

EPIDEMIOLOGY OF RESPIRATORY SYNCYTIAL VIRUS INFECTION AMONG INFANTS AND CHILDREN IN CHICAGO

MAURICE A. MUFSON¹, HARRY D. LEVINE², RAYMOND E. WASIL³,
HILDA E. MOCEGA-GONZALEZ³ AND HELEN E. KRAUSE³

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Mufson, M. A. (Abraham Lincoln School of Medicine, Univ. of Illinois at the Medical Center, Box 6998, Chicago, Illinois 60680), H. D. Levine, R. E. Wasil, H. E. Mocega-Gonzalez and H. E. Krause. Epidemiology of respiratory syncytial virus infection among infants and children in Chicago. *Am J Epidemiol* 98: 88-95, 1973.—From January 1, 1967 to December 1971, the temporal pattern of respiratory syncytial virus infection was investigated in infants and children younger than 18 months hospitalized for acute lower respiratory tract disease. Of 4696 infants and children with acute lower respiratory tract disease admitted to the Cook County Hospital, 2530 were tested for virus infection by virus isolation or serologic procedures or both. Overall, respiratory syncytial virus infections were detected in 12% and parainfluenza 3 virus in 10.8% of individuals tested. Other respiratory viruses were less commonly identified. Respiratory syncytial virus epidemics occurred annually and were temporally synchronous with the peak periods of respiratory disease admissions. Only during epidemics of respiratory syncytial virus did admission for respiratory tract disease usually reach 40 patients or more weekly. The peak months of respiratory syncytial virus epidemics were December 1966, January 1968, February-March 1969, April 1970 and January 1971. Epidemics lasted about 17 weeks. No similar annual epidemic pattern was seen with the other myxoviruses.

bronchiolitis; epidemiology; infants; myxovirus; parainfluenza virus; pneumonia; respiratory syncytial virus; respiratory tract diseases

Long term surveillance programs of lower respiratory tract disease in infants and children have provided evidence that respi-

ratory syncytial virus (RSV) is a major cause of pneumonia and bronchiolitis in infants; during epidemic periods, RSV has

Abbreviations: HEK, human embryonic kidney; RMK, rhesus monkey kidney; RSV, respiratory syncytial virus.

¹Departments of Medicine and Preventive Medicine and Community Health, Abraham Lincoln School of Medicine, and the Epidemiology Section, School of Public Health, University of Illinois at the Medical Center; and the West Side Veterans Administration Hospital.

Reprint requests to Dr. Mufson: Department of Medicine, Abraham Lincoln School of Medicine, University of Illinois at the Medical Center, Box 6998, Chicago, Illinois 60680.

²Division of Pediatrics, Cook County Hospital and Hektoen Institute for Medical Research, Chicago, Illinois.

³West Side Veterans Administration Hospital, Chicago, Illinois.

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been associated with approximately one-half of such cases (1-9).

Respiratory syncytial virus epidemics occur annually, usually during the winter months in temperate zones, but the pattern of their epidemic occurrence, which has been systematically investigated in only a few metropolitan areas, has been reported to vary somewhat among differing population groups and cities (2, 3, 6, 9, 10). In Washington, D.C., RSV epidemics exhibited alternating periodicity or a two-year bimodal cycle, appearing early in winter one year and later in the next year (6). A similar pattern has been reported for the occurrence of this infection among infants and children in Chapel Hill, North Carolina (10). By comparison, in Chicago, Illinois, and Seattle, Washington, during the last six years RSV infection apparently followed a four-year cycle, with successively later epidemics annually for three years, and then an early winter occurrence after a short fourth cycle (9, 11).

This report describes the periodic pattern of RSV infection in infants and children with lower respiratory tract disease admitted to the Cook County Hospital in Chicago, between January 1, 1967 and December 31, 1971. Four epidemiologic years of RSV infection are included in this 60-month study period. In a previous communication, a mathematical model was described which simulated the occurrence of RSV epidemics during the first three years (11). The occurrence during this time of coronavirus infections is reported in detail elsewhere (12).

MATERIALS AND METHODS

Population. The study group comprised infants and children younger than 18 months of age admitted to the Cook County Hospital because of acute lower respiratory tract disease. The population has been described previously (13). Categories of acute respiratory tract disease were pneumonias, bronchiolitis, laryngo-tracheo-bronchitis.

Most infants and children ill with respi-

ratory tract disease admitted between Sunday and Friday mornings were tested for virus infection by virus isolation or serologic procedures or both. On some days the number of infants and children admitted with acute lower respiratory tract disease exceeded the capacity of our laboratory, and in these instances individuals whose illnesses were of most recent onset were tested.

Virus isolation procedures. Oropharyngeal swab specimens for virus isolation were obtained within 24 hours after admission from study children (13). The oropharynx was vigorously rubbed with a sterile swab and the swab was then extracted in 4 ml of veal infusion broth containing 0.5 per cent bovine serum albumin. For virus isolation, 0.2 ml of broth was inoculated into each of two roller tube cultures of primary rhesus monkey kidney (RMK), HEp-2 and fetal human diploid (strain WI-38) cells. Infrequently, during the first two years of the study, primary human embryonic kidney (HEK) cells were also inoculated. Each oropharyngeal swab specimen was pre-treated with penicillin, streptomycin and amphotericin at 4 C for one hour prior to inoculation, as previously described (13).

Cell cultures were incubated on a rotating drum at 33 C for at least 18 days, and often for as long as 28 days. Subpassages of negative cultures were not made. HEp-2, WI-38 and HEK cell cultures were examined for cytopathic effects at about five-day intervals, and the culture media were changed at these times. Viral isolates were identified by serologic procedures (13).

RMK cultures were tested for hemadsorption at five- to seven-day intervals, and the culture media changed at these times. For hemadsorption, 0.25 ml of a 0.4 per cent suspension of guinea pig erythrocytes was added to each culture tube and the tubes refrigerated at 4 C for 30 minutes. Hemadsorbing isolates were identified by hemadsorption-inhibition procedures using antisera for influenza A and B, parainfluenza 1, 2 and 3, mumps and SV-5 viruses.

Antibody determinations. Acute and convalescent phase sera collected usually about 18 to 21 days apart, but at least 10 days apart, were tested for complement-fixing antibodies to parainfluenza 1, 2 and 3, RSV, influenza A and B viruses, adenoviruses, coronavirus 229E and *M. pneumoniae*. Micro-titer complement-fixation tests were employed with overnight fixation at 4 C and 1.7 to 1.8 units of complement. Eight units of RSV and the parainfluenza virus antigens and four units of the other antigens were used. Evidence of infection was a four-fold or greater rise in antibody titer between the acute and convalescent phase sera.

Data analyses. The occurrence of virus infections was analyzed by epidemiologic year, extending from July 1 to June 30. Cases were plotted by day of admission. Demographic, virus isolation and antibody assay data were coded for computer processing. Computer assisted analyses were done using the IBM 360/155 computer in the Research Resources Laboratory of the University of Illinois College of Medicine.

RESULTS

Population. During the 60-month study period, 4696 infants and children younger than 18 months of age with acute lower respiratory tract diseases were admitted to the hospital (table 1). Usually between 900

TABLE 1

Admission to Cook County Hospital of children younger than 18 months of age for acute lower respiratory tract disease from January 1, 1967 through December 31, 1971

Category	No. of children by indicated epidemiologic year*						Total
	1967†	1967-1968	1968-1969	1969-1970	1970-1971	1971†	
Total population	422	938	986	898	1008	444	4696
Tested for virus infection	178 (42.2)‡	630 (56.5)	539 (54.7)	477 (53.1)	578 (57.3)	228 (51.4)	2530 (51.7)

* Epidemiologic year extends from July 1 to June 30.

† Six months only.

‡ Percentage in parentheses.

TABLE 2

Virus infection associated with lower respiratory tract disease in 2530 inpatient children younger than 18 months of age

Virus	Virus infections detected*	
	No	%
Respiratory syncytial	304	12.0
Parainfluenza 1	107	4.2
Parainfluenza 2	41	1.7
Parainfluenza 3	274	10.8
Influenza A	73	2.9
Influenza B	3	0.1
Adenovirus	92	3.6

* Evidence of infection determined by virus isolation and serologic procedures.

and 1000 infants and children were admitted each epidemiologic year. Most infants suffered from pneumonia or bronchiolitis and these comprised nearly 85 per cent of the total population. Of the total population of infants admitted for lower respiratory tract disease, 2530 (53.8 per cent) were tested for virus infection by virus isolation or serologic procedures or both.

Frequency of virus infection. Overall, RSV infections were detected in 304 (12.0 per cent) of lower respiratory tract illnesses tested (table 2). It was the predominant infection in respiratory disease in children younger than 18 months of age. As a group, however, myxovirus infections were even more frequently associated with such cases. Parainfluenza 3 virus, the second most common infection, was associated with 274 (10.8 per cent) of these illnesses. In contrast, parainfluenza 1 and 2 viruses, influenza A virus and adenovirus infection occurred much less often. Influenza B virus infections were rare (table 2).

During the five-year observation period, RSV epidemics occurred annually. Proportionately more respiratory syncytial infections were detected in alternate epidemiologic years (table 3); the proportions were highest during 1967-1968 and 1969-1970. Parainfluenza 1 virus occurred most frequently during 1968-1969,

TABLE 3
Myxovirus infections associated with lower respiratory tract disease in hospitalized children younger than 18 months of age

Virus	Evidence of infection by virus isolation and serologic response among infants with lower respiratory disease in indicated epidemiologic year*											
	1967†		1967-1968		1968-1969		1969-1970		1970-1971		1971†	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Respiratory syncytial	18	10.1	93	17.5	51	9.5	69	14.5	71	12.3	2	0.9
Parainfluenza 1	3	1.7	18	3.4	36	6.7	4	0.8	29	5.0	17	7.5
Parainfluenza 2	5	2.8	19	3.6	4	0.7	4	0.8	7	1.2	2	0.9
Parainfluenza 3	14	7.9	103	19.4	66	12.2	59	12.4	28	4.8	4	1.8
Influenza A	0		13	2.5	15	2.8	21	4.4	23	4.0	1	0.4
No. tested	178		530		539		477		578		228	

* Epidemiologic year extends from July 1 to June 30.

† Six months only.

1970-1971 and the second half of 1971. Influenza A virus was detected with about equal frequency during all epidemiologic years. In contrast, parainfluenza 3 virus infections predominated during 1967-1968 and then showed a trend to fewer infections each succeeding year. In the second half of 1971, fewest parainfluenza 3 virus infections were detected. Parainfluenza 2 virus was detected more often in 1967-1968 than in any of the other epidemiologic years.

Periodicity of respiratory syncytial virus epidemics. Epidemics of RSV temporally paralleled the peak periods of respiratory disease admission (figure 1). The start of each epidemic was signalled by a marked increase in admission of infants and young children for serious lower respiratory tract disease. During these epidemics, admissions to the hospital exceeded 20 patients weekly and usually reached 40 patients weekly at the peak of the epidemic. Other virus infection outbreaks did not have as evident an impact on the number of admissions for lower respiratory tract diseases.

The pattern of RSV disease epidemics can be clarified and simplified by plotting a three-week moving average of the raw admissions data (figure 1). Using this curve, the peak months of RSV epidemics were December 1966 (estimated by extrapolation),

January 1968, February-March 1969, April 1970 and January 1971. In 1972, the peak month of occurrence was March (table 4). Virus identification and serologic procedures are incomplete for this year. On the average, respiratory syncytial virus epidemics lasted 17 weeks.

From the three-week moving average plot of admissions, the time intervals between peaks were calculated (table 4). The first three epidemics after January 1967 occurred on a nearly regular cycle. These epidemics occurred at 55- to 58-week intervals from the peak of one epidemic to the peak of the next, the peak of each appearing successively later each year than the previous one.

The following epidemic, however, occurred between December 1970 and March 1971, after only a 39-week interval after the previous epidemic peak. The peak of the 1972 epidemic in March was about 63 weeks after this early peak.

Prevalence of other myxoviruses. In addition to the five major admission peaks associated with epidemics of RSV infection, other smaller peaks of admission of infants and children with respiratory tract disease can be delineated (figure 1). Although parainfluenza 3 virus occurred endemically in this population, clusters of infection oc-

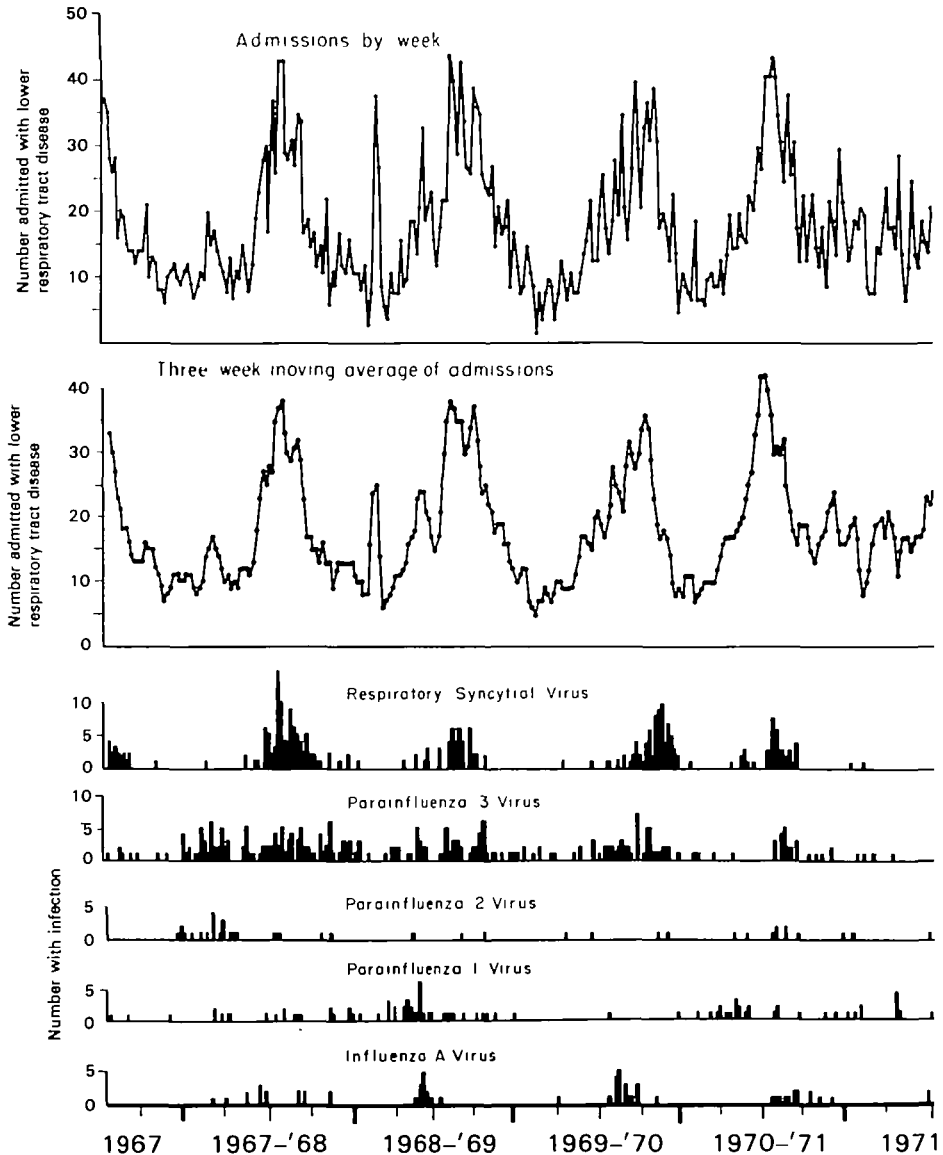


FIGURE 1. Weekly occurrence of respiratory syncytial, parainfluenza 1, 2 and 3 and influenza A virus infections among children younger than 18 months of age admitted to the hospital with acute lower respiratory tract disease.

curred at certain periods. Apparently this virus, together with a parainfluenza 2 virus outbreak, contributed to short but sharp peaks of lower respiratory disease admission in July–September 1967; and then in February–March 1970, when influenza A virus was prevalent; and in March–April 1971 (figure 1). Parainfluenza 3 virus was also prevalent during the 1968 and 1969 respiratory syncytial virus epidemics.

Parainfluenza 1 virus epidemics occurred in September through December 1968, also when influenza A virus was prevalent, and in September through November 1970 (figure 1). A smaller cluster of parainfluenza 1 virus infections occurred in October 1971. Influenza A virus was also epidemic during December 1971 through February 1972. Although these myxovirus epidemics led to an overall increase in admis-

TABLE 4

Seasonal occurrence of respiratory syncytial virus infection among children younger than 18 months of age requiring hospitalization for acute lower respiratory tract disease, January 1, 1967 to December 31, 1971

Year	Months	Peak month	Outbreak duration† (weeks)	Weeks since peak of previous outbreak
1966-1967	Dec.-Jan., Feb.	Dec. 1966*	16*	
1967-1968	Dec.-Jan., Feb., March	Jan. 1968	16	58
1969	Jan., Feb., March, April, May	Feb.-March 1969	18	57
1970	Feb., March, April, May	April 1970	16	55
1970-1971	Dec.-Jan., Feb., March	Jan. 1971	19	39
1972	Feb., March, April	March 1972	15	63

* Estimated.

† Includes weeks in which 20 or more children were admitted with respiratory tract disease.

sions of infants and children with lower respiratory tract disease, these were not as large as those observed during respiratory syncytial virus epidemics.

A brief, sharp peak of admission for lower respiratory tract diseases occurred "unseasonally" in August 1968, and was not associated with infections with viruses included in this study. Although we have no specific etiologic explanation for this peak, the data indicate that other infectious agents are etiologically related to these diseases.

DISCUSSION

This continuing surveillance study of virus infections in infants and young children with acute lower respiratory tract disease describes the cyclical pattern of occurrence of RSV infections. From the winter of 1966-1967 until April 1970 in Chicago, RSV epidemics occurred on a regular cycle with a periodicity of about 58 weeks. This cycle interval placed succeeding epidemics slightly later each year. Following the Spring epidemic in April 1970, the interval between this peak and the next was only 39 weeks, reorientating the epidemics to the colder months. Thus it appears that a four-year cycle of respiratory syncytial virus epidemics occurred with about three equal long cycles and one short one. Whether this four-year pattern was coinci-

dental or will repeat during the next four years remains to be investigated. The most recent epidemic of RSV, however, occurred in March 1972 or at a relatively later time compared to the 1968 epidemic.

Data on the timing of RSV epidemics from other populations located in different large cities agree with our findings (6, 9, 10). In the largescale study of respiratory tract infections conducted in Seattle, Washington, RSV epidemics occurred in nearly the same months as in Chicago during the same period of observation. Peak months of these epidemics in Seattle were January 1967, February 1968, March 1969, April-May 1970, January 1971 and March-April 1972 (9). From these data it appears that the cyclical occurrence in Seattle was the same as it is in Chicago. Similarly, for the years 1967 to 1970 in Washington, D.C., peak months of RSV epidemics in Children's Hospital were January 1967, February 1968, February 1969 and April 1970 (6). In Chapel Hill, North Carolina, the peak months were January 1967, March 1968 and January-February 1969, slightly different than in Chicago in these three years (10). It is of interest that from 1963 to 1967 Berglund (3) described the occurrence of RSV epidemics in children in Turku, Finland, which followed a pattern similar to the latter half of the four-year cycle in Chicago.

For Chicago, Seattle and Washington, D.C., three widely separated cities with differing but characteristic climatic conditions, the temporal occurrence of RSV epidemics was very similar. Respiratory syncytial virus infection does not appear to move wavelike over the country but rather starts nearly simultaneously in these three areas, and perhaps throughout the country as a whole. Weather conditions do not appear to influence the occurrence of these epidemics, except that outbreaks do not develop in epidemic fashion during the summer months in the northern temperate zone. In Chicago, temperature and humidity as predictors (or independent variables) of RSV occurrence showed a minor, but statistically significant, effect.

Other variables which might contribute to the initiation of respiratory syncytial virus epidemics are undefined, as are those that terminate the outbreaks. Infants and children younger than one year of age comprise the major group of individuals with significant clinical illness consequent to RSV infection. In any one year, this group of susceptibles to a large extent were born subsequent to the previous respiratory syncytial virus epidemic. As the susceptible pool of infants enlarges it is probable that a critical size is reached which encourages effective spread of the virus, and an epidemic is initiated. However, the short cycle epidemic of 1970–1971 is evidence against the hypothesis that the accumulation of a sufficient pool of susceptibles requires more than one year for an RSV epidemic to develop, unless the previous epidemic failed to exhaust the susceptible pool or new susceptibles entered the community at a higher rate. In either instance, no data exist to explain the short cycle epidemic.

Lacking confirmation on the variables which might contribute to RSV epidemics precludes describing a mathematical model of the epidemics. Previously we reported on a model to describe the regular cycle of outbreaks (11), viz:

$$y = a_0 + \sum_{i=1}^p \left[a_i \sin \left(\frac{2\pi it}{k} \right) + b_i \cos \left(\frac{2\pi it}{k} \right) \right] + \epsilon$$

The dependent (predicted) variable was the number of admissions, possibly smoothed by moving average, of infants and children with lower respiratory tract disease for a given week. The a 's and b 's are the coefficients determined by least squares, t is time measured from the start of the study, k the number of observed points in a single cycle and i is the harmonic number.

Auto-correlations computed for the 1966–1967, 1967–1968 and 1968–1969 epidemics were found to peak at 58 weeks, and suggested that this interval was the fundamental frequency. The intervals between peaks computed from the seven-week moving average plot agree fairly well with this value. Using three harmonics, the model generated values for admissions which fit the three-week moving average data closely; the unbiased multiple correlation was 0.93. Because of the shortened interval between the March 1970 and April 1971 epidemics, the model did not predict the April 1971 epidemic.

Although the model cannot be modified to simulate the four-year cycle observed, it does suggest that the variables which influence RSV outbreaks are cyclical, and studies to delineate such variables in RSV epidemics are required. The definition of these factors could contribute to a means for modifying the impact of RSV epidemics on the population of susceptible infants and young children.

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