Seasonality of Respiratory Syncytial Virus-Positive Hospitalizations in Children in Kiel, Germany, over a 7-Year Period

J.A.I. Weigl, W. Puppe, H.-J. Schmitt

Abstract

Background: Elaborate, long-term data on the rhythm, seasonality and severity of the yearly respiratory syncytial virus (RSV) epidemics in Germany are lacking.

Patients and Methods: A longitudinal investigation was undertaken of children from birth to 16 years of age admitted with an RSV infection in the two pediatric hospitals in Kiel between July 1994 and June 2001. To compare the severity of the individual seasons, the incidences and the proportion of RSV-positive hospitalized children aged 0 to 2 years from the denominator area of Kiel were compared.

Results: During the 7-year period, the nasopharyngeal aspirates of 2,367 children were investigated; RSV was detected in 384 (16.2%). The seasons from 1994/95 to 1996/97 started late (December to January) and ended between March and May. Since 1997/98 it seems that a late season is followed by an early season (start in September to October) in a 2-year pattern.

Conclusion: No fixed rhythm of the RSV season can be identified as yet. Ascertainment bias is unlikely to explain the differences in rhythm. The incidence of RSV-positive hospitalizations seems to be increasing.

Key Words

Respiratory syncytial virus · Seasonality · Rhythmicity · Incidence

Infection 2002; 30: 186–192
DOI 10.1007/s15010-002-2159-1

Introduction

Data on the seasonality, rhythm and the severity of the yearly respiratory syncytial virus (RSV) epidemic are important for several reasons: Clinical observations suggest that the yearly incidence of RSV-associated diseases is increasing. Furthermore, a monoclonal antibody preparation (palivizumab, Synagis®, Abbott) for prophylactic intervention is available and was licensed in the United States in October 1998 and in the European Union in September 1999. The prophylactic intervention with palivizumab is, however, costly and requires considerable organizational and logistic effort; the limited half-life of the monoclonal antibody requires monthly vaccination. At present it is unclear whether the seasonal vaccination campaign can be started in a fixed month or whether it has to be altered because of variability in the onset of the season.

The aims of this analysis were: to generate data on the seasonality, rhythm and the severity of the yearly RSV epidemic; to provide data on the stability of the rhythm of the yearly RSV seasons as needed to tailor the intervention with palivizumab to the RSV season; and to generate hypotheses for further research on the epidemiology of RSV in our population.

Patients and Methods

From July 1994 to June 2001, nasopharyngeal aspirates (NPA) of children from birth to 16 years of age hospitalized because of an acute respiratory tract infection (ARI) in the two pediatric hospitals in Kiel (University Children's Hospital or Municipal Hospital) were tested for RSV. From July 1994 to November 1995 the rapid EIA DirectigenTM (Becton Dickinson) was used, thereafter m-RT-PCR as recently described [1, 2]. The nonovalent RT-PCR includes primers for RSV, parainfluenza viruses 1 and 3, influenza virus A and B, adenovirus, enterovirus, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. Analysis of RSV subtypes (groups A and B) and genotypes has not yet been completed. As the case ascertainment was over 60% after July 1996, detailed analysis is provided for the period July 1996 to June 2001. Nosocomial transmission was presumed when the reason for hospitalization was not an ARI or an ARI-related symptom and the ARI infection was diagnosed later than 72 h after admission. For illustration of seasonality and rhythm, all cases from the catchment area of the two hospitals (Kiel all), irrespective of the place of residence, were included. The absolute number of NPAs and the number of RSV-positive hospitalizations independent of the place of residence were plotted per month. To compare different seasons, the unit "epidemiological year," i.e. the

J.A.I. Weigl *(corresponding author)*, **W. Puppe**
Pediatric Infectious Diseases, University Children's Hospital, Schwanenweg 20, D-24105 Kiel, Germany; Phone (+49/431) 597-1678, Fax: -1680, e-mail: weigl@pediatrics.uni-kiel.de
H.-J. Schmitt
Pediatric Infectious Diseases, Center for Preventive Pediatrics, University Children's Hospital Mainz, Germany

Received: November 14, 2001 • Revision accepted: March 15, 2002

period from July to June the following year, was used. The recruitment area for ARI patients was constant over the time interval under observation. To avoid a biased perception of severity and trend over time, cumulative incidences and cumulative incidence ratios taking a certain time period as reference were calculated for the denominator area Kiel ("Kiel") [3]. Children of the denominator area "Kiel" consisting of Kiel itself, Kronshagen and Ottendorf, two suburbs, would be admitted exclusively to the two local hospitals and therefore form a population-based fraction of all cases admitted to the two local hospitals. To test the hypothesis whether a shift to older children occurs in late-starting (low) seasons [3], the proportions between the age-group 0–2 years and > 2–5 years were compared. Children are assumed to have their primary contact with the virus in the first 2 years of life and a shift to older age-groups would mainly be a shift out of the age-group 0–2 years [4–7].

Statistics

For calculation of incidences, only cases with a community-acquired infection from the geographical area "Kiel" were included [3]. For calculation of the denominators, population data for Schleswig-Holstein from 1997 were used [3, 8]. The data were stored in a MS Access data base and analyzed by SPSS version 10. The χ^2-test for 2×2 tables, 1 degree of freedom, and Fisher's exact test in case of low cell counts were applied for comparison between different epidemiologic years.

Results

In the study period from July 1994 to June 2001, which included seven RSV seasons, NPAs of 2,367 children were tested and 384 (16.2%) were diagnosed positive for RSV. From July 1994 to November 1995 the NPAs of 139 children were tested by EIA; 19 (13.7%) were positive. From December 1995 to June 1996 the NPAs of 120 patients were tested by m-RT-PCR, rendering 17 (14.2%) positive results. In the time period from July 1996 to June 2001, the time period of detailed analysis, 3,469 children were admitted with an ARI in the two hospitals. The NPAs of 2,108 children were tested by m-RT-PCR, generating 348 (16.6%) RSV-positive results.

Descriptive Data and Case Ascertainment

Table 1 shows the age distribution of all ascertained cases independent of residency. The median age in ARI cases in general was 522 days (mean 1,001, range 0–5,809). In contrast, the median age of RSV-positive cases was 199 days (mean 373, range 12–4,958). The age-group-specific case ascertainment rate was highest in the youngest age-group (0–3 months) with 82.5% and declined in the group > 2–5 years, when it leveled off to 53.7%. Detailed data on children 0–2 years of age for the different epidemic years are presented in table 2. The

Table 1
Age distribution of RSV-positive hospitalized children in Kiel between July 1996 and June 2001 and tested by m-RT-PCR.

Age-group	RSV positive cases	% of total RSV positives	No. of ARI patients tested by PCR	% RSV-positive of total tested by PCR	Total no. hospitalized with ARI	Age-specific case ascertainment rate
0–3 months	106[a]	(30.5)	349	(30.4)	423	82.5
> 3–12 months	140	(40.2)	524	(26.9)	780	67.2
> 1–2 years	51	(14.7)	383	(13.3)	668	57.3
> 2–5 years	41	(11.8)	451	(9.1)	851	53.0
> 5–16 years	10	(2.9)	401	(2.5)	747	53.7
Total	348	(100)	2,108	(16.6)	3,469	60.5

[a] 22 cases (6.3%) were less than 1 month old; RSV: respiratory syncytial virus; ARI: acute respiratory tract infection

Table 2
Ascertainment in children under 2 years of age hospitalized with community-acquired ARI per epidemic year.

1	2	3	4	5	6
Epidemic year	RSV-positive cases "Kiel" (% col. 2 : col. 4) {% col. 2 : col. 3}	RSV-positive cases "Kiel all" (positive rate % col. 3 : col. 4)	No. of cases tested by PCR "Kiel all"	ARI cases total	Case ascertainment rate (% col. 4 : col. 5)
2000/2001	68 (22.8) {63.0}	108 (36.2)	298	410	72.7
1999/2000	38 (14.4) {69.1}	55 (20.8)	264	425	62.1
1998/1999	29 (11.5) {69.1}	42 (16.7)	252	349	72.2
1997/1998	18 (8.0) {72.0}	25 (11.2)	224	322	69.6
1996/1997	33 (15.1) {70.2}	47 (21.6)	218	365	59.7
Total/average	186 (14.8) {67.1}	277 (22.2)	1,256	1,871	67.1

RSV: respiratory syncytial virus; ARI: acute respiratory tract infection; col.: column; "Kiel": denominator area Kiel

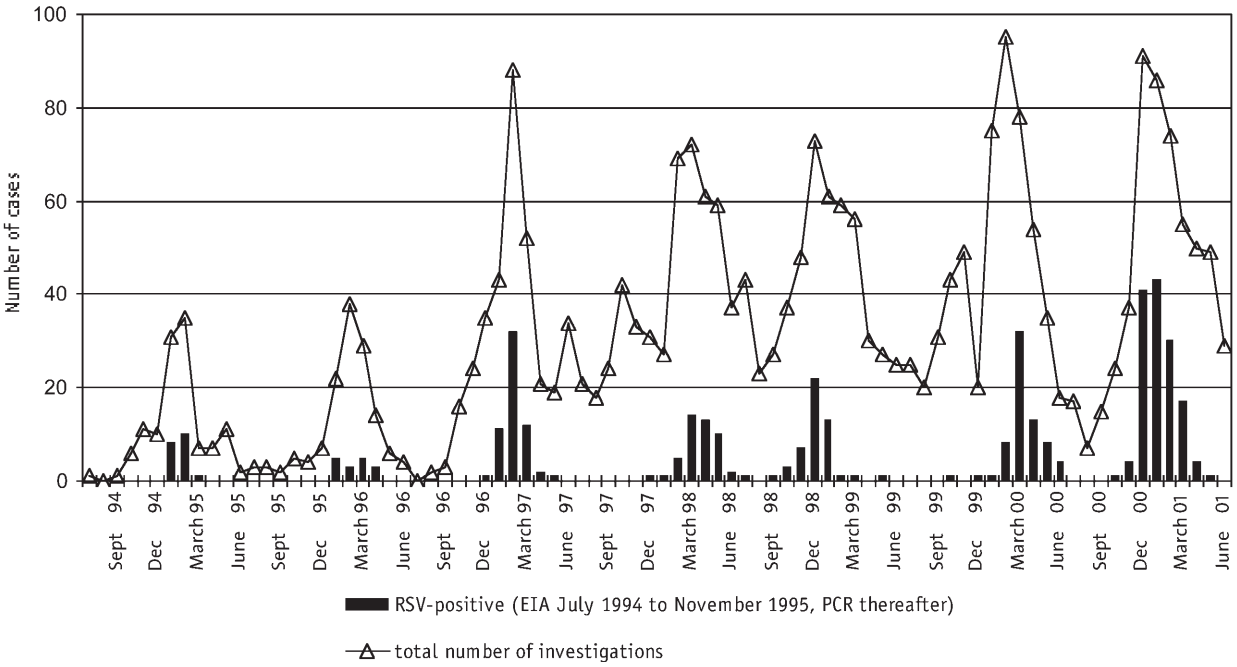

Figure 1. Number of hospitalized cases in whom nasopharyngeal aspirates were investigated and RSV-positive in Kiel per month from July 1994 to June 2001.

columns defined are used throughout the tables. These data provide the basis for the analysis of the intensity of the epidemics. The case ascertainment rate per epidemiological year was between 59.7–72.7% (Table 2, column 6) giving a range of 13%. The rate of positive results by the nonovalent RT-PCR (columns 2 and 3) increased steadily. The percentage of RSV-positive cases residing in the denominator area "Kiel" as a fraction of all RSV-positive hospitalizations was more or less constant over the years with an average of 67% (Table 2, column 2). The average rate of nosocomial transmission was 6.3%: 7.6% in 1996/97, 14.3% in 1997/98, 1.3% in 1998/99, 3.8% in 1999/2000 and 7.2% in 2000/01.

Seasonality and Rhythm of RSV-Positive Hospitalizations

Figure 1 gives the seasonal distribution of children admitted with an ARI tested by m-RT-PCR and RSV-positive results by month in a longitudinal analysis. The RSV season started between the end of September and January and ended between March and July, lasting 5–7 months per year. From 1997/98 onwards, a 2-year pattern with a late season starting between December and February followed by an early season starting in September to October was observed. Taking data from 1994 onwards into consideration the season regularly started late until 1998/99.

Table 3
Cumulative incidence of RSV-positive hospitalizations of different epidemiological years.

Age-group (in years)	0–1		> 1–2		0–2		> 2–5		0–16	
Denominator	2,830		2,830		5,660		7,745		43,895	
Epidemiological year	N (n)	i	N (n)	i	N (n)	i	N (n)	i	(N) n	i
2000/2001	77 (58)	2,721	13 (10)	459	90 (68)	1,590	14 (8)	181	108 (78)	246
1999/2000	52 (32)	1,837	10 (6)	353	62 (38)	1,095	10 (5)	129	72 (43)	164
1998/1999	32 (23)	1,131	10 (6)	353	42 (29)	742	3 (2)	39	47 (32)	107
1997/1998	24 (17)	848	1 (1)	35	25 (18)	442	13 (7)	168	38 (25)	87
1996/1997	45 (27)	1,590	10 (6)	353	55 (33)	972	5 (2)	65	60 (35)	137
Total/average	230 (157)	1,625	44 (29)	311	274 (186)	933	50 (24)	116	373 (213)	148

Numerator (N) and incidence (i) per 100,000 corrected by age-group and year-specific case ascertainment rate (crude numerator, n);
[a] denominator

Severity of RSV Epidemics

The calculated age-dependant cumulative incidences of the 5 epidemic years 1996/97 to 2000/01 are presented in table 3. In the age-group 0–2 years 186 children (crude data) admitted with a community-acquired RSV infection from the denominator area "Kiel" are included. Adapting the figures by the year and age-group-specific case ascertainment rate (for children under 2 years see table 2, column 6) the total number rose to 274. After the trough of 1997/98 (442/10^5, 0.44%), the cumulative incidence rose steadily to 1,590/10^5 (1.59%) in the year 2000/01. The incidence of the year 1996/97 was only reached again in the 1999/2000 epidemic.

The hypothesis that a shift to older children occurs regularly in the late (low) epidemiological years has to be rejected as only the 1997/98 year showed a significant shift to older children ($p = 0.001$, in comparison to 1998/99 $p = 0.002$, Table 4). Because of this very strong significance the difference between the late and early pool was also significant ($p = 0.037$).

The intensities of the individual epidemiological years were compared by the cumulative incidences (population-based analysis) of RSV-positive children 0–2 years and the proportions between RSV-positive and all ARI hospitalized children under 2 years of age (Table 5). Taking 1996/97 as a reference, the season 1997/98 was significantly less severe ($p = 0.003$). Thereafter, a continuous rise in cumulative incidence occurred. The cumulative incidence ratio (1.64) proves the season 2000/01 to be the most severe so far ($p = 0.014$).

The late-starting epidemiological year to the following early-starting epidemiological year was compared for the 2-year cycles 1997/1998 versus 1998/1999 and 1999/2000 versus 2000/01 in a second step. This shows that the early-starting epidemic years had a higher incidence than the late-starting years ($p = 0.065$ and 0.006, respectively). In a third step the two late (low) seasons (1997/98 and 1999/00) and the two early (high) seasons (1998/99 and 2000/01) were pooled. The early season pool was 1.52 times more intense than the late season pool ($p = 0.002$).

The pooled 2-year packs of 1997–1999 and 1999–2001 were compared in a fourth step. The recent two-year pack (1999–2001) was 2.27 times as strong as the previous one ($p < 0.001$). This, together with the latest season being the most intense so far, confirms the impression that the incidence of RSV-positive hospitalization is increasing.

Discussion

Descriptive Data and Ascertainment

It should be mentioned here that ascertainment of NPA from eligible patients was completely dependent upon the compliance of the ward teams to which the patient was admitted as no study or research nurses were available.

The age distribution of cases in this study was as commonly expected [7]. The median age in RSV-positive children was considerably younger than in ARI in general. The younger the patients, the higher the case ascertainment rate. This may be due to the fact that clinicians expect a higher diagnostic output of viral diagnoses in younger children.

Table 4
Shift in proportions of age-group 0–2 years versus > 2–5 years between epidemiologiological years.

Age-group Epidemiological year	0–2 years no.	> 2–5 years no.	Incidence in 0–2 year relative to season year 1996/97	χ^2-test for 0–2 and > 2–5 year group	P-values
2000/2001	90	14	1.64	0.977	0.323
1999/2000	62	10	1.13	1.003	0.317
1998/1999	42	3	0.76	0.101	1.000
1997/1998	25	13	0.45	10.390	0.001
1996/1997	55	5	ref.	ref.	ref.
Late vs early					
2000/2001	90	14	1.45	0.007	0.935
1999/2000	62	10	ref.	ref.	ref.
1998/1999	42	3	1.68	10.045	0.002
1997/1998	25	13	ref.	ref.	ref.
Late vs early					
98/99+00/01	132	17	1.52	4.373	0.037
97/98+99/00	87	23	ref.	ref.	ref.
2-year packs					
1999–2001	152	24	2.27	1.374	0.241
1997–1999	67	16	ref.	ref.	ref.

Numbers corrected by age-group and year-specific case ascertainment rate

The fraction of positive results for at least one of the seven viruses in the nonovalent multiplex RT-PCR was significantly higher in children under 5 years than in older ones [2] and increased in younger patients.

The year-specific case ascertainment varied between 59.7–72.7%, with no trend after 1998/99. Different alertness or compliance of the referring ward teams is one possible explanation. 60–73% is, however, a realistic case ascertainment rate in settings in Germany where no study nurses are available (*J. Forster* personal communication). The recruitment area of the two hospitals for ARI patients was constant over the time period; likewise, the fraction of RSV-positive cases in the denominator area "Kiel" versus "Kiel all." On the other hand, the positive rate (i.e. the percentage RSV-positive to total number of patients tested) rose continuously. This could be explained by a true increase and/or a learning effect to predict RSV etiology clinically, which would mean that there has to be a more specific constellation of signs and symptoms which makes the clinical teams think of RSV as the pathogen involved. That there was a true increase could be proven by the comparison of the cumulative incidence (population-based analysis) between epidemiological years and between the 2-year cycles. To make up for different rates of samples sent for PCR testing, the numbers were corrected by the year and age-specific ascertainment rate. However, this did not alter the message and conclusions to be drawn from the crude cumulative incidence rates and for the sake of precision we preferred to use the corrected rates.

Laboratory Investigations

As widely accepted, PCR techniques are superior to EIA with regard to sensitivity and specificity [7, 9]. The overall positive rate of 13.7% for the EIA between July 1994 and November 1995 was, however, very similar to the 14.2% and the 16.6% for the periods when m-RT-PCR was used. As the nonavalent RT-PCR had to be developed, it only could be applied from December 1995 onwards. It was validated for RSV against the diagnostic outcome of culture on A549 and MDCK cell lines plus immunfluorescence in collaboration with the Department of Virology of the Erasmus University Rotterdam (unpublished data). The kappa statistic of 93% agreement was excellent according to the criteria of *Byrt* [10]. In 1998/99 a strain of RSV occurred with a mutation in the detection probe binding site within the genome of the F1 subunit of the fusion protein. The probe used so far could therefore not specify the amplicon seen on the gel; only the addition of a second probe resolved the problem [3]. This phenomenon, however, cannot be the reason for the low incidence of the earlier 1997/98 season because it occurred afterwards. As no protocol alterations were introduced and the laboratory team was ba-

Table 5
Comparison of cumulative incidences of RSV-positive hospitalizations between epidemiological years, cycles, patterns and trends in children under 2 years of age.

1	2	4	6	7	8	9
Epidemiological year	**RSV-positive cases "Kiel" crude**	**Total number of ARI cases**	**Cumulative incidence**	**Cumulative incidence ratio relative to ref.**	**χ^2-test col. 2 vs col. 4**	**P-values**
2000/2001	90	410	1,590	1.64	6.014	0.014
1999/2000	62	425	1,095	1.13	0.036	0.850
1998/1999	42	349	742	0.76	1.399	0.237
1997/1998	25	322	442	0.45	8.872	0.003
1996/1997	55	365	972	ref.	ref.	ref.
Late vs early						
2000/2001	90	410	1,590	1.45	7.598	0.006
1999/2000	62	425	1,095	ref.	ref.	ref.
1998/1999	42	349	742	1.68	3.398	0.065
1997/1998	25	322	442	ref.	ref.	ref.
Late vs early pool						
98/99+00/01	132	759	1,166[a]	1.52	9.998	0.002
97/98+99/00	87	747	769	ref.	ref.	ref.
2-year packs						
1999–2001	152	835	1,343[a]	2.27	20.221	0.000
1997–1999	67	671	592	ref.	ref.	ref.

[a] average; RSV: respiratory syncytial virus; col.: column; ref.: reference

sically the same over the investigated time period, the diagnostic technique is an unlikely reason for variation of the incidences.

Seasonality and Rhythm

Studies so far reported in the literature give a divergent view of the stability of the rhythm of the RSV season. Some studies from the US state a more or less constant time of the start of the yearly RSV epidemic in November/December [11, 12]. Most other investigators, however, found considerable variability in the time of onset of the outbreak. It mainly begins in the winter months, but can start even as late as April [13] or even summer [14]. *Waris* [15] published the longest longitudinal series (10 years) to date, demonstrating a weaker late season (starting in December/January) followed by a more severe early season in a regular 2-year cyclic pattern in Finland. *Lyon* et al. [16] confirmed this 2-year cyclic pattern in the state of Utah. The 2-year cycle could only be detected in our population from 1997/98 onwards. The low total number of NPAs tested before 1996 and therefore the possibility of missed cases, however, seem an unlikely explanation for an ascertainment bias as a reason that this pattern was not detected before 1997. It appears that the RSV season started regularly in January from 1994 to 1997/98 and a change in the rhythm occurred between 1996 and 1999 in our population. Why this happened can only be speculated. Most likely an as yet unknown factor contributed to this event.

Severity and Trend

The intensity of the epidemic years after 1996/97 increased as shown by the incidence rates. In the literature, circulation of a varying number of group A and group B genetic subtypes with up to six variants of RSV contributing to one season are considered responsible for this [17–19]. Studies from Denmark emphasize host factors and herd immunity in contrast to the variation of the virus itself [20, 21].

Furthermore, our data also demonstrate a trend of increasing incidence and intensity of the RSV seasons since 1997/98. This finding has to be treated with caution, however, as further underlying longer year cycles (more than 2 years) could be present as indicated by the 1996/97 year. This suspicion can only be clarified if the surveillance of the same population is continued for many more years to come. Time series analyses of long-term data bases have to be conducted for this purpose. It appears that the clinical observation that wheezing airway conditions, either pneumonia with wheezing or wheezing bronchitis (including bronchiolitis) are on the increase, is valid. This observation cannot be explained by ascertainment bias, variation of the diagnostic technique or the rate of nosocomial transmission.

Environmental pollution, as found in studies from the UK [22], and climatic factors [23, 24] can have an influence on the rhythm and severity beyond just viral and host factors. For the suspected underlying long-term cycle or even a true continuous upward trend of the population-based incidence of RSV-positive hospitalization, an as yet unknown factor is likely to be of major importance. If children still have their first contact with the virus in the first 2 years of life, as postulated earlier [4–6], a rise in RSV-positive hospitalizations would mean that children today fall victim to a more severe course of RSV-related disease in higher numbers than in earlier years. The proportion of children who are admitted with RSV after 2 years of age is about 15% in our population; therefore the major toll is still paid by very young infants.

Conclusion

The start, end, duration and intensity of the yearly RSV seasons in terms of RSV-positive hospitalizations show considerable variation. The 2-year pattern with a late season followed by an early season is a recent phenomenon in our population. The late season is regularly less severe in contrast to the following early season. Only by means of a population-based analysis can differences in the severity of the yearly epidemics be assured. The incidence of RSV-positive hospitalizations and therefore the severity of the yearly RSV epidemics seem to be on the increase.

Extensive longitudinal series on the same population have to be generated to investigate long-term trends and to elucidate the so far unknown factors influencing the dynamics of the evolving epidemiology of RSV in young children in Germany. Molecular epidemiological investigations and studies outside the hospital are urgently warranted to narrow down the fields contributing to RSV-related disease.

Epidemiological surveillance is crucial to focus and tailor the use of palivizumab according to the duration of the epidemic. Vaccinees should not be put at risk of infection by a premature end of the seasonal vaccination campaign according to a rigid 4-month interval starting in a fixed month in autumn/winter. In this way the efficiency of this prophylactic approach can be increased and costs saved.

Health-care systems which use or plan to use costly interventions like passive immunization have to establish epidemiological early warning and surveillance systems to know when to start passive immunization and for how long to continue it. Criteria for decision making in this regard are urgently needed. In this way expenditure for epidemiological work should pay off.

Acknowledgments

We appreciate the help of our coworkers B. Reckewitz, S. Rockahr, O. Belke, J. Neusüß and F. Bagci. We thank Dr. von Klinggräff, Head of the Pediatric Department, Municipal Hospital, Kiel, for his cooperation and Dr. A. Sewell for the revision of the manuscript.

This work was supported by the grant (01KI9910/1) for "PID-ARI-Net," a pediatric infectious diseases network on acute respiratory tract infections, awarded by the Bundesministerium für Forschung (BMBF) via the Deutsches Zentrum für Luft- und Raumfahrt e.V.

References

1. Gröndahl B, Puppe W, Hoppe A, Kühne I, Weigl JAI, Schmitt H-J: Rapid identification of nine microorganisms causing acute respiratory tract infections by single-tube multiplex reverse transcription-PCR: feasibility study. J Clin Microbiol 1999; 37: 1–7.
2. Weigl JAI, Puppe W, Gröndahl B, Schmitt H-J: Epidemiological investigation of nine respiratory pathogens in hospitalized children in Germany using multiplex reverse-transcriptase polymerase chain reaction. Eur J Clin Microbiol Infect Dis 2000; 19: 336–343.
3. Weigl JAI, Puppe W, Schmitt H-J: The incidence of respiratory syncytial virus-associated hospitalisation in Germany. Eur J Clin Microbiol Infect Dis 2001; 20: 452–459.
4. Parrott RH, Kim WH, Arrobio JO, Hodes DS, Murphy BR, Brandt CD, Camargo E, Chanock RM: Epidemiology of respiratory syncytial virus infection in Washington, D.C. II. Infection and disease with respect to age, immunologic status, race and sex. Am J Epidemiol 1973; 98: 289–300.
5. Glezen WP, Paredes A, Allison JE, Taber LH, Frank AL: Risk of respiratory syncytial virus for infants from low-income families in relationship to age, sex, ethic group, and maternal antibody level. J Pediatr 1981; 98: 708–715.
6. Holberg CJ, Wright AL, Martinez FD, Ray CG, Taussig LM, Lebowitz MD: Risk factors for respiratory syncytial virus-associated lower respiratory illnesses in the first year of life. Am J Epidemiol 1991; 133: 1135–1151.
7. Hall CB: Respiratory Syncytial Virus. In: Mandell GL, Bennett JE, Dolin R (eds): Mandell, Douglas and Bennett's principles and practice of infectious diseases. Churchill Livingstone, Philadelphia 2000, pp 2084–2111.
8. Ministerium für Arbeit, Gesundheit und Soziales des Landes Schleswig-Holstein: Zur Gesundheitslage der Kinder in Schleswig-Holstein – Daten, Einschätzungen, Fragen. b+c computergraphik, Kiel 1997, pp 3–4.
9. Tristram DA, Welliver RC: Respiratory syncytial virus. In: Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH (eds): Manual of clinical microbiology. American Society for Microbiology, Washington DC 1999, pp 942–950.
10. Byrt T: How good is that agreement ? (Letter to the editor) Epidemiology 1996; 7: 561.
11. Hendry RM, Pierik LT, McIntosh K: Prevalence of respiratory syncytial virus subgroups over six consecutive outbreaks: 1981-1987. J Infect Dis 1989; 160: 185–190.
12. Gilchrist S, Török TJ, Gary Jr HE, Alexander JP, Anderson LJ: National surveillance for respirators syncytial virus, United States, 1985-1990. J Infect Dis 1994: 170: 986–990.
13. Ørstavik I, Grandien M, Halonen P,Arstila P, Mordhorst CH, Hornsleth A, Popow-Kraupp T, McQuillin J, Gardner PS, Almeida J, Bricout F, Marques A: Viral diagnoses using the rapid immunfluorescence technique and epidemiological implications of acute respiratory infections among children in different European countries. Bull WHO 1984; 62: 307–313.
14. Halstead D, Jenkins SG: Continuous non-seasonal epidemic of respiratory syncytial virus infection in the Southeast United States. South Med J 1998; 91: 433–436.
15. Waris M: Pattern of respiratory syncytial virus epidemics in Finland: two-year cycles with alternating prevalence of groups A and B. J Infect Dis 1991; 163: 464–469.
16. Lyon Jl, Stoddard G, Ferguson D, Caravati M, Kaczarek A, Thompson G, Hegmann K, Hegmann C: An every other year cyclic epidemic of infants hospitalized with respiratory syncytial virus. Pediatrics 1996; 97: 152–153.
17. Cane PA, Pringle CR: Molecular epidemiology of human respiratory syncytial virus. Semin Virol 1995; 6: 371–378.
18. Walsh EE, McConnchie KM, Long CE, Hall CB: Severity of respiratory syncytial virus infection is related to virus strain. J Infect Dis 1997; 175: 814–820.
19. Lukic-Grlic A, Cane PA, Bace A, Mlinaric-Galinovic G, Popow-Kraupp T: Antigenic and genomic diversity of central European respiratory syncytial virus strains. Arch Virol 1998; 143: 1441–1447.
20. Christensen LS, Larsen LB, Johansen J, Andersen EA, Klug WB, Hornsleth A: The fluctuating pattern of various genome types of respiratory syncytial virus in Copenhagen and some other locations in Denmark. APMIS 1999; 107: 843–850.
21. Johansen J, Christensen LS, Hornsleth A, Klug B, Hansen KS, Nir M: Restriction pattern variability of respiratory syncytial virus during three consecutive epidemics in Denmark. APMIS 1997; 105: 303–308.
22. Martin AJ, Gardner PS, McQuillin J: Epidemiology of respiratory viral infection among pediatric inpatients over a six-year period in North-East England. Lancet 1978; 2: 1035–1038.
23. Ørstavik I, Carlsen K-H, Halvorsen K: Respiratory syncytial virus infections in Oslo 1972-1978. I. Virological and epidemiological studies. Acta Paediatr Scand 1980; 69: 717–722.
24. Florman AL, McLean LC: The effect of altitude and weather on the occurrence of outbreaks of respiratory syncytial virus infections. J Infect Dis 1988; 158: 1401–1402.