute otitis media, and 61 per 100 children (95% CI, 55–68) for rhinovirus-associated antibiotic treatment. The prevalence of rhinovirus at 2, 13, or 24 months of age was 14 to 24%, and 9% of asymptomatic children were positive for rhinovirus.

CONCLUSIONS: Rhinovirus infections impose a major burden of acute respiratory illness and antibiotic use on young children.

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Dr Toivonen contributed to the clinical follow-up and data collection, carried out data analyses, and drafted the initial manuscript; Drs Schuez-Havupalo, Karppinen, Teros-Jaakkola, and Rulli contributed to the clinical follow-up and data collection and reviewed and revised the manuscript; Dr Mertsola contributed to the study design and reviewed and revised the manuscript; Dr Waris contributed to the study design, carried out virological analyses, and reviewed and revised the manuscript; Dr Peltola conceptualized and designed the study, coordinated and supervised data collection and analyses, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: Rhinoviruses commonly cause respiratory infections ranging from asymptomatic infections and the common cold to asthma exacerbations and severe respiratory diseases requiring hospitalization. However, the burden of rhinovirus infections in young children has not been comprehensively described.

WHAT THIS STUDY ADDS: Rhinovirus infections impose a major burden on young children with an estimated mean annual rate of 3.5 in children aged 0 to 23 months. Rhinoviruses associate with half of acute otitis media episodes, antibiotic treatments, and outpatient visits for acute respiratory infections.

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Acute respiratory infections are a major cause of morbidity in infants and young children, and rhinovirus is the most common causative agent.[1–3] Clinical manifestations of rhinovirus infection range from asymptomatic infections and the common cold to asthma exacerbations and severe respiratory diseases requiring hospitalization.[4–8] With the use of sensitive polymerase chain reaction (PCR) and other molecular assays for diagnosis and typing, the detection rates of rhinoviruses have increased, group A, B, and C rhinoviruses have been identified, and the spectrum of rhinovirus illnesses has been better recognized.[9] However, the illness burden of rhinovirus infections in young children is poorly defined. Previous studies have been either small, conducted in selected populations, done before the era of PCR diagnostics, or they have not covered noncomplicated upper respiratory tract infections that may contribute substantially to the disease burden because of high frequency.[3,10–17]

We followed up on the occurrence and clinical outcomes of acute respiratory infections caused by rhinovirus in a cohort of children from birth to 2 years of age. In addition to nasal swab sampling at the study clinic, we used home sampling by parents. We also determined the prevalence of rhinovirus at the age of 2, 13, and 24 months and the presence of associated symptoms.

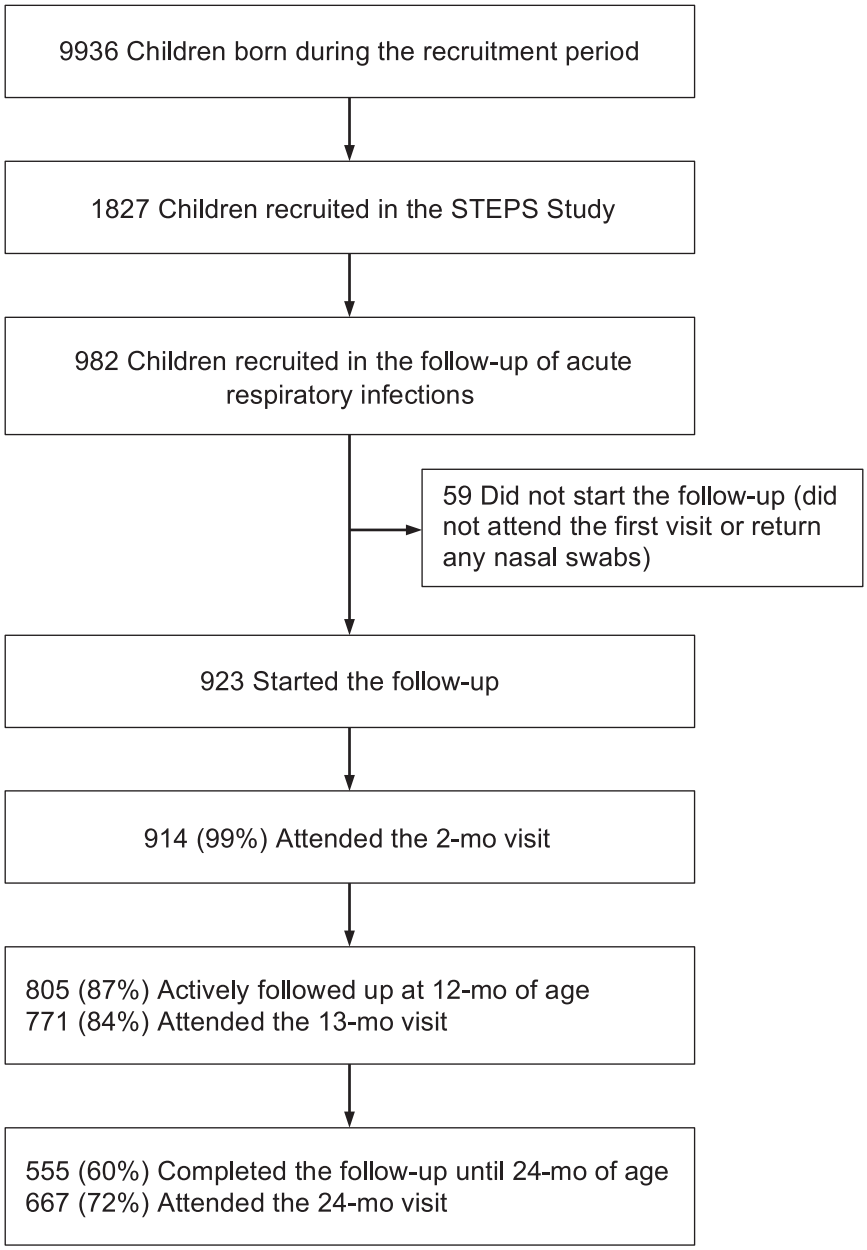

FIGURE 1
Enrolment and follow-up of the study children. Follow-up was considered complete at the age of 12 and 24 months if the symptom diary was filled, or if there were records of outpatient clinic visits or nasal swab specimens at the age of ≥10 or ≥22 months, respectively.

METHODS

Study Design and Conduct

From all children born in the Hospital District of Southwest Finland from January 2008 through April 2010 to Finnish or Swedish-speaking mothers (eligible cohort, *n* = 9811 mothers; *n* = 9936 children), families of 1827 children (30 pairs of twins) were recruited either during the first trimester of pregnancy or soon after birth in the prospective, observational birth cohort study, Steps to the Healthy Development and Well-being of Children (STEPS).[18] Parents of all children recruited for the STEPS Study were asked about participation of the child in an intensive follow-up of respiratory infections from birth to 2 years of age, and 982 children participated (Fig 1). No selection criteria other than language were applied with regard to the recruitment of families for the STEPS Study or for the subcohort with infection follow-up.

The follow-up was conducted from April 2008 to April 2012. Parents were asked to record all respiratory and other symptoms, physician visits with associated diagnoses and treatments, and illness-related

absenteeism of the child from day care and the parent from work into a daily symptom diary. Background information was gathered by structured question forms before birth or soon after birth, and information on day care attendance was collected at ages 13, 18, and 24 months.

Families were encouraged to visit the study clinic whenever the child experienced an acute respiratory infection and parents believed that an evaluation by a physician was needed. At the study clinic, children were examined by a study physician and clinical findings were documented using a structured form. Pneumatic otoscopy and tympanometry were used for diagnosing otitis media. Nasal swabs from both nostrils at a depth of 2 to 3 cm were obtained by using flocked nylon swabs (Copan, Brescia, Italy) by the study physician. Alternatively, if the family felt that a physician visit was not needed, or if they visited a physician elsewhere, nasal flocked swab specimens were taken at home by the parents at the onset of illness and sent to the laboratory by standard mail as described previously.[19,20] Parents were trained by study personnel to collect nasal swab samples at the first visit to the study clinic. Data on emergency department visits and hospitalizations of the child, including results of virus diagnostics performed as part of patient care, were collected from the Electronic Registry of the Hospital District of Southwest Finland, which comprises information from both hospitals providing inpatient pediatric care in the area (Turku University Hospital and Salo District Hospital).

Children were invited to visit the study clinic at the age of 2, 13, and 24 months. Any current respiratory symptoms were documented and nasal swab specimens were taken.

The Ministry of Social Affairs and Health and the ethics committee of the Hospital District of Southwest Finland approved the STEPS Study. Parents of participating children gave their written, informed consent.

Respiratory Virus Detection

The nasal swab specimens were stored at −80°C before analysis. Swabs were suspended in phosphate buffered saline and nucleic acids were extracted by NucliSense easyMag (BioMerieux, Boxtel, the Netherlands) or MagnaPure 96 (Roche, Penzberg, Germany) automated extractor. Extracted RNA was reverse transcribed and the complementary DNA was amplified using real-time, quantitative PCR for rhinovirus, human enteroviruses, and respiratory syncytial virus (RSV) as described previously (all samples).[21,22] Laboratory-developed antigen detection tests were performed for influenza A and B viruses, parainfluenza type 1, 2, and 3 viruses, RSV, adenovirus, and human metapneumovirus for samples collected in January 2009 or later (89% of samples). All specimens collected during influenza seasons were subjected to reverse transcription-PCR for influenza A and B viruses.[23] The first and last day of each influenza season were defined on the basis of the influenza antigen test results and data from the infectious disease surveillance registry of the National Institute for Health and Welfare, Finland. Routine respiratory viral diagnostics were performed by PCR or rapid antigen detection methods for 26 patients as part of their care at the Turku University Hospital.

Statistical Analysis

An episode of acute respiratory infection was defined as the presence of rhinitis or cough, with or without fever or wheezing, documented in the diary by parents, or as a diagnosis of an acute respiratory infection by a physician.

If several nasal specimens were collected during continuous symptoms, nasal swabs taken within 14 days were considered as 1 episode, and the date of a new nasal swab taken >14 days from the earlier sample was considered as the first day of a new episode. Coinfections were defined as detection of ≥2 viruses from 1 or several specimens during the same episode within 14 days from each other. If there were repeated diagnoses of acute otitis media, wheezing illness, pneumonia, laryngitis, or pharyngitis during continuous respiratory symptoms, diagnoses within 14 days were calculated as 1 episode. If the diary data were missing, outpatient visits and hospitalizations for acute respiratory infection 1 day before through 14 days after the nasal swab collection were linked with the virologic result.

When calculating the annual respiratory illness days associated with rhinovirus infections, the length of an acute respiratory infection was limited to a maximum of 60 days. When analyzing other characteristics and outcomes of virus infections, data were included from the symptomatic period with a maximum duration of 14 days before and 14 days after collection of the nasal sample. Coinfections involving rhinoviruses were excluded from analyses of characteristics of rhinovirus infections because of the unclear role of different viruses in the pathogenesis of coinfections.

Categorical data were compared by using the χ^2 test. Continuous data were described and compared by using means, SDs, or 95% confidence intervals (CI), and Student's *t* test, or medians, interquartile ranges (IQR), and Mann–Whitney *U* test, as appropriate. The proportion of children positive for rhinovirus at 2, 13, and 24 months of age was compared with the Friedman test. Generalized linear models were used to describe and analyze rates

TABLE 1 Baseline Characteristics of the Study Children

Characteristic	Study Children, *n* (%) (*N* = 923)
Female	435 (47)
Older siblings	376 (41)
Mother's educational level at least professional	574/892 (64)
Living in the urban area	544/895 (61)
Mother smoked during pregnancy	44/801 (5)
Parent smoked during pregnancy	141/818 (17)
Breast-fed for at least 6 mo	432/716 (60)
Attendance at outside-home day care	
At the age of 13 mo	185/784 (24)
At the age of 18 mo	285/685 (42)
At the age of 24 mo	370/681 (54)
Vaccinated against influenza[a]	
2008–2009	13/59 (22)
2009–2010, with seasonal influenza vaccine	173/366 (47)
2009–2010, with pandemic influenza vaccine	296/366 (81)
2010–2011	130/371 (35)
2011–2012	12/54 (22)

[a] Calculated among children ≥6 mo of age actively followed-up at the beginning of each influenza season.

for rhinovirus-associated outcomes. Outcome counts were analyzed by using negative binomial distribution and log link with natural logarithm of follow-up time as an offset variable. Pneumonia counts were low and negative binomial regression failed; thus, for pneumonia, Poisson distribution was used instead. Binomial distribution with logit link was used to determine the proportion of rhinovirus-positive infections from infections with a nasal swab analyzed for viruses. The number of rhinovirus-associated acute respiratory infections was determined as a product of the proportion of rhinovirus infections and total infections. CIs for the product were determined by using 500 bootstrap samples. *P* values < .05 were considered statistically significant. The data were analyzed with the use of SPSS software, version 23.0 (IBM SPSS Statistics for Macintosh, IBM Corporation, Armonk, NY), and SAS software for Windows, version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Study Population

A total of 982 children were recruited for follow-up of respiratory infections. Fifty-nine children did not start the follow-up, resulting in the study group of 923 children (Fig 1, Table 1). Data on acute respiratory infections were received from 95% of these children, and the mean duration of the follow-up was 1.69 (SD, 0.47) years. Based on data from the Finnish National Birth Registry, 55% of mothers in the eligible cohort (*n* = 9811) had ≥1 children.[18] Thus, our study population with 41% of children having ≥1 older siblings was skewed toward including more first-born children than the general child population.

Documentation of Acute Respiratory Infections

A total of 8847 episodes of acute respiratory infection, causing 4691 outpatient visits and 85 hospitalizations, were documented. Of all outpatient visits, 2142 (46%) occurred at the study clinic, 2338 (50%) at other outpatient clinics or physician offices, and 211 (4%) at the emergency department. Antibiotics were prescribed less frequently at the study clinic (in 29% of episodes) compared with other sites (in 50% of episodes, *P* < .001). A nasal swab sample was collected during 4728 (53%) acute respiratory infections with 70% of swabs being taken at home by parents. Characteristics of acute respiratory infections with and without a nasal sample are compared in Supplemental Table 5.

Incidence and Characteristics of Rhinovirus Infections

Rhinovirus was detected in 59% of acute respiratory infections with a specimen analyzed for viruses (Table 2). RSV was detected in 6% and 1 of the other respiratory viruses studied in 5% of acute respiratory infections. Coinfections were confirmed in 2% of episodes, and 29% remained negative in virologic analysis. Symptoms, diagnoses, and treatment of acute respiratory infections positive or negative for rhinovirus are compared in Table 3. Children with an acute respiratory infection positive for rhinovirus experienced fever, cough, poor appetite, or gastrointestinal symptoms less frequently than those with an acute respiratory infection negative for rhinovirus.

Rates of Acute Respiratory Infections

The mean annual rate of all acute respiratory infections, including those lacking a specimen for virologic analysis, was 5.9 per child (95% CI, 5.7–6.1) (Table 4). The rate of acute respiratory infections positive for rhinovirus was 2.0 (95% CI, 1.9–2.1). Assuming that the proportion of rhinovirus infections is similar in infections not analyzed as in those analyzed for viruses, we estimated that the annual rate of acute respiratory infections caused by rhinovirus was 3.5 per child (95% CI, 3.3–3.6) in children <2 years of age. Rhinovirus infections were estimated to cause a mean of 31 respiratory illness days per child annually. The rate of rhinovirus infections was highest among children 6 to 23 months of age, but noticeably high already before 6 months of age.

TABLE 2 Viruses Detected in Nasal Swabs During Acute Respiratory Infections and Associated Diagnoses and Outcomes

Detected Virus	Acute Respiratory Infection (n = 4728)	Acute Otitis Media (n = 702)	Wheezing Illness (n = 172)	Laryngitis (n = 92)	Pneumonia (n = 17)	Outpatient Office Visits (n = 2503)	Antibiotic Treatments (n = 882)	Hospitalization (n = 41)
Any virus	3340 (71)	489 (70)	130 (76)	55 (60)	11 (65)	1664 (66)	606 (69)	28 (68)
Rhinovirus	2775 (59)	351 (50)	71 (41)	33 (36)	5 (29)	1201 (48)	436 (49)	16 (39)
RSV	262 (6)	82 (12)	45 (26)	9 (10)	4 (24)	239 (10)	101 (11)	7 (17)
HEV	69 (1)	11 (2)	0 (0)	0 (0)	0 (0)	30 (1)	11 (1)	0 (0)
PIV 1, 2, or 3	66 (1)	5 (1)	1 (1)	10 (11)	0 (0)	61 (2)	11 (1)	1 (2)
Influenza virus A or B	45 (1)	9 (1)	1 (1)	1 (1)	0 (0)	38 (2)	12 (1)	3 (7)
HMPV	41 (1)	11 (2)	2 (1)	2 (2)	2 (12)	31 (1)	14 (2)	0 (0)
Adenovirus	10 (0)	2 (0)	0 (0)	0 (0)	0 (0)	7 (0)	1 (0)	0 (0)
Coinfection	72 (2)	18 (3)	10 (6)	0 (0)	0 (0)	57 (2)	20 (2)	1 (2)

Values are n (%) for acute respiratory infections with a nasal swab specimen collected. HEV, human enterovirus; HMPV, human metapneumovirus; PIV, parainfluenza virus.

Complications, Antibiotic Treatments, Day Care Absences, and Hospitalizations

Acute otitis media was documented in 13% of all rhinovirus-positive acute respiratory infections (Table 3). Antibiotic treatment was prescribed in 15% of cases, and use of over-the-counter pain or fever medications was common. Thirty-six percent of rhinovirus infections led to a physician visit, and acute otitis media was diagnosed in 35% of rhinovirus infections during which a child was evaluated by a physician. As a result of the high frequency of rhinovirus infections, they accounted for 50% of acute otitis media episodes, 41% of wheezing illnesses, 49% of antibiotic treatments, and 48% of physician visits during virologically studied acute respiratory infections (Table 2). The estimated mean annual rate of rhinovirus-associated acute otitis media was 47 per 100 children (95% CI, 42–52) and 61 per 100 children (95% CI, 55–68) for rhinovirus-associated antibiotic treatment (Table 4). Rhinovirus was associated with 39% of hospitalizations for an acute respiratory infection studied for viruses. The annual rate of lower respiratory tract infections (wheezing or pneumonia) associated with rhinovirus was estimated as 8.5 per 100 children (95% CI, 6.3–11.1), and the rate of hospitalizations as 2.3 per 100 children (95% CI, 1.2–3.9).

Over half (51%) of all children attending day care stayed at home during rhinovirus infection, thereby also often necessitating parental absenteeism from work. Of a total of 856 lost work days for children's acute respiratory infections, 439 (51%) were associated with rhinovirus infections. The estimated rate of lost work days because of a child's rhinovirus infections was 3.4 per child per year (95% CI, 2.9–4.0) among children attending day care.

Seasonality

Rhinoviruses were detected throughout the year with high-incidence periods from August to November and from April to May (Supplemental Fig 3). From August to November, rhinovirus was found in 73% of acute respiratory infections and in 68% of acute otitis media cases.

Rhinovirus Prevalence at 2, 13, and 24 Months of Age

The proportion of children positive for rhinovirus regardless of symptoms increased from 14% at 2 months of age to 18% at 13 months of age and to 24% at 24 months of age ($P < .001$) (Fig 2). At the scheduled visits, 653 of 2316 children (28%) had respiratory symptoms when specifically asked by the study nurse. Children with respiratory symptoms were more frequently positive for rhinovirus (41%) than asymptomatic children (9%, $P < .001$) (Supplemental Table 6). Comparing rhinovirus-positive and rhinovirus-negative asymptomatic children, symptoms occurring from 14 days before to 7 days after sampling, and respiratory symptoms in other family members, were more frequently documented in those who were rhinovirus-positive (Supplemental Table 7). Asymptomatic rhinovirus-positive children had lower numbers of rhinovirus copies in nasal swabs (mean [SD] log of copies per swab, 4.5 [1.3]) than did children with respiratory symptoms (mean [SD] log of copies per swab, 5.7 [1.5]; $P < .001$).

DISCUSSION

Rhinoviruses were detected in more than half of all acute respiratory infections in this birth cohort study, resulting in an estimated annual rate of 3.5 infections per child. Only a minority of the children were hospitalized but, still, the total burden of illness caused by

TABLE 3 Characteristics of Acute Respiratory Infections Positive or Negative for Rhinovirus in Children 0 to 23 Months of Age

Characteristic	Acute Respiratory Infections[a]		*P*
	Rhinovirus-Positive (*n* = 2775)	Rhinovirus-Negative (*n* = 1884)	
Symptoms			
Duration of respiratory symptoms, median [IQR], d	9.0 [6.0–13.0]	9.0 [5.0–13.0]	.16
Rhinorrhea	2358/2383 (99.0)	1488/1623 (91.7)	<.001
Cough	1449/2383 (60.8)	1173/1623 (72.3)	<.001
Fever ≥38.0°C	715/2383 (30.0)	784/1623 (48.3)	<.001
Wheezing reported by the parents or by the doctor	215/2391 (9.0)	218/1627 (13.4)	<.001
Poor appetite	495/2197 (22.5)	409/1341 (30.5)	<.001
Vomiting or diarrhea	211/2197 (9.6)	206/1341 (15.4)	<.001
Outcomes			
Child absent from day care[b]	197/384 (51.3)	171/273 (62.6)	.004
Duration of absenteeism from day care, median [IQR], d	2.0 [1.0–4.0]	3.0 [2.0–4.0]	.14
Parent absent from work because of child's illness[b]	163/384 (42.4)	130/273 (47.6)	.19
Duration of absenteeism from work, median [IQR], d	2.0 [1.0–3.0]	2.0 [1.0–4.0]	.26
Episodes with an outpatient clinic or emergency department visit	999 (36.0)	1030 (54.7)	<.001
Hospitalization	16 (0.6)	24 (1.3)	.01
Duration of hospitalization, median [IQR], d	1.0 [1.0–2.0]	1.0 [1.0–2.0]	.39
Diagnosis (other than acute respiratory infection)			
Acute otitis media	351 (12.6)	333 (17.7)	<.001
Wheezing illness (bronchiolitis or recurrent wheezing)	71 (2.6)	91 (4.8)	<.001
Laryngitis	33 (1.2)	59 (3.1)	<.001
Conjunctivitis	48 (1.7)	43 (2.3)	.18
Pharyngitis or tonsillitis	33 (1.2)	48 (2.5)	<.001
Pneumonia	5 (0.2)	12 (0.6)	.01
Treatment			
Antibiotic treatment during episode	408 (14.7)	392 (20.8)	<.001
Systemic corticosteroids	20 (0.7)	18 (1.0)	.38
Analgesics or antipyretics	992/2197 (45.2)	749/1341 (55.9)	<.001
Antitussives	57/2197 (2.6)	64/1341 (4.8)	.001

Values are *n* (%) of acute respiratory infections unless otherwise specified. Two-sided *P* values calculated by Mann–Whitney *U* test for continuous variables and by χ^2 test for categorical variables.

[a] Episodes positive for rhinovirus and another virus were excluded from the analysis (*n* = 69). Of 1884 rhinovirus-negative acute respiratory infections, 262 were positive for RSV, 69 for human enterovirus, 66 for parainfluenza virus type 1, 2 or 3, 41 for human metapneumovirus, 24 for influenza virus A, 21 for influenza virus B, 10 for adenovirus, 2 for RSV and human metapneumovirus, 1 for human enterovirus and influenza virus A, and 1388 were virus-negative.

[b] Calculated among children attending outside-home day care at the time of acute respiratory infection.

TABLE 4 Rates of Acute Respiratory Infections and Associated Outcomes

	Acute Respiratory Infections	Rhinovirus-Positive Acute Respiratory Infections	Proportion of Rhinovirus-Positive Infections from Infections Analyzed for Viruses	Estimated Rhinovirus-Associated Acute Respiratory Infections[a]
	Mean/Child/y (95% CI)		Proportion (95% CI)	Mean/Child/y (95% CI)
At the age of 0–23 mo	5.9 (5.7–6.1)	2.0 (1.9–2.1)	0.59 (0.57–0.60)	3.5 (3.3–3.6)
At the age of 0–5 mo	3.9 (3.7–4.2)	1.5 (1.3–1.6)	0.57 (0.54–0.60)	2.3 (2.1–2.4)
At the age of 6–11 mo	6.5 (6.2–6.7)	2.4 (2.2–2.6)	0.61 (0.58–0.63)	3.9 (3.7–4.2)
At the age of 12–23 mo	7.1 (6.8–7.3)	2.1 (1.9–2.2)	0.58 (0.56–0.60)	4.1 (3.9–4.3)
Days with respiratory symptoms	50.4 (47.8–53.2)	18.8 (17.1–20.6)	0.61 (0.60–0.61)	30.7 (29.0–32.5)
Outpatient office visits	3.1 (2.9–3.3)	0.9 (0.8–0.9)	0.48 (0.46–0.50)	1.5 (1.4–1.6)
	Mean/100 Children/y (95% CI)			Mean/100 Children/y (95% CI)
Hospitalization	5.9 (4.4–7.9)	1.2 (0.7–2.0)	0.39 (0.25–0.55)	2.3 (1.2–3.9)
Additional diagnoses and treatment				
Acute otitis media	94.2 (86.9–102.3)	24.9 (22.0–28.2)	0.50 (0.46–0.54)	47.2 (41.9–52.2)
Wheezing	18.8 (15.4–23.0)	5.1 (3.8–6.8)	0.41 (0.34–0.49)	7.8 (5.8–10.2)
Pneumonia	2.4 (1.8–3.4)	0.4 (0.2–0.9)	0.29 (0.13–0.54)	0.7 (0.2–1.3)
Antibiotic treatment	123.5 (114.2–133.6)	30.8 (27.3–34.7)	0.49 (0.46–0.53)	61.2 (54.5–68.2)

[a] The number of rhinovirus-associated acute respiratory infections was determined as the product of the proportion of rhinovirus infections and total infections.

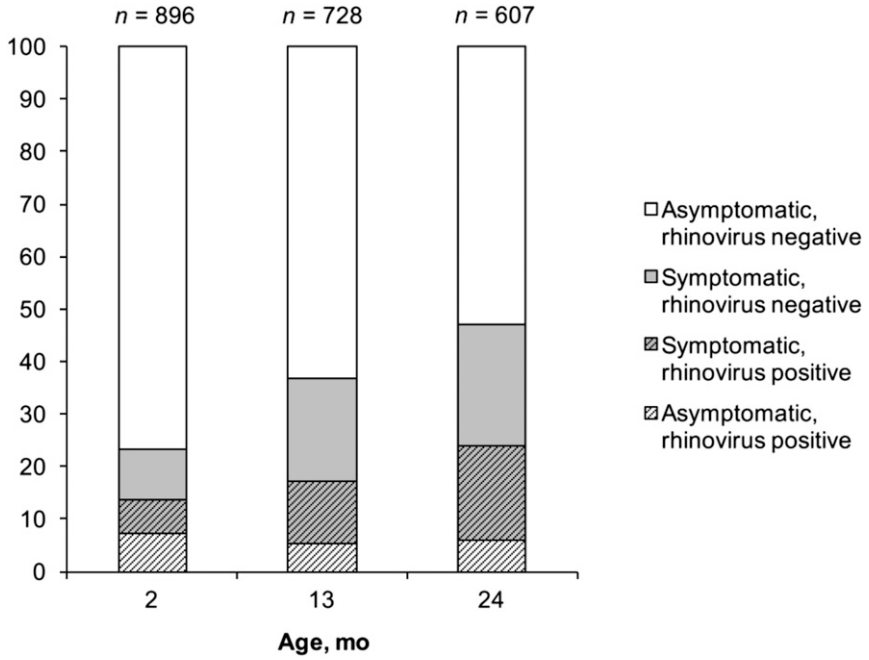

FIGURE 2

Prevalence of rhinovirus infections and respiratory symptoms in children at scheduled visits at the age of 2, 13, and 24 months.

rhinovirus was heavy. This disease burden was particularly seen in the number of outpatient visits for acute respiratory infections, of which almost half were associated with rhinovirus, and in the use of antibiotics, with an annual rate of 61 antibiotic treatments per 100 children associated with rhinovirus infections. Even illness episodes that do not require a physician visit may be burdensome for the families. We report that rhinovirus infections associate with a high annual number of days with respiratory symptoms, frequent over-the-counter medication use, and half of all parental workdays lost because of a child's acute respiratory infection.

Our results show that, similar to earlier studies,[2,24] acute otitis media complicates rhinovirus infections more infrequently than respiratory infections caused by RSV or other viruses, but the high frequency of rhinovirus infections makes it the most important virus associated with acute otitis media. We also found that 41% of acute wheezing illnesses were associated with rhinovirus, which is in line with a previous birth cohort study.[13]

By using home sampling in addition to sample collection at study clinic visits, we were able to study viral etiology in 53% of all acute respiratory infections from birth to 2 years of age. Home nasal sampling for respiratory viruses has been found feasible previously, and it may increase the virus detection rate in studies of outpatient infections.[19,20,25] Based on the frequency of complications and other outcomes in rhinovirus-positive versus rhinovirus-negative infections, we estimated rhinovirus-associated morbidity. This estimation is subject to an assumption that rhinoviruses would occur with a similar frequency and severity in infections that were not analyzed for viruses as in those that were analyzed. This assumption is supported by the fact that the rates of acute otitis media or pneumonia did not differ between infections with or without nasal samples (Supplemental Table 5). Antibiotic prescriptions were even more frequent in infections without a virologic analysis.

Rhinoviruses have been detected by sensitive PCR techniques in 11% to 47% of asymptomatic children.[13,26] This has raised concern about the clinical relevance of rhinovirus-positive PCR results. In the current study, the prevalence of rhinovirus was rather high at 2, 13, or 24 months of age, and it increased with age. However, when parents were specifically asked about respiratory symptoms in the child at the time of the visit, we found that rhinovirus was detected infrequently in completely asymptomatic children. Furthermore, rhinovirus detections were often associated with respiratory symptoms before or after sampling, or with respiratory symptoms in other members of the family. Our results suggest that totally asymptomatic rhinovirus infections are less frequent than previously thought, and incidental rhinovirus findings are often due to infections with mild symptoms. This is in accordance with previous studies reporting high rates of recurrent infections caused by different rhinovirus types, and limited duration of virus shedding in immunocompetent individuals, rather than prolonged carriage of the same rhinovirus type.[27–29] The prevalence of rhinovirus increased with age, as did the rates of respiratory infections, probably because of increased contact with other children.

Viruses other than rhinovirus and coinfections by ≥2 viruses were found in a low proportion of respiratory infections in this study, which may be explained by our study setting and the virologic methodology. We investigated mostly mild infections in a healthy child cohort. The influenza A/H1N1 pandemic in 2009 was mild in this

population with high vaccination coverage against it, and the 4-year study period probably evened the effects of epidemic variation in the circulation of respiratory viruses.

Our study has limitations. Because we focused on rhinovirus, our virologic methods were not comprehensive for all other respiratory viruses. PCR was performed for rhinovirus, RSV, human enterovirus, and influenza A and B viruses, whereas an antigen detection test, with lower sensitivity than PCR, was performed for 5 other viruses. The sensitivity of the PCR may be better for rhinoviruses and enteroviruses than for RSV in home-collected specimens because nonenveloped viruses endure the environment better than enveloped viruses. Because consulting the study physician was easy and free for the study families, the rate of physician visits might be overestimated. However, only about half of all outpatient visits occurred at the study clinic, which was not open during evenings and weekends. Our study children had older siblings less frequently than those who did not participate. Because respiratory tract infections are more frequent in children with large families,[17] this difference might have led to underestimation of the impact of rhinovirus infections.

CONCLUSIONS

This study provides new information about the major role of rhinovirus in acute respiratory infections in young children. Rhinovirus infections are generally mild, but because of their high frequency, the impact of rhinovirus on the total number of acute otitis media and antibiotic treatments in young children is greater than that of any other respiratory virus. In addition to other benefits, novel prevention or treatment modalities of rhinovirus infections could substantially decrease the use of antibiotics for respiratory tract infections in children.

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ABBREVIATIONS

CI: confidence interval
IQR: interquartile range
PCR: polymerase chain reaction
RSV: respiratory syncytial virus
STEPS: Steps to the Healthy Development and Well-being of Children

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