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Respiratory Syncytial Virus Infections in Children 0-24 Months of Age in the Community

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Abbreviations:

AOM	acute otitis media
ARI	acute respiratory infection
CI	confidence interval
LRTI	lower respiratory tract infection
RSV	respiratory syncytial virus
RT-PCR	real-time, quantitative reverse-transcription polymerase chain reaction
STEPS	Steps to the Healthy Development and Well-being of Children

Keywords: children, infant, respiratory syncytial virus, respiratory tract infection, STEPS Study

Abstract

Objectives

Respiratory syncytial virus (RSV) is a major cause of hospitalization in young children, but there are little data on RSV infections in early childhood in the community. We conducted a prospective population-based birth-cohort study to determine the rates and characteristics of RSV infections in young children.

Methods

We followed 923 children for acute respiratory infections (ARIs) from birth to age 24 months with daily diaries and study clinic visits. Nasal swab samples were obtained at the onset of ARIs and analyzed for RSV by RT-PCR and antigen tests. The rates of RSV infections and associated outcomes were estimated.

Results

RSV was detected in 289 (6%) of 4728 ARIs with a nasal sample. The mean estimated annual rate of RSV infections was 37 (95% confidence interval [CI], 35-38) per 100 children at age 0-24 months. For RSV-associated outcomes, the estimated annual rates per 100 children were 34 (95% CI, 32-37) physician visits, 16 (95% CI, 15-17) antibiotic treatments, 12 (95% CI, 11-13) acute otitis media, and 6 (95% CI, 4-7) wheezing illnesses. The prevalence of RSV was 0.6% in asymptomatic children.

Conclusions

RSV infections impose a high burden of disease in healthy young children in the community.

Introduction

Respiratory syncytial virus (RSV) is globally the most common cause of acute lower respiratory tract infections (LRTI) and a major cause of hospitalization due to severe LRTI in children under 5 years of age.[1] RSV is the most frequent cause of bronchiolitis[2] and an important causative agent of pneumonia in young children.[3,4] Young age and prematurity are the most important risk factors for severe RSV infection requiring hospitalization.[5-7]

In addition to its major role in LRTIs, RSV is also a frequent cause of upper respiratory tract infections in children.[8-15] Acute respiratory infections (ARI) caused by RSV are often complicated by acute otitis media (AOM),[13,16] and up to two-thirds of medically-attended children with an RSV infection receive an antibiotic prescription.[14] Serological studies show that more than 80% of children encounter RSV in the first years of life and RSV reinfections are common.[17,18] Yet, there is little data on the burden of RSV infections in healthy young children in the community.[14,19] Previous studies have been based on hospitalized or medically attended patients,[1,5,7,14,20-23] restricted to children with LRTIs[1,22] or influenza-like illness,[24] or have used serology or virus isolation as diagnostic methods.[8,25] No data are available on RSV infections that are managed at home without a physician visit, but still can cause over-the-counter medication use, absences of the child from day care and the parent from work. As new antivirals and vaccines are developed against RSV, more data are needed on the incidence and clinical manifestations of RSV infections in the community.

To address this knowledge gap, we conducted a prospective population-based birth-cohort study to estimate the rates and investigate the characteristics of RSV infections at 0-24 months of age.

Patients and Methods

Study Design and Conduct

This study was conducted within the prospective, observational birth-cohort study Steps to the Healthy Development and Well-being of Children (the STEPS Study).[26] 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), 1827 were recruited to the STEPS study before or soon after birth without other selection criteria than language. An intensive follow-up of ARIs from birth to 24 months of age of the child was offered to these families, and 923 children were enrolled.[27] The children were followed with daily symptom diaries where parents filled in all respiratory symptoms of the child, physician visits, diagnoses, treatment, and ARI-associated absences from day care or parent from work. The families were encouraged to visit the study clinic during ARIs. At the study clinic, the children were evaluated by a physician. Pneumatic otoscopy and tympanometry were used for diagnosing otitis media. Nasal swab samples for virologic analysis were taken from both nostrils from the depth of 2-3 centimeters by using flocked nylon swabs (Copan, Brescia, Italy). If the parents felt that an evaluation was not needed, or visited physician elsewhere, the parents collected the nasal samples at home at the onset of respiratory symptoms and sent them to the study clinic as previously described.[27,28] Parents were trained to collect nasal samples by the study personnel at the first visit to the study clinic. Data on emergency department visits and hospitalizations of the child including results of virus diagnostics were collected from the electronic medical records of Hospital District of Southwest Finland. Background data was retrieved from the National Birth Registry and by structured questionnaires. Children visited the study clinic at the age of 2, 13, and 24 months. Any current respiratory symptoms were documented and nasal swab specimens were taken by the study personnel.

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. The study complied with the Declaration of Helsinki.

Respiratory Virus Detection

The nasal swab samples were stored at -80°C. The swabs were suspended in phosphate buffered saline and nucleic acids were extracted by NucliSense easyMag (BioMerieux, Boxtel, Netherlands) or MagnaPure 96 (Roche, Penzberg, Germany) automated extractor. Extracted RNA was reverse transcribed and the cDNA was amplified using real-time, quantitative reverse-transcription polymerase chain reaction (RT-PCR) for RSV, rhinovirus, and enteroviruses.[29,30] RT-PCR for influenza A and B viruses was performed for samples collected during influenza seasons.[31] In addition to the RT-PCR tests, a laboratory developed antigen detection test for RSV, influenza A and B viruses, parainfluenza type 1, 2, and 3 viruses, adenovirus, and human metapneumovirus was performed for samples collected in January 2009 or later. Specimens were defined RSV-positive if RSV was detected by RT-PCR or antigen test.

Definitions

An episode of an ARI was defined as the presence of nasal discharge or cough, with or without fever or wheezing, documented in the diary by parents, or as a diagnosis of an ARI by a physician. Episodes were defined separate if there was at least one day without respiratory symptoms in between. In case several nasal samples were collected during continuous respiratory symptoms, the date of a second nasal swab taken more than 14 days from the first one was considered as the first day of a new episode. If the diary data of the symptoms were missing, outpatient visits and hospitalizations for an ARI were linked with the virologic result from one day before through 14 days after the nasal swab collection into an episode of an ARI.

Diagnoses of AOM, wheezing illnesses (bronchiolitis or other wheezing illness), laryngitis, pharyngitis, and pneumonia were performed by a study physician, or recorded into the diary or medical records by a physician at another outpatient office or hospital. Diagnoses were linked to the virus result from a maximum time of 14 days from the nasal sample. Absence of the child from day care or a parent from work because of a child's ARI were analyzed among children in day care at the time of ARI. When calculating days with ARI symptoms associated with RSV infections, the length of an ARI was limited to a maximum of 60 days.

Statistical Analysis

RSV-positive infections were first compared with RSV-negative infections. Then, RSV infections were compared between children 0-11 months and 12-24 months of age. Categorical variables were compared by using the chi-square or Fisher's exact test and continuous variables by using Wilcoxon-Mann-Whitney test. Epidemic RSV seasons were defined as 3 months with the highest incidence of RSV infections each season (2008-2009: March-May; 2009-2010: February-April; 2010-2011: February-April; and 2011-2012: December-February).

The rates of ARIs and RSV-associated outcomes per 100 children were determined using generalized linear models. Overdispersed outcome counts were analyzed by using negative binomial distribution and log link with natural logarithm of follow-up time as an offset variable. For low or non-overdispersed outcome counts, Poisson distribution was used instead. The data were described by using rates and 95% confidence intervals (CI). Binomial distribution with logit link was used to determine the proportion of RSV-positive infections from infections with virus testing. The number of RSV-associated outcomes was estimated as a product of the proportion of RSV infections and all infections. CIs for the product were determined using 500 bootstrap samples. Hospitalization rates were reported only for virologically confirmed RSV infections as virus diagnostics was done for 95% of hospitalizations. We reported P-values as two-tailed, with $P<0.05$

considered statistically significant. The data were analyzed with the use of SPSS software, version 24.0 (IBM SPSS Statistics for Macintosh, Armonk, NY, USA: IBM Corp.), and SAS software for Windows, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Study Population

Data on ARIs were received from 876 (95%) out of 923 children and the median follow-up time was 23.9 (interquartile range [IQR], 16.8-24.0) months. At least one nasal swab sample was obtained from 817 children during an ARI and 7 children were reported to stay healthy throughout the follow-up. Baseline characteristics of the study children are shown in Table 1. Based on the data from National Birth Registry, our study population included more families with first-born children than the general child population.[26] None of the children received palivizumab.

Epidemiology of RSV Infections

A total of 8847 ARIs were documented. A nasal swab specimen was collected during 4728 (53%) ARIs with 70% of the samples being collected at home by the parents. RSV was detected in a total of 289 (6%) ARIs with a nasal sample. In 277 (96%) of the 289 cases RSV was detected by RT-PCR. Antigen test detected 224 of 277 RT-PCR-positive RSV infections (sensitivity 81%). In 12 cases, the diagnosis of RSV infection was based only on an antigen test: in 6 cases RT-PCR was negative and in 6 cases only antigen test was performed. RSV detection rate did not differ between samples collected at the study clinic (6.5%) and at home (5.4%; P=0.16). RSV was detected as a sole pathogen in 262 (91%) cases and with another virus in 27 (9%) cases, most commonly with rhinovirus (n = 25) and twice with human metapneumovirus. Rhinovirus was detected in altogether 2844 (60%), enterovirus in 85 (2%), influenza virus in 53 (1%), and other virus in 142 (3%) ARIs.

The highest incidence in RSV infections occurred between February and May in three winter seasons in 2008-2011, and from December through February in winter 2011-2012 (Figure 1). Altogether 256 (89%) RSV infections were detected during the epidemic seasons defined as 3 months with the highest incidence of RSV infections each season. During these epidemic seasons, RSV was detected in 17% of ARIs, 30% of AOM episodes, 51% of wheezing illnesses, and 44% of pneumonia episodes (eTable 1). Furthermore, during the epidemic seasons, RSV was associated with 25% of physician visits and 35% of hospitalizations for ARI, and 30% of antibiotic treatments for ARIs were prescribed for RSV-positive ARIs.

Characteristics of RSV Infections

RSV-positive infections were more severe than RSV-negative infections (Table 2). Cough, fever, and wheezing were more common in RSV-positive than in RSV-negative infections (all $P<0.001$). RSV infection necessitated the child to stay at home from day care in almost all cases thereby frequently necessitating the absence of the parent from work. Physician visits, hospitalizations, and diagnoses of AOM and antibiotic treatments were more frequent in RSV infections than in RSV-negative infections (all $P\leq0.01$). LRTI was diagnosed during 18% of RSV-infections as compared to 3% of RSV-negative ARIs ($P<0.001$). Of ARIs during which the child was evaluated by a physician, AOM was diagnosed in 90 (44%) RSV infections as compared to 612 (32%) RSV-negative infections ($P=0.001$). Seven children were hospitalized for RSV infection with the mean age of 3.5 (SD, 2.4) months (range 0.8-7.3 months). This is 0.8% of 923 children in the cohort and 2.4% of 289 documented RSV infections. None of the children required intensive care.

The mean age at the first RSV infection was 10.5 (SD, 6.3) months. Of all RSV infections, 29 (10%) occurred before 3 months of age, 45 (16%) at 3-5 months of age, 93 (32%) at 6-11 months of age, and 122 (42%) at 12-24 months of age. Fever was more often documented in children 12-24 months of age with RSV infection than in younger children ($P<0.001$; Table 3).

Wheezing illness was diagnosed more frequently in children 0-11 months of age with RSV infection as compared to children 12-24 months of age (P=0.01).

Burden of RSV Infections

A symptomatic RSV infection was detected at least once in 254 (31%) of 824 children with virology data during the follow-up at 0-24 months of age. An RSV-positive ARI was documented once in 223 (27%) children, twice in 27 (3%) children, and three times in 4 children. The mean interval between recurrent RSV infections was 270 (SD, 161) days.

The rate of detected RSV infections was 21 per 100 children at 0-24 months of age (Table 4). Assuming that the proportion of RSV infections was similar in ARIs not analyzed compared to those analyzed for respiratory viruses, we estimated that the annual rate of RSV infections was 37 per 100 children at 0-24 months of age. Confirmed and estimated rates of RSV infections by age and associated outcomes are shown in Table 4.

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

RSV was detected in 24 (1%) of 2270 nasal samples taken at scheduled study clinic visits at 2, 13, and 24 months of age; in 13 (1%) of 901 children at 2 months, in 4 (0.5%) of 738 children at 13 months, and in 7 (1%) of 631 children at 24 months of age. Among 24 RSV-positive cases, 15 had respiratory symptoms, and 9 were asymptomatic, which is 0.6% of the total of 1609 asymptomatic children at scheduled visits. Among the asymptomatic RSV-positive children, 2 (22%) had had respiratory symptoms within 14 days before sampling and all were asymptomatic during the 7 days following the sampling. There were no respiratory symptoms in the families of asymptomatic RSV-positive children (data available for 8 families).

Discussion

In this prospective, population-based birth-cohort study covering 4 consecutive years and capturing both upper ARIs and LRTIs, RSV infections were associated with substantial morbidity. RSV was detected in 6% of all ARIs resulting in an estimated rate of 37 RSV infections per 100 children per year at 0-24 months of age. The rates of RSV-associated outcomes such as physician visits, diagnoses of acute otitis media, and antibiotic treatments were high, contributing to the disease burden. To our knowledge, this is the largest birth-cohort study investigating the total rates of RSV infections and associated outcomes in young children to date.

In this study, we were able to investigate the burden of all RSV infections, including even non-medically attended cases, in an unselected child cohort. The estimated incidence rate of RSV infections in our study was higher than that in previous studies. In hospital-based or outpatient studies, the incidence rates of medically-attended RSV infections have been 80-171 per 1000 children[5,20] being highest among children <24 months of age.[20] In a prospective study of 2231 children ≤13 years of age followed for a respiratory season and examined at the study clinic at the time of an ARI, Heikkinen and colleagues reported an incidence rate of 275 RSV infections per 1000 children in children <3 years of age.[14] Similarly, Nokes and colleagues reported an incidence estimate of 261 RSV infections per 1000 children per year in a birth-cohort of 635 Kenyan children followed for three RSV epidemics.[19] Differences in the study settings, populations, diagnostic methods, and data analysis may explain the higher estimation of RSV infection rate in our study, which included intensive follow-up with diaries, study clinic visits, home sampling, and review of medical records. The validity of our results is buttressed by the comprehensive follow-up extending over four consecutive years and evening the epidemic variation in circulation of viruses. Our data from this prospective, population-based birth-cohort study corroborate findings from earlier studies

and document the high disease burden caused by RSV infections in healthy children in the community.

We found that RSV infections were by several measures more severe than RSV-negative ARIs, which were mostly caused by rhinovirus. When considering medically attended RSV infections in this study, 44% were diagnosed with AOM, which is consistent with previous studies documenting 47-58% AOM rate during RSV infections.[13,14] Importantly, antibiotics were prescribed during RSV infection in a high rate of 16 per 100 children per year. Bronchiolitis or other wheezing illness was diagnosed frequently, in 17% of RSV infections. Only a minor part of wheezing illnesses would have been captured in a hospital-based study.

Of the child cohort, 1% were hospitalized for RSV infection during the first two years of life. In line with our results, previous studies have documented rates of 3-17 RSV-associated hospitalizations per 1000 children per year, depending on the age of the child.[5,7,19,21,22] Consistent with earlier data,[14] only 2% of children with a documented RSV infection were hospitalized in the present study, highlighting the fact that most RSV infections are treated at outpatient clinics, or even at home without a physician visit. Notably, we found rather stable incidence of RSV infections in different age groups from birth to 24 months while the rate of RSV-associated hospitalizations is highest in infants less than 6 months of age.[5,7]

Serologic studies support our findings on high frequency of RSV infections. According to serologic data, most children encounter RSV in the first years of life.[18] We previously studied RSV infections in a subcohort of 291 children from the STEPS Study using serology, and found that RSV seroprevalence increased from 37% at age 1 year to 68% at age 2 years, and to 86% at age 3 years.[17] The rate of RSV reinfections was at least 37% in children who were seropositive at 1 year of age. Serologic studies detect also asymptomatic infections. However, in line with previous

reports, asymptomatic RSV infections were infrequent in this study and RSV was found by RT-PCR in only 0.6% of asymptomatic children.[32,33]

The current study has potential limitations. First, respiratory viruses were analyzed from nasal swab samples instead of nasopharyngeal samples. Nevertheless, nasal swabs have been shown to offer reliable diagnosis of RSV infection as compared to nasopharyngeal aspirates when using PCR.[34] The collection of nasal swabs is simple and well tolerated for repeated sampling. Second, home nasal swab sampling by the parents was used. Home nasal sampling and mailing of the samples has been found feasible for detection of respiratory viruses in previous studies[27,35] and the RSV detection rate did not differ between samples collected at home and at the study clinic. Importantly, home nasal sampling enabled us to investigate ARIs treated only at home or at other outpatient clinics. Third, as we focused on RSV infections, our methods were not comprehensive for all other respiratory viruses. The proportion of coinfections was low, which may be explained by the healthy study population with mainly non-hospitalized ARIs and lower sensitivity of antigen test used for broader virus testing. However, RSV, rhinovirus, enterovirus and influenza viruses were tested by RT-PCR. Of note, the rate of influenza infections was low, which may be explained by the high influenza vaccination coverage in the study population.[36] Fourth, when estimating rates of RSV infections, we assumed that the viral etiology of ARIs without nasal samples was similar to ARIs with a nasal sample. We have earlier reported the clinical characteristics of ARIs with and without a nasal sample; AOM and pneumonia were equally common in both groups whereas wheezing was more frequent in ARIs with a nasal sample (11%) than in those without a sample (9%).[27] Fifth, separating of ARIs in children with frequent or long-lasting symptoms is challenging. Sixth, our population had more first-born children than the general child population. As older siblings are an important risk factor for ARIs and a source of RSV infection,[37,38] this difference may

have led to underestimation of the rate of RSV infections. Lastly, all findings from this Finnish child cohort cannot be directly generalized to other populations.

Conclusion

In this study, we documented a high disease burden caused by RSV infections in young children in the community. Our findings and the data from previous studies underline the need for safe, effective, and affordable RSV vaccines and antivirals.

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Table 1. Baseline Characteristics and Detected RSV Infections in the Study Children.

Characteristic	Children, No. (%) (n = 923)
Male	488 (52.9)
Premature (gestational age < 37 wk)	38 (4.1)
Older siblings	376 (40.7)
Maternal educational level at least professional	547/892 (64.3)
Living in the urban area	544/895 (60.8)
Breast-fed for at least 6 months	432/716 (60.3)
Maternal smoking during pregnancy or after birth	44/801 (5.5)
Parental smoking at the time of pregnancy or birth	141/818 (17.2)
Maternal physician-diagnosed asthma	70/891 (7.9)
Parental physician-diagnosed asthma	119/896 (13.3)
Atopy at 13 months of age	132/756 (17.5)
At outside-home day care	
At the age of 13 months	185/784 (23.6)
At the age of 18 months	285/685 (41.6)
At the age of 24 months	370/681 (54.3)
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)

RSV infection during the follow-up[b]	254/824 (30.8)
Recurrent RSV infection (≥2)	31/824 (3.8)
RSV-positive AOM	85/824 (10.3)
RSV-positive wheezing illness	50/824 (6.1)
RSV-positive laryngitis	9/824 (1.1)
RSV-positive pneumonia	4/824 (0.5)
RSV-associated physician visit	188/824 (22.8)
RSV-associated hospitalization	7 (0.8)
RSV-associated antibiotic treatment	94/824 (11.4)
Non-medically attended RSV infection	77/824 (9.3)

Abbreviations: RSV, respiratory syncytial virus

[a] Calculated among children 6 months of age or older actively followed up at the beginning of each influenza season.

[b] Calculated among children who provided at least 1 nasal swab or who were reported to stay healthy during their entire follow-up. Data on hospitalizations available for all children.

Table 2. Characteristics of RSV Infections in Children 0 to 24 Months of Age.

Characteristic	Acute Respiratory Infections[a]		*P*
	RSV-Positive (N = 289)	RSV-Negative (N = 4439)	
Age, median (IQR), months	9.8 (5.8-16.0)	11.3 (6.5-16.3)	0.06
Symptoms			
Duration of respiratory symptoms, median (IQR), days	10.0 (8.0, 14.0)	9.0 (6.0, 13.0)	<0.001
Rhinorrhea	262/270 (97.0)	3645/3797 (96.0)	0.40
Cough	257/270 (95.2)	2416/3797 (63.6)	<0.001
Fever ≥38.0°C	170/270 (63.0)	1370/3797 (36.1)	<0.001
Wheezing reported by the parents or a physician	87/270 (32.2)	353/3797 (9.3)	<0.001
Poor appetite	106/233 (45.5)	815/3352 (24.3)	<0.001
Vomiting or diarrhea	58/233 (24.9)	366/3352 (10.9)	<0.001
Outcomes			
Child absent from day care[b]	39/42 (92.9)	342/633 (54.0)	<0.001
Duration of absenteeism from day care, median (IQR), days	3.0 (2.0, 5.0)	1.0 (0.0, 3.0)	<0.001

Parent absent from work because of child's illness[b]	33/42 (78.6)	273/633 (43.1)	<0.001
Duration of absenteeism from work, median (IQR), days	2.0 (1.0, 4.0)	0.0 (0.0, 2.0)	<0.001
Outpatient or emergency department visit	205 (70.9)	1889 (42.6)	<0.001
Hospitalization	7 (2.4)	34 (0.8)	0.01
Hospital length of stay, median (IQR), days	2.0 (1.0, 5.0)	1.0 (1.0, 2.0)	0.05
AOM	90 (31.1)	612 (13.8)	<0.001
Wheezing illness	50 (17.3)	122 (2.7)	<0.001
Laryngitis	9 (3.1)	83 (1.9)	0.14
Pharyngitis or tonsillitis	4 (1.4)	78 (1.8)	0.64
Pneumonia	4 (1.4)	13 (0.3)	0.02
Treatment			
Antibiotic treatment	102 (35.3)	717 (16.2)	<0.001
Systemic corticosteroids	1 (0.3)	38 (0.9)	0.35
Analgesics or antipyretics	168/233 (72.1)	1605/3352 (47.9)	<0.001

Values are No. (%) of acute respiratory infections (ARI) unless otherwise specified. AOM, acute otitis media; IQR, interquartile range; RSV, respiratory syncytial virus.

[a] RSV was detected as a sole pathogen in 262 ARIs and co-detected with rhinovirus (RV) in 25 ARIs and with human metapneumovirus in 2 ARIs. Of the 4439 RSV-negative infections, 2819 (63.5%) were positive for RV, 85 (1.9%) for enterovirus, 76 (1.7%) for parainfluenza virus 1-3, 53 (1.2%) for influenza A or B virus, 46 (1.0%) for human metapneumovirus, and 18 (0.4%) for adenovirus.

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

Table 3. Characteristics of RSV Infections in Children 0 to 24 Months of Age Stratified by Age.[a]

Characteristic	RSV-infections, Age		*P*
	0-11 mo (N = 167)	12-24 mo (N = 122)	
Symptoms			
Duration of respiratory symptoms, median (IQR), days	10.0 (8.0-13.0)	11.0 (9.0-15.0)	0.11
Rhinorrhea	155/159 (97.5)	107/111 (96.4)	0.60
Cough	152/159 (95.6)	105/111 (94.6)	0.71
Fever ≥38.0°C	84/159 (52.8)	86/111 (77.5)	<0.001
Wheezing reported by the parents or a physician	57/159 (35.8)	30/111 (27.0)	0.13
Outcomes			
Outpatient or emergency department visit	120 (71.9)	85 (69.7)	0.69
Hospitalization	7 (4.2)	0 (0)	0.02
AOM	50 (29.9)	40 (32.8)	0.61
Wheezing illness	37 (22.2)	13 (10.7)	0.01
Laryngitis	6 (3.6)	3 (2.5)	0.58
Pneumonia	2 (1.2)	2 (1.6)	0.75
Treatment			
Antibiotic treatment	53 (31.7)	49 (40.2)	0.14
Analgesics or antipyretics	98/144 (68.1)	70/89 (78.7)	0.08

Values are No. (%) of acute respiratory infections (ARI) unless otherwise specified. AOM, acute otitis media; IQR, interquartile range; RSV, respiratory syncytial virus.

[a] RSV was detected as a sole pathogen in 262 ARIs and co-detected with rhinovirus (RV) in 25 ARIs and with metapneumovirus in 2 ARIs.

Table 4. Rates of Confirmed and Estimated RSV Infections and Associated Outcomes.

Variable	**All ARIs**, mean/100 children/y (95% CI)	**Confirmed RSV Infections**, mean/100 children/y (95% CI)	**Proportion of RSV Infections**[a] (95% CI)	**Estimated RSV Infections**,[b] mean/100 children/y (95% CI)
At the age of 0-24 mo	588.1 (569.4-607.5)	20.6 (18.4-23.2)	0.06 (0.05-0.07)	36.6 (35.2-38.1)
At the age of 0-5 mo	393.3 (370.7-417.4)	18.2 (14.5-22.8)	0.07 (0.06-0.09)	28.0 (26.3-30.0)
At the age of 6-11 mo	645.8 (618.6-674.2)	24.2 (19.8-29.7)	0.06 (0.05-0.08)	39.7 (37.9-41.4)
At the age of 12-24 mo	707.0 (681.5-733.6)	20.1 (16.8-24.0)	0.06 (0.05-0.07)	39.6 (37.9-41.6)
Days with symptoms of ARI	5040.2 (4777.9-5316.8)	238.3 (188.7-301.0)	0.08 (0.07-0.10)	443.9 (420.7-466.7)
AOM	94.2 (86.9-102.3)	6.4 (5.2-7.9)	0.13 (0.10-0.16)	12.3 (11.4-13.4)
Wheezing illness	18.8 (15.4-23.0)	3.6 (2.7-4.7)	0.29 (0.22-0.38)	5.5 (4.4-6.6)
Pneumonia	2.4 (1.8-3.4)	0.3 (0.1-0.8)	0.24 (0.09-0.63)	0.6 (0.4-0.8)
Lower respiratory tract infection	21.2 (17.6-25.5)	3.9 (3.0-5.0)	0.29 (0.22-0.37)	6.1 (5.0-7.2)
Antibiotic treatment	123.5 (114.2-133.6)	7.9 (6.5-9.7)	0.13 (0.10-0.15)	15.9 (14.8-17.4)
Outpatient or ER visit	309.5 (291.1-329.1)	19.1 (16.5-22.1)	0.11 (0.10-0.12)	34.4 (32.3-36.6)

Hospitalization	5.9 (4.4-7.9)	0.5 (0.2-1.1)	0.17 (0.08-0.36)	NA
Parent absent from work, days[c]	668.7 (584.4-765.2)	49.2 (29.5-82.1)	0.13 (0.08-0.20)	83.4 (72.4-97.1)

Abbreviations: AOM, acute otitis media; ARI, acute respiratory infection; CI, confidence interval; NA, not applicable; RSV, respiratory syncytial virus.

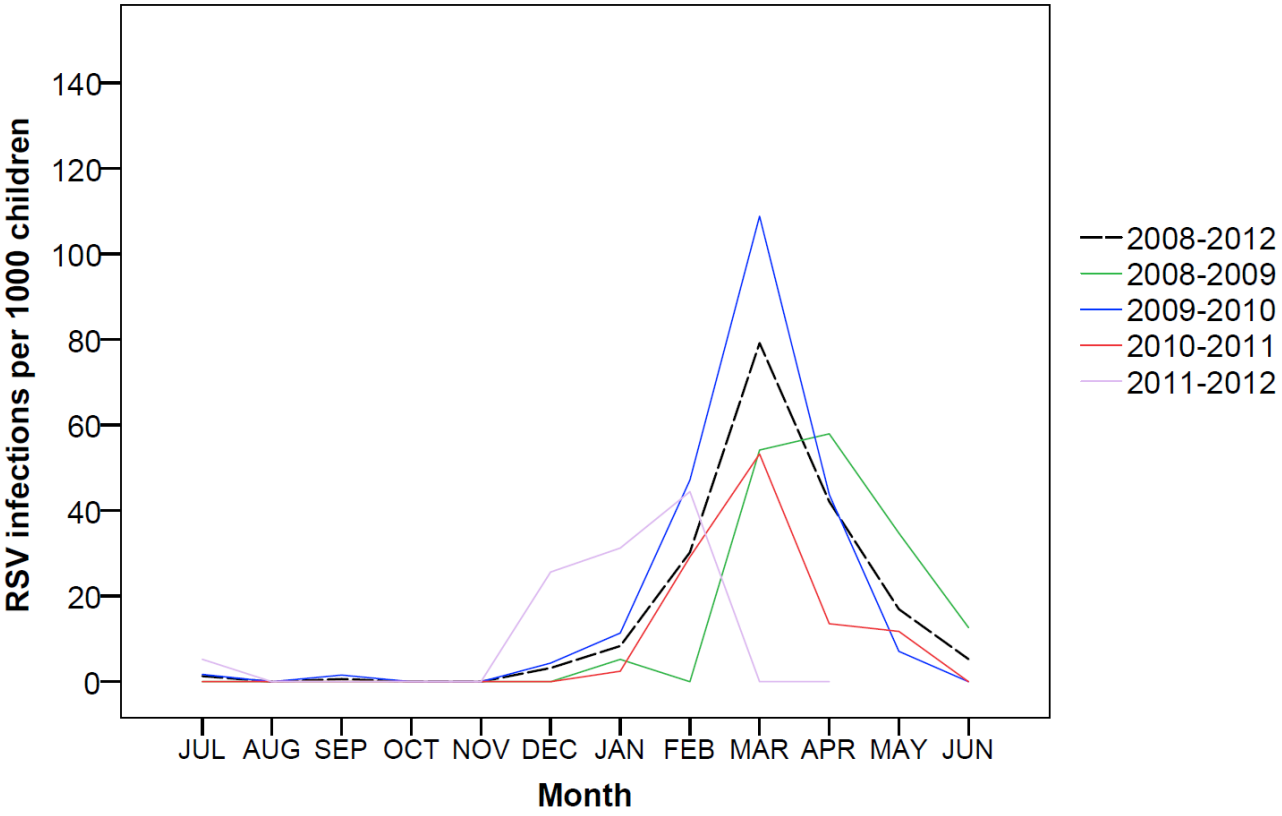
[a] Proportion of RSV infections from ARIs analyzed for viruses.

[b] The estimated number of RSV-associated ARIs was determined as the product of the proportion of confirmed RSV infections and all ARIs. Only confirmed RSV infection rates are given for hospitalizations because 95% of them were analyzed for viruses.

[c] Calculated among children attending outside-home day care from the duration of day care.

Figure legend

Figure 1. Epidemiology of respiratory syncytial virus (RSV) infections during the study period. Monthly distributions of RSV-associated ARIs are shown per 1000 children for each season and as combined from the four-year study period.



ONLINE SUPPLEMENT

Respiratory Syncytial Virus Infections in Children 0-24 Months of Age in the Community

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eTable 1. Proportion of RSV-associated Infections of All Acute Respiratory Infections During the Epidemic Seasons in 2008-2012 in Children 0 to 24 Months of Age.[a]

Characteristic	All ARIs, No.	RSV-Positive, No. (%)
Total No.	1537	256 (16.7)
No. of days child absent from day care	452	125 (27.7)
No of days parent absent from work	305	98 (32.1)
No. of outpatient or emergency department visit	932	236 (25.3)
Hospitalization	17	6 (35.3)
AOM	257	76 (29.6)
Wheezing illness	89	45 (50.6)
Laryngitis	40	9 (22.5)
Pharyngitis or tonsillitis	20	4 (20.0)
Pneumonia	9	4 (44.4)
No. of antibiotic treatments	322	95 (29.5)

AOM, acute otitis media; ARI, acute respiratory infection; RSV, respiratory syncytial virus.

[a] Epidemic seasons were defined as 3 months with the highest incidence of RSV infections each season (2008-2009: March-May, 2009-2010: February-April, 2010-2011: February-April, 2011-2012: December-February).