Two-Year Periodicity of Respiratory Syncytial Virus Epidemics in Switzerland

A. Duppenthaler, M. Gorgievski-Hrisoho, U. Frey, C. Aebi

Abstract

Background: The annual respiratory syncytial virus (RSV) epidemics vary in time and severity. The aims of this study were (1) to describe the time-related pattern of RSV epidemics in Switzerland and (2) to deduce the most effective time period for administration of prophylactic measures to high-risk patients.

Patients and Methods: Descriptive study of (1) RSV hospitalizations between 1997 and 2001 at a pediatric hospital serving a population of 1 million and (2) of national RSV detection rates reported by diagnostic laboratories between 1988 and 1999.

Results: 497 RSV hospitalizations and 8,574 reported RSV detections occurring during four and 12 epidemics, respectively, were analyzed. There was fixed alternation of minor and major epidemics differing in the number of RSV infections (two to fourfold), evolution (median interval from onset to peak 13 weeks, range 4–13 weeks vs 8 weeks, range 7–10 weeks; p = 0.065) and median duration (26 weeks, range 24–29 weeks vs 19.5 weeks, range 18–21 weeks; p = 0.005). For minor epidemics it was estimated that a maximum of 85.6% (range, 79.4–86.6%) of annual RSV infections could be covered by a standard five-dose regimen of the monoclonal anti-RSV antibody palivizumab, if initiated in week 50. During major epidemics the most effective time of initiation would be week 43 (88.7%; range 81.9–94.6%).

Conclusion: RSV epidemiology in Switzerland is characterized by fixed biannual variation. In the absence of active RSV surveillance, such periodicity is useful for scheduling RSV prophylaxis and for hospital resources management.

Infection 2003; 31: 75–80
DOI 10.1007/s15010-002-3124-8

Introduction

Respiratory syncytial virus (RSV) is the leading cause of acute lower respiratory tract infections in infants [1]. Up to 70% of children are infected during the 1st year of life [2], 1–2% of the annual birth cohort are hospitalized because of RSV infection [3, 4] and a causative role of RSV in respiratory long-term morbidity is debated [5]. Host factors associated with increased RSV hospitalization rates include prematurity ≤ 35 weeks of gestation [2, 6] and chronic lung disease [2, 6]. In absolute numbers, however, the vast majority of severe RSV infections requiring hospitalization occur in previously healthy infants born at term [4]. While antiviral drugs and vaccines for active immunization are not currently available, passive immunization using the humanized monoclonal antibody palivizumab is efficacious in reducing RSV hospitalization rates in these two risk groups [7]. Palivizumab has recently been approved in several countries for RSV prophylaxis in certain risk groups [8], but in many parts its routine use remains controversial [4, 9, 10] because of unfavorable cost-effectiveness, and because the approved eligibility criteria may not accurately target infants at greatest risk for severe RSV infection [4, 11].

A means of both economizing and optimizing the use of palivizumab would be to administer it precisely during the annual RSV epidemic. Such a strategy implies that both onset and duration of each RSV season are predictable. Because of considerable year-to-year variability, the time-related course of RSV epidemics has been studied extensively. While some investigators did not observe predictable periodicity [12–15], others found cyclic patterns for the duration of peak-to-peak intervals, RSV detection and hospitalization rates and for the prevalence of RSV subtypes [16–22].

A regional survey of RSV hospitalization rates in Bern, Switzerland [4], (Figure1), was reminiscent of the 2-year periodicity described in Scandinavia [16–19]. The purpose of this study was to extend these observations in an attempt to search for a pattern of long-term periodicity of RSV epidemiology for use in clinical practice.

Andrea Duppenthaler, U. Frey, C Aebi *(corresponding author)*
Dept. of Pediatrics, University of Bern, Inselspital, CH-3010 Bern, Switzerland; Phone : (+41/31) 632-9487, Fax: -9468, e-mail: christoph.aebi@insel.ch
Meri Gorgievski-Hrisoho
Institute for Infectious Diseases, University of Bern, CH-3010 Bern, Switzerland

Received: July 15, 2002 • Revision accepted: December 1, 2002

Patients and Methods

Local RSV Surveillance

In an ongoing RSV surveillance program at the University Children's Hospital of Bern all cases of RSV infection occurring between July 1, 1997 and June 30, 2001 were evaluated. This institution provides inpatient pediatric care for a population of 1 million including an annual birth cohort of 10,000. Emergency department guidelines require that all children less than 5 years of age who are admitted with clinical manifestations compatible with RSV infection (i.e. rhinorrhea, tachypnea, signs of airway obstruction, apnea or supplemental oxygen requirement) undergo testing for RSV irrespective of the season of the year. Nasopharyngeal secretions were sampled using a Vygon® infant mucus aspirator (Ecouen, France) [4]. RSV was detected by direct immunofluorescence (Light Diagnostics® Respiratory Panel DFA, Chemicon International, Inc., Temecula, CA). A negative RSV test was repeated once if clinical suspicion persisted. Patients who first tested positive for RSV more than 72 h after admission were excluded.

National RSV Surveillance

From January 1, 1988 to March 31, 1999, detection of RSV was a nationally reportable event. During this period of time the Federal Office of Public Health required all diagnostic laboratories to report positive RSV test results from both inpatients and outpatients on a weekly basis.

Analysis of National Data

A year was defined as the period of time extending from week 27 to week 26 of the following year. Weekly rates of RSV detection are given as moving average of 3 consecutive weeks. For quantitative comparison of epidemics, the proportion (%) of the total annual number of RSV detections reported in a given week was defined as the relative RSV detection rate. Onset and end of an epidemic were arbitrarily defined using a threshold relative RSV detection rate of 1%. Data on individual epidemics of a given type (i.e. minor or major) were merged into a representative curve by determining the mean, maximum and minimum of relative RSV detection rates for each weak. For calculating the optimum time of onset of RSV prophylaxis with palivizumab the following assumptions were made. Prophylaxis was assumed to consist of five injections given at monthly intervals and providing protection for 22 weeks. Based on mean relative RSV detection rates, the 22-week period covering the largest proportion of the total annual number of RSV detections was calculated by moving a 22-week window across the 52-week period and by determining the time point at which the 22-week sum of weekly RSV detection rates was largest.

Statistics

StatView® version 5.0 (SAS Institute, Inc., Cary, NC) was used.

The two-sided Mann-Whitney U-test was used to compare distributions of independent samples. Proportions were compared by the χ^2-test with Yates's correction or Fisher's exact test. Trends in the total number of annual RSV detections were calculated by linear regression analysis and compared by analysis of variance (ANOVA). Results were considered significant if the p-value was < 0.05.

Results

Local RSV Epidemiology

During the four-season study period, 497 children were hospitalized with RSV infection. There were two minor and two major epidemics. Table 1 summarizes clinical characteristics classified according to these types of epidemics. Intensive care unit admission occurred more frequently during major epidemics. Other features did not differ between the two types or between different epidemics of the same type (data not shown). The two minor epidemics were characterized by late onset, late peak (week 19 and 13, respectively), late end (week 23) and low hospitalization rates. The intervening major epidemics began early, peaked early

Table 1
Major clinical characteristics of patients admitted with RSV infection to the University Children's Hospital of Bern during four consecutive RSV epidemics.

		Type of epidemic		
Parameter [a]	Total	Minor [b]	Major [c]	P-value [d]
No. of patients	497	130	367	
Age (months)	3.8 (1.6–10.0)	5.0 (1.8–12.2)	3.7 (1.6–9.0)	0.107
Chronological age ≤ 30 days	63 (12.7)	13 (10.0)	50 (13.6)	0.413
Gestational age ≤ 35 weeks	56 (11.3)	11 (8.5)	45 (12.3)	0.310
Chronic lung disease [e]	15 (3.0)	5 (3.8)	10 (2.7)	0.729
Congenital heart disease	12 (2.4)	4 (3.1)	8 (2.2)	0.806
Intensive care unit admission	56 (11.3)	8 (6.2)	48 (13.1)	0.047
Mechanical ventilation	15 (3.0)	2 (1.5)	13 (3.5)	0.396
Death	1 (0.2)	1 (0.8)	0	
Duration of hospitalization (days)	5 (4–8)	5 (4–8)	6 (4–8)	0.562
Admission before January 1		4 (3.1)	115 (31.3)	< 0.0001
Admission after March 31		56 (43.1)	4 (1.1)	< 0.0001

[a] figures indicate the number of patients (%) or median (interquartile range); [b] comprises the epidemics 1997/1998 (53 patients) and 1999/2000 (77 patients); [c] comprises the epidemics (1998/1999 (165 patients) and 2000/2001 (202 patients); [d] two-sided Mann-Whitney U-test or χ^2-test with Yates's correction; [e] defined as supplemental oxygen requirement at 36 weeks of gestational age

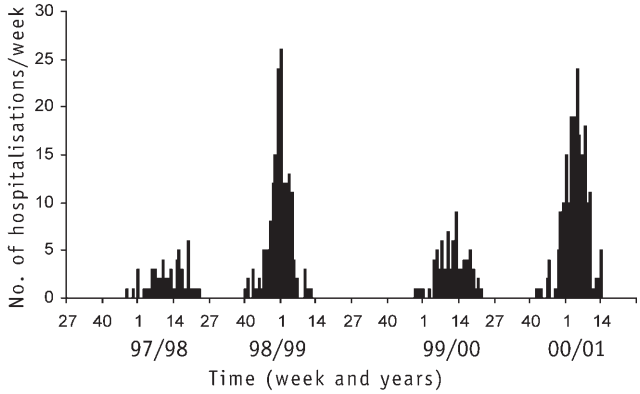

Figure 1. Weekly RSV hospitalization rates during a 4-year observation period at the University Children's Hospital of Bern, Switzerland.

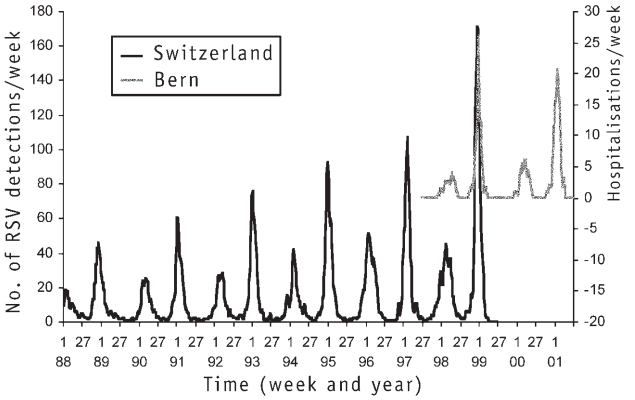

Figure 2. Weekly RSV detection rates reported by diagnostic laboratories to the Swiss Federal Office of Public Health from 1988 to 1999. Each data point represents the moving average of 3 consecutive weeks. The top right insert depicts the weekly RSV hospitalization rates at the University Children's Hospital of Bern.

(week 1 and 5, respectively), ended by week 14 and caused two to fourfold higher hospitalization rates.

National RSV Epidemiology

During 12 consecutive years of observation, 8,574 reports of RSV detection were recorded. In chronological order, the numbers of RSV detections in each year were 227, 620, 384, 639, 426, 779, 497, 933, 808, 1,005, 750 and 1,506. The fluctuation of weekly detection rates over time is depicted in figure 2. There was a statistically significant increase in the number of annual RSV detections over time for both major epidemics (regression coefficient, 81.2 per year; $p = 0.008$) and minor epidemics (regression coefficient, 56.5 per year; $p = 0.004$). These trends were compared by analysis of variance and found not to be significant (interaction trend $p = 0.24$). There was biannual periodicity in both the magnitude and distribution of RSV detection rates which was in-phase with RSV hospitalization rates in Bern (Figure 2, insert). Using the threshold value for the weekly relative RSV detection rate of 1%, minor epidemics lasted significantly longer than major epidemics (median 26 weeks, range 24–29 weeks vs 19.5 weeks, range 18–21 weeks; $p = 0.0051$) and the interval between onset and peak was longer (median 13 weeks, range 4–13 weeks vs 8 weeks, range 7–10 weeks; $p = 0.065$). This calculation includes the 1987/88 epidemic for which data were only available from January 1 onward. Representative curves of weekly means for minor and major epidemics, respectively, are shown in figure 3. Based on these data, the proportion of annual RSV infections potentially preventable by the use of palivizumab was calculated. During an average minor RSV season, a five-dose regimen affording 22 weeks of protection would have covered a maximum of 85.6% of annual RSV infections if initiated in week 50 (Figure 3A, open squares). Applied to individual minor epidemics between 1988 and 1999, the range of coverage of such a regimen would have been 79.4–86.6% (Table 2). During an average major season, a maximum coverage of 88.7% would have been achieved by

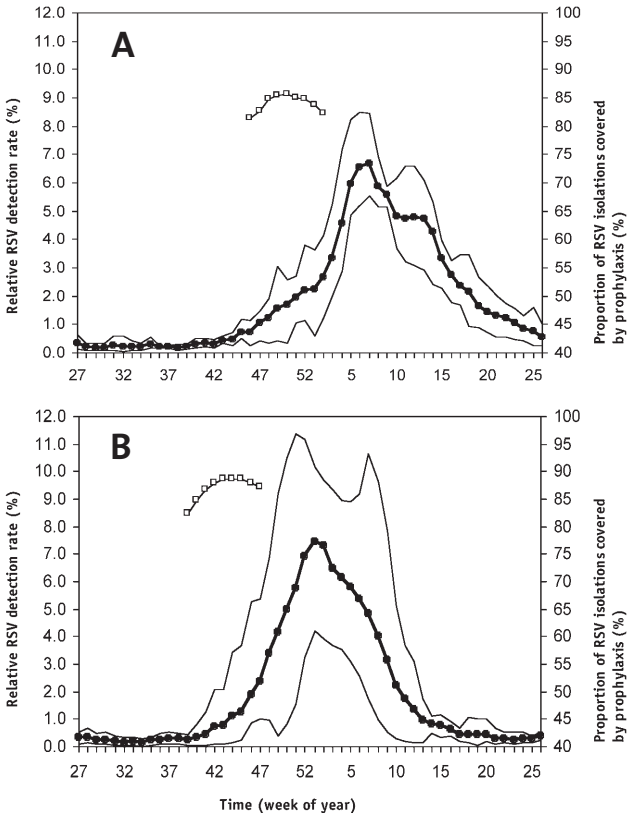

Figure 3. Representative course of a minor (panel A) and major RSV epidemic (panel B) based on weekly RSV detection rates reported to the Swiss Federal Office of Public Health. ● mean value of five or six relative weekly RSV detection rates reported during individual epidemics; – maximum and minimum of observed relative RSV detection rates; ❑ proportion of annual RSV isolations covered by a five-dose, 22-week RSV prophylaxis initiated in a given week (secondary y-axis).

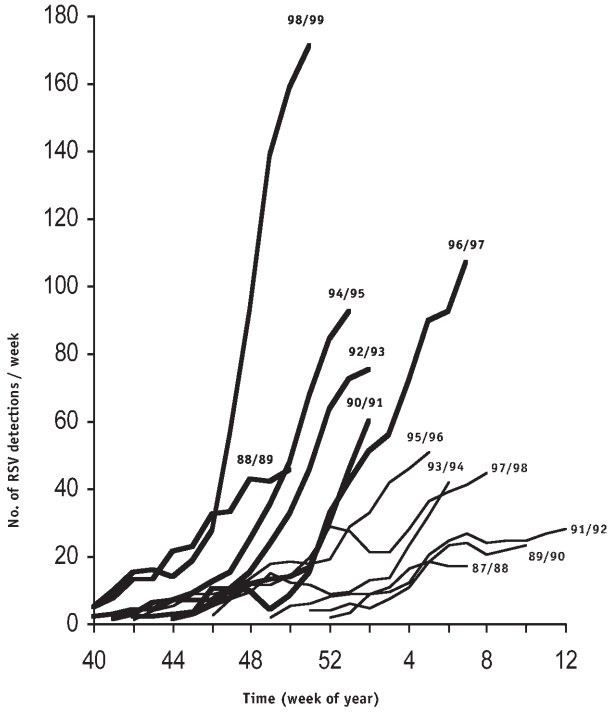

Figure 4. Weekly RSV detection rates reported by diagnostic laboratories to the Swiss Federal Office of Public Health. Each curve represents the ascending portion of an individual RSV epidemic. — major epidemic; — minor epidemic.

initiation of prophylaxis in week 43 (Figure 3B, open squares) (range 81.9–94.6%). Four-dose regimens (17 weeks of protection) were calculated to cover a maximum of 78.3% and 82.7%, respectively. Six-dose regimens (27 weeks) would have provided 92.4% and 92.5%, respectively (data not shown). In addition, figure 3 demonstrates that – in comparison with the major epidemic – both peak and end of the minor epidemic were shifted to the right, but there was no clear difference in the time of onset. Figure 4 depicts the ascending portion of each epidemic and indicates that minor and major epidemics overlapped with respect to the time of onset but varied with respect to the weekly increment of RSV detections. This finding corresponds with the prolonged onset-to-peak interval of minor epidemics.

Discussion

Both the magnitude and time of occurrence of annual RSV epidemics are subject to variation. While the extent of year-to-year fluctuation is unpredictable in some places [12–15], a pattern of periodicity has been noticed in others [16–22]. Today, with new prophylactic options available and an increasing demand for cost-effective patient care, predictability of RSV epidemics could be made useful in several ways. It could assist in optimizing RSV prophylaxis for high-risk infants and be a valuable tool for the design of RSV vaccine or antiviral drug studies (e.g. sample size calculation for efficacy trials) and for hospital management.

Based on local RSV hospitalization data observed over a 4-year period and national laboratory notification data spanning 12 years, we describe a fixed "every-other-year" pattern of RSV epidemiology in Switzerland. Periodicity relates to both the frequency and time-course of RSV infections, but not to the clinical severity of infection in hospitalized patients (Table 1). The steady increase in the number of RSV detections during the 12 years of national RSV surveillance (Figure 2) is likely the result of widening availability and use of commercial RSV detection kits. A true increase in RSV infections cannot be ruled out, but appears unlikely. The motif of alternating occurrence of minor epidemics (slow onset, low peak and long duration) and major epidemics (rapid onset, high peak, short duration) has been observed in Norway, Finland, Sweden and several locations in the USA [23, 24]. In Norway, *Ørstavik* et al. [25] and *Anestad* [17] observed such a pattern in sequential studies between 1972 and 1985. In Finland, national laboratory data collected from 1981 to 1990 showed a periodicity which is indistinguishable from the data presented here [16]. Such biannual periodicity appears to be restricted to certain geographic areas and its cause is unknown. An annual switch in the predominance of one of the RSV subtypes A and B does not appear to occur [13, 22]. *Waris* [16] found that one subtype prevailed during a minor and the subsequent major season, before being replaced by the

Table 2
Effect of the time of initiation of a five-dose RSV prophylaxis using palivizumab on the coverage of annual RSV detections based on 12 years of observation of RSV epidemiology in Switzerland.

	Minor epidemic (odd-numbered year)		Major epidemic (even-numbered year)	
Week no.[a]	% covered[b]	Range[c]	% covered[a]	Range[c]
43	69.9	59.9–74.7	88.7	81.9–94.6
50	85.6	79.4–86.6	78.4	52.4–92.7

[a] week of year at which initiation of prophylaxis yields a maximum coverage of annual RSV detections as calculated from the weekly means of relative RSV detection rates (Figure 3); [b] proportion of annual RSV detections occurring during prophylaxis as calculated from the weekly means of relative RSV detection rates (Figure 3); [c] range of coverage of annual RSV detections when prophylaxis initiated at the indicated week is applied to individual epidemics in Switzerland between 1988 and 1999

other subtype. Variation of RSV genotypes [26, 27] may play a role, but has not been studied in areas with known biannual periodicity. Factors influencing RSV transmission, such as the duration of protective immunity, herd immunity or the mode of cohorting of children, have not been evaluated. Such factors may be important because mathematical modeling of RSV epidemics allows to simulate biannual periodicity with alternating short and long intervals by modulating a single factor, i.e. the seasonal amplitude of the transmission parameter [28]. Environmental factors such as temperature, humidity and the duration of sunshine have been found to correlate with the severity of RSV epidemics in some locations [29–31] but not in others [19]. Such influences may help to explain the geographic restriction of biannual periodicity, but are unlikely to account for 2-year cycles in a particular location.

While the mechanism governing stable 2-year periodicity remains unknown, its clinical utility in the absence of an RSV surveillance system is obvious. Most recently, predictability of onset and duration of RSV epidemics has become of interest because passive immunization of high-risk infants by monthly injections of the anti-RSV antibody palivizumab should be timed correctly to assure both maximum effectiveness and minimum cost. Our calculations suggest that week 50 (mid-December) may be the most effective time for starting standard five-dose prophylaxis in minor seasons, week 43 (late October) in major seasons (Table 2). Starting prophylaxis in week 43 – as is customarily recommended – during an average minor season would be expected to reduce coverage by 15.7% and overall coverage could be as low as 60% (Table 2). The validity of these calculations depends on the assumption that nationally reported laboratory data reliably represent RSV hospitalizations of infants. Figure 2 indicates that this was the case for the RSV seasons 1998/1999 and 1999/2000. In addition, figure 3 indicates that year-to-year variation of RSV detections in a given week was large during the weeks of peak frequencies, but small near the beginning and end of the epidemic. Thus, the bases of the time-frequency curves were fixed in time for both types of epidemics.

In conclusion, stable 2-year cycles of RSV epidemiology were observed. Clinicians who choose to administer palivizumab to high-risk patients should take this periodicity into consideration for adjusting both time of onset and the duration of prophylaxis. Hospital administrators struggling with large fluctuations of admission rates in pediatric hospitals may use such data to predict peak admission frequencies.

Acknowledgments

National RSV notification data were provided by the Swiss Federal Office of Public Health (Dr. H. P. Zimmermann) and are used with permission. The authors thank Kathrin Muehlemann, M.D., Ph.D., for her assistance in statistical analyses.

References

1. Hall CB: Respiratory syncytial virus and parainfluenza virus. N Engl J Med 2001; 344: 1917–1928.
2. Glezen WA, Taber LL, Frank AL, Kasel JA: Risk of primary infection and reinfection with respiratory syncytial virus. Am J Dis Child 1986; 140: 543–546.
3. Prober CG: Reducing the morbidity of lower respiratory tract infections caused by respiratory syncytial virus: still no answer. Pediatrics 1997; 99: 472–475.
4. Duppenthaler A, Gorgievski-Hrisoho M, Aebi C: Regional impact of prophylaxis with the monoclonal antibody palivizumab on hospitalizations for respiratory syncytial virus. Swiss Med Wkly 2001; 131: 146–151.
5. Sigurs N: Epidemiologic and clinical evidence of a respiratory syncytial virus - reactive airway disease link. Am J Respir Crit Care Med 2001; 163: 2–6.
6. Cunningham CK, McMillan JA, Gross SJ: Rehospitalization for respiratory illness in infants of less than 32 weeks' gestation. Pediatrics 1991; 88: 527–532.
7. The IMPACT study group: Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. Pediatrics 1998; 102: 531–537.
8. American Academy of Pediatrics: Prevention of respiratory syncytial virus infections: Indications for the use of palivizumab and update on the use of RSV-IVIG. Pediatrics 1998; 102: 1211–1216.
9. Aebi C, Nadal D, Kind C, Pfister R, Barazzone C, Hammer J: Konsensus Statement zur Prävention von Respiratory Syncytial Virus (RSV)-Infektionen bei Neugeborenen und Säuglingen mit dem humanisierten monoklonalen Antikörper Palivizumab (Synagis). Paediatrica 2000; 11: 37–45.
10. Berner R, Schwoerer F, Schumacher RF, Meder M, Forster J: Community and nosocomially acquired respiratory syncytial virus infection in a German pediatric hospital 1988 to 1999. Eur J Pediatr 2001; 160: 541–547.
11. Shay DK, Holman RC, Roosevelt GE, Clarke MJ, Anderson LJ: Bronchiolitis-associated mortality and estimates of respiratory syncytial virus-associated deaths among US children 1979-1997. J Infect Dis 2001; 183: 16–22.
12. Hall CB, Walsh EE, Schnabel KC, Long CE, McConnochie KM, Hildreth SW, Anderson LJ: Occurrence of groups A and B of respiratory syncytial virus over 15 years: epidemiologic and clinical characteristics in hospitalized and ambulatory children. J Infect Dis 1990; 162: 1283–1290.
13. Brouard J, Freymuth F, Constantini S, Petitjean J, de Schrevel G, Duhamel JF : Prevalence et aspects cliniques de l'infection par les sous-types A et B du virus respiratoire syncytial. Arch Fr Pediatr 1993; 50: 639–643.
14. Sims DG, Downham MA, McQuillan J, Gardner PS: Respiratory syncytial virus infection in north-east England. Br Med J 1976; 2: 1095–1098.
15. Anderson LJ, Parker RA, Strikas RL: Association between respiratory syncytial virus outbreaks and lower respiratory tract deaths in infants and young children. J Infect Dis 1990; 161: 640–646.
16. 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.
17. Anestad G: Surveillance of respiratory viral infections by rapid immunofluorescence diagnosis, with emphasis on virus interference. Epidemiol Infect 1987; 99: 523–531.
18. Eriksson M, Bennett R, Rotzen-Ostlund M, von Sydow M, Wirgart BZ: Population-based rates of severe respiratory syncytial virus

infection in children with and without risk factors, and outcome in a tertiary care setting. Acta Paediatr 2002; 91: 593–598.
19. Reyes M, Eriksson M, Bennet R, Hedlung KO, Ehrnst A: Regular pattern of respiratory syncytial virus and rotavirus infections in relation to the weather in Stockholm 1984-1993. Clin Microbiol Infect 1997; 3: 640–646.
20. Foy HM, Cooney MK, Maletzky AJ: Incidence and etiology of pneumonia, croup and bronchiolitis in preschool children belonging to a prepaid medical care group over a four-year period. Am J Epidemiol 1973; 97: 80–92.
21. Monto AS, Bryan ER, Rhodes LM: The Tecumseh study of respiratory illness. VII. Futher observations on the occurrence of respiratory syncytial virus and *Mycoplasma pneumoniae* infections. Am J Epidemiol 1974; 100: 458–468.
22. Reese PE, Marchette NJ: Respiratory syncytial virus infection and prevalence of subgroups A and B in Hawaii. J Clin Microbiol 1991; 29: 2614–2615.
23. Lyon JL, Stoddard G, Ferguson D, Caravati M, Kaczmarek 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.
24. Mufson MA, Levine HD, Wasil RE, Mocega-Gonzalez HE, Krause HE: Epidemiology of respiratory syncytial virus infection among infants and children in Chicago. Am J Epidemiol 1973; 98: 88–95.
25. Ørstavik I, Carlson KH, Halvorsen K: Respiratory syncytial virus infections in Oslo 1972-1978. I. Virological and epidemiological studies. Acta Paediatr Scand 1980; 69: 717–722.
26. Peret TC, Hall CB, Hammond GW, Piedre PA, Storch GA, Sullender WM, Tsou C, Anderson LJ: Circulation patterns of group A and B human respiratory syncytial virus genotypes in 5 communities in North America. J Infect Dis 2000; 181: 1891–1896.
27. Brandenburg AH, van Beek R, Moll HA, Osterhaus ADME, Claas ECJ: G protein variation in respiratory syncytial virus group A does not correlate with clinical severity. J Clin Microbiol 2000; 38: 3849–3852.
28. Weber A, Weber M, Milligan P: Modeling epidemics caused by respiratory syncytial virus (RSV). Math Biosci 2001; 172: 95–113.
29. Weigl JA, Puppe W, Schmitt HJ: Incidence of respiratory syncytial virus-positive hospitalizations in Germany. Eur J Clin Microbiol Infect Dis 2001; 20: 452–459.
30. Martin AJ, Gardner PS, McQuillin J: Epidemiology of respiratory viral infection among paediatric inpatients over a six-year period in north-east England. Lancet 1978; 2: 1035–1038.
31. Florman AL, McLaren LC: The effect of altitude and weather on the occurrence of outbreaks of respiratory syncytial virus infections. J Infect Dis 1988; 158: 1401–1402.