J Microbiol Immunol Infect.
2007;40:293-301

Original Article

Epidemiology of respiratory syncytial virus infection in northern Taiwan, 2001-2005 — seasonality, clinical characteristics, and disease burden

Jian-Te Lee[1], Luan-Yin Chang[1], Li-Chieh Wang[1], Chuan-Liang Kao[2], Pei-Lan Shao[1], Chun-Yi Lu[1], Ping-Ing Lee[1], Jong-Min Chen[1], Chin-Yun Lee[1], Li-Min Huang[1]

[1]Department of Pediatrics, and [2]School and Graduate Institute of Medical Technology, College of Medicine, National Taiwan University, Taiwan

Received: May 30, 2006 Revised: July 1, 2006 Accepted: August 28, 2006

Background and Purpose: Respiratory syncytial virus (RSV) is an important pathogen in children less than 2 years old. However, there is limited epidemiological data about RSV infection in Taiwan. This study aimed to investigate the clinical, epidemiological, virological, and economical aspects of RSV infections in Taiwan.

Methods: We collected data of children with positive RSV respiratory specimens at the Laboratory of Virology, National Taiwan University Hospital, between January 2001 and December 2005. Medical charts were reviewed retrospectively.

Results: 892 children in whom acute bronchiolitis was the predominant diagnosis (60.7%) were enrolled. Compared with those without underlying disease (n = 630), children with underlying disease (n = 262) were older (11 vs 9 months), required longer oxygen therapies (7 vs 4 days), were more likely to have lower respiratory tract involvement (96.2% vs 92.3%) and intensive care unit stays (49.0% vs 9.4%), endotracheal intubations (21.0% vs 2.0%), ribavirin use (35.0% vs 1.4%), and had higher medical costs (US$ 1250 vs 688), and nosocomial infection (24.8% vs 1.0%). Compared with those without endotracheal intubation (n = 824), cases requiring endotracheal intubation (n = 68) had higher rates of underlying diseases (80.9% vs 25.1%), especially congenital heart diseases (45.6% vs 8.1%), chronic lung disease (13.2% vs 3.2%) and neurological disorders (17.6% vs 3.5%). There was a biennial pattern with peaks in the spring and fall. Medical cost was estimated to be US$ 250,000 annually in our hospital.

Conclusion: In children with underlying diseases, RSV infection is associated with significant morbidity, and even mortality. Nosocomial infections appear to be an important cause of RSV transmission. The seasonality of RSV infections in Taiwan showed a biennial pattern with peaks in spring and fall.

Key words: Epidemiology; Health care costs; Respiratory syncytial virus, infections; Seasons

Introduction

Respiratory syncytial virus (RSV) infection is a major respiratory illness of children less than 2 years of age. It can cause significant morbidity — from upper respiratory infections, acute bronchiolitis, and bronchopneumonia to apnea or sepsis [1]. Acute respiratory distress syndrome could occur in immunocompromised patients. Treatment of RSV respiratory illness is mainly supportive; in the absence of other effective vaccines, ribavirin remains the only specific treatment. With high-titer RSV immunoglobulin and humanized monoclonal antibody against RSV becoming available, the American Academy of Pediatrics recommended prophylaxis for RSV infections in high-risk infants [2]. The so-called "RSV season" is the key to RSV immunoprophylaxis.

Information on the epidemiology of RSV infections in Taiwan is still limited [3,4] and the severity, risk factors, seasonality, and medical cost of RSV infections in

Corresponding author: Dr. Li-Min Huang, Department of Pediatrics, National Taiwan University Hospital, 7F, No.7, Chung-Shan South Road, Taipei 100, Taiwan.
E-mail: lmhuang@ha.mc.ntu.edu.tw

Taiwan need further elucidation. We aimed to study the clinical, epidemiological, virological, and economic aspects of RSV infections in Taiwan in order to pave the way for future studies.

Methods

Data collection

RSV respiratory specimens (suctioned sputum or nasopharyngeal aspirates) diagnosed between January 2001 and December 2005 at the Laboratory of Virology, National Taiwan University Hospital, were identified by screening its database. They included those with positive RSV antigen tests or culture results. Medical charts were reviewed retrospectively. Fever was defined as body temperatures >38.3°C. Leukocytosis was arbitrarily defined as white blood cells in the peripheral blood >12,000/μL. The severity of RSV infection was scored by modification of a previous study [5,6]. We incorporated the respiratory effort score, respiratory rate, and oxygen saturation to categorize cases without underlying diseases into mild, moderate, or severe illnesses (Table 1).

Nosocomial infection referred to RSV-related respiratory illness manifesting 7 days after admission. Reinfection was defined as repeated infections with at least 3 months between the 2 episodes of RSV-related illness. Rehospitalization within 2 months was considered the same infection episode.

Virological examination

The RSV antigen of the respiratory specimen was detected by an immunofluorescence assay (IMAGEN™ RSV, DakoCytomation Ltd, Cambridge, UK). Virus culture was done using HEp-2 cell lines. Cases with positive RSV antigens and cultures in the same episode were counted only once.

Statistical analysis

The seasonal variation was verified by the method described by Freedman [7]. Statistical analysis was done using Statistical Package for the Social Sciences (SPSS) for Windows (Version 11.5; SPSS, Chicago, IL, USA). Categorical variables were assessed for statistical significance by chi-squared test. Fisher's exact test was used adjunctively if the expected values were less than 5. The Mann-Whitney *U* test was used for continuous variables with skewed sample distributions. A p value <0.05 was considered statistically significant.

Results

Demographics and clinical features

A total of 892 children were enrolled; 775 were positive for RSV antigen in the respiratory specimens and 239 were culture-proven for RSV. Children who were positive for both (n = 122) were regarded as a single episode. Demographic data and clinical features are shown in Table 2. There were 555 boys and 337 girls, with a median

Table 1. Calculation of the severity score

Variable	Not present	Present	Weighting factor	Summation	Severity score
Respiratory effort score					
Intercostal retraction	0	1	× 1.0	0.0-2.4	1 (mild)
Subcostal retraction	0	1	× 1.0	2.5-3.9	2 (moderate)
Substernal retraction	0	1	× 1.0	4.0-6.0	3 (severe)
Suprasternal retraction	0	1	× 1.5		
Nasal flaring	0	1	× 1.5		
Oxygen saturation (%)					
95-100					0
90-94					1
<90					2
Respiratory rate[a]					
<2 SD					0
2-3 SD					1
>3 SD					2
Overall severity score					
					<2 (mild)
					2-3 (moderate)
					>3 (severe)

Abbreviation: SD = standard deviation

[a]Respiratory rate was compared to that of healthy infants of the same age [6].

age of 10 months (range, 0-195 months). Children with underlying diseases comprised 29.4% of the total cases (Table 3). Fever was detected in 68.6% of cases, with a median duration of 3 days (range, 1-15 days). Approximately one-third (31.2%) of the cases reported respiratory illness in family members. Acute bronchiolitis was the predominant diagnosis (60.7%), followed by bronchopneumonia or pneumonia (32.6%), upper respiratory infection (4.3%) and croup (1.7%). The severity of cases without underlying disease ranged from mild (73.7%) to moderate (21.4%) and severe (4.9%).

We evaluated the factor of age in RSV infections among 630 previously healthly children, excluding 6 nosocomial cases. In infants below 6 months of age (n = 193), RSV infection was associated with less fever (36.3% vs 81.4%, $p<0.001$), and shorter median duration of fever (1 day vs 4 days, $p<0.001$), but more respiratory illness in the family (43% vs 32.3%, $p=0.011$) than those over 6 months of age (n = 431). The former consumed fewer antibiotics (31.1% vs 57.3%, $p<0.001$), but were prone to intensive care unit (ICU) stays (22.3% vs 3.2%, $p<0.001$) and developing lower respiratory illnesses (96.4% vs 91.0%, $p=0.017$), although chances of endotracheal intubation and ribavirin use were not significantly higher (Table 4).

Table 2. Clinical features and demographic data

Variable	No. of cases (%) (n = 892)
Demographics	
Male gender	555 (62.2)
Age (months; median [range])	10 (0-195)
Cases with underlying diseases	262 (29.4)
Respiratory illness of family members	279 (31.2)
Symptoms or signs	
Fever	612 (68.6)
Duration of fever (days; median [range])	3 (1-15)
Severity of condition[a]	
Mild	317/430 (73.7)
Moderate	92/430 (21.4)
Severe	21/430 (4.9)
Diagnosis	
Acute bronchiolitis	541 (60.7)
Bronchopneumonia or pneumonia	291 (32.6)
Fever or upper respiratory tract infection	38 (4.3)
Croup	15 (1.7)
Others[b]	6 (0.7)
Management	
Outpatient	21 (2.4)
Emergency department	9 (1.0)
Hospitalization	862 (96.6)
Intensive care unit admissions	188 (21.0)
Endotracheal intubation	68 (7.6)
Ribavirin use	101 (11.3)
Antibiotic use	487 (54.6)
Bronchodilator nebulization	457 (51.2)
Systemic corticosteroids	100 (11.2)

[a]See text for definition. Only cases without underlying diseases (n = 630) were assessed, of which only 430 cases (68.3%) were available for analysis; others contained missing data.
[b]Other diagnoses include bronchial asthma (n = 2); hand, foot, and mouth disease (n = 1); atypical Kawasaki disease (n = 1); febrile convulsion (n = 1); and acute gastritis (n = 1).

Table 3. Profile of underlying diseases

Underlying disease[a]	No. of cases (%)
Prematurity (weeks)	75 (8.4)
<24	5 (0.6)
24-28	18 (2.0)
28-32	26 (2.9)
32-35	26 (2.9)
Chronic pulmonary disease	35 (3.9)
Congenital heart disease	98 (11.0)
Acyanotic	63 (7.0)
Cyanotic	35 (4.0)
Neurological disorder	41 (4.6)
Hemato-oncological disorder	21 (2.4)
Gastrointestinal disorder	16 (1.8)
Metabolic or endocrine disorder	12 (1.3)
Other chronic condition[b]	9 (1.0)

[a]The categories shown are not mutually exclusive, since some cases had more than 1 condition.
[b]Other chronic conditions include multiple congenital anomalies (n = 6), sequelae of perinatal insult (n = 2), and immunodeficiency (n = 1).

Reinfection vs nosocomial infections

There were 30 cases of reinfection and 6 cases of rehospitalization. Twenty seven cases had 2 episodes of RSV infection with intervals between 3 months and 3 years. Three patients had RSV infections up to 3 times. Six episodes of RSV infection led to 14 hospitalizations and required 8 ICU stays. Significant morbidities after RSV infection included acute respiratory distress syndrome, chronic lung disease, subglottic stenosis, ventilator-associated pneumonia, and other nosocomial infections related to invasive interventions. Three deaths were attributable to acute respiratory distress syndrome after RSV infection. Two of these occurred in cases of Down syndrome with congenital heart disease. Both were infected shortly before cardiopulmonary bypass (CPB) and open-heart surgery. One boy with acute myeloid leukemia and neutropenia developed acute respiratory distress syndrome after

Table 4. Comparison of clinical profiles, disease severity, and management in children with community-acquired respiratory syncytial virus (RSV) infections without underlying diseases (n = 624)

Variable	<6 months of age (n = 193) No. (%)	>6 months of age (n = 431) No. (%)	*p*
Male gender	127 (65.8)	271 (62.9)	0.528
Fever	70 (36.3)	351 (81.4)	<0.001
Duration of fever (days; median [range])	1 (1-6)	4 (1-14)	<0.001
Family history of respiratory illness	83 (43.0)	139 (32.3)	0.011
Hospitalization	189 (97.9)	409 (94.9)	0.086
Leukocytosis	54/191 (28.3)	124/412 (30.1)	0.701
C-reactive protein (mg/dL; median [range])	0.165 (0-12)	0.585 (0-18.91)	<0.001
Upper respiratory illness	7 (3.6)	39 (9.0)	0.017
Lower respiratory illness	186 (96.4)	392 (91.0)	0.017
Total severity score			0.172
Mild	94/135 (69.6)	221/291 (75.9)	
Moderate	36/135 (26.7)	55/291 (18.9)	
Severe	5/135 (3.7)	15/291 (5.2)	
Days requiring O_2 tent/hood (FiO_2 ≥0.3; median [range])	5 (0-43)	4 (0-30)	<0.001
ICU stay	43 (22.3)	14 (3.2)	<0.001
Endotracheal intubation	5 (2.6)	8 (1.9)	0.553
Ribavirin use	4 (2.1)	5 (1.2)	0.469
Antibiotic use	60 (31.1)	247 (57.3)	<0.001
Hospitalization (days; median [range])	6 (2-46)	6 (1-34)	0.067
Medical cost (US$; median [interquartile range])	894 (597-1288)	613 (466-800)	<0.001

Abbreviations: O_2 = oxygen; FiO_2 = fraction of inspired O_2; ICU = intensive care unit.

nosocomial RSV infection. He survived with the sequela of chronic lung disease following therapy consisting of ribavirin, steroids, and antibiotics. Table 5 lists co-infectious pathogens other than RSV in each episode.

Comorbid diseases and severity

Compared with those without underlying disease (n = 630), children with underlying disease (n = 262) were older (11 vs 9 months, p=0.011), required longer durations of oxygen therapy (7 vs 4 days, p<0.001), had more involvement of lower respiratory tracts (96.2% vs 92.3%, p=0.037) and ICU stays (49..0% vs 9.4%, p<0.001), endotracheal intubations (21.0% vs 2.0%, p<0.001), and ribavirin usage (35.0% vs 1.4%, p<0.001) [Table 6].

Compared with those without endotracheal intubation (n = 824), cases requiring endotracheal intubation (n = 68) had higher rates of underlying diseases (80.9% vs 25.1%, p<0.001). Three most pertinent underlying diseases were congenital heart disease (45.6% vs 8.1%, p<0.001), chronic lung disease (13.2% vs 3.2%, p<0.001), and neurological disorder (17.6% vs 3.5%, p<0.001).

We further analyzed risk factors associated with endotracheal intubation after RSV infections in 98 cases with congenital heart diseases. Among these, 35 were cyanotic and 63 acyanotic, and 52 cases (53%) underwent CPB and open-heart surgery. Potential risk factors

Table 5. Coinfectious pathogens other than respiratory syncytial virus

Coinfectious pathogen	No. of cases
Bacterial agent	
Mycoplasma pneumoniae[a]	18
Chlamydia pneumoniae	7
Streptococcus pneumoniae[b]	5
Haemophilus influenzae[b]	2
Moraxella catarrhalis[c]	1
Group A streptococcus	1
Staphylococcus haemolyticus[c]	1
Viridans streptococci (intermedius, oralis)[c]	2
Salmonella spp.[c]	3
Klebsiella pneumoniae[c]	1
Viral agent	
Parainfluenza virus	3
Metapneumovirus	1
Rotavirus	1

[a]*M. pneumoniae* was diagnosed by enzyme-linked immunosorbent assay for serum immunoglobulin M.
[b]*S. pneumoniae* and *H. influenzae* were isolated from the sputum or via urine antigen detection (in the case of *S. pneumoniae*).
[c]All organisms were isolated by blood culture, except for 1 *Salmonella* sp. which was isolated from stools. Cardiac vegetation was visible on echocardiogram, in this case of ventricular septal defect.

Table 6. Comparison of demographic data, clinical profiles, and management according to the pressure or absence of underlying diseases

Variable	Underlying diseases		*p*
	Yes (n = 262) No. (%)	No (n = 630) No. (%)	
Age (months; median [range])	11 (0-195)	9 (0-77)	0.015
Male gender	153 (58.4)	402 (63.8)	0.130
Fever	188 (71.8)	424 (67.5)	0.234
Duration of fever (days; median [range])	3 (1-15)	3 (1-14)	0.529
Family history of respiratory illness	57 (22.0)	222 (35.0)	<0.001
Hospitalization	258 (98.5)	604 (95.9)	0.064
Leukocytosis	68/260 (26.2)	178/609 (29.2)	0.367
C-reactive protein (mg/dL; median [range])	0.6 (0-20)	0.4 (0-19)	0.011
Days requiring O_2 tent/hood (FiO_2 ≥0.3; median [range])	7 (0-133)	4 (0-43)	<0.001
Upper respiratory illness[a]	10 (3.8)	48 (7.7)	0.037
Lower respiratory illness[b]	252 (96.2)	582 (92.3)	0.037
ICU stay	129 (49.0)	59 (9.4)	<0.001
Endotracheal intubation	55 (21.0)	13 (2.0)	<0.001
Nebulized bronchodilator	159 (60.7)	298 (47.3)	<0.001
Systemic corticosteroids	26 (10.0)	74 (11.7)	0.471
Ribavirin use	92 (35.0)	9 (1.4)	<0.001
Antibiotic use	179 (68.3)	308 (48.9)	<0.001
Hospitalization (days; median [range])	8 (2-133)	6 (1-46)	<0.001
Medical cost (US$; median [interquartile range])	1256 (681-3975)	675 (488-931)	<0.001
RSV by nosocomial route	65 (24.8)	6 (1.0)	<0.001

Abbreviations: O_2 = oxygen; FiO_2 = fraction of inspired O_2; ICU = intensive care unit; RSV = respiratory syncytial virus

[a]Denotes the diagnosis of upper respiratory infection or croup.

[b]Includes acute bronchiolitis, bronchopneumonia, or pneumonia.

are age less than 6 months (p=0.011), CPB within 3 months (p=0.001), and furosemide use of more than 2 mg/kg/day (p=0.001).

Seasonal epidemiology

RSV-related illness occurred year-round in Taiwan. We plotted composite positive RSV antigen or culture, and episodes of acute bronchiolitis against weeks for children below 2 years old. The analysis of seasonality showed a biennial pattern with peaks in the spring and fall (Fig. 1 and Fig. 2). However, variations in this trend were substantial from one year to another. In 2001, 2003, and 2004, the major peak was seen in fall, but 2002 and 2005 showed peaks in the spring. We adopted the statistical method proposed by Freedman [7] and further confirmed this seasonal variation. The major peak for positive RSV antigen was in the fall, whereas that for acute bronchiolitis was in the spring.

Medical costs

Disease burden was calculated by adding together the medical costs of hospitalization, and outpatient and emergency department visits. Nosocomial RSV infections were excluded. Among the cases without hospitalization, the average medical cost was US$ 72 per infection. The average medical cost was US$ 44 per outpatient visit and US$ 91 per emergency visit. The medical cost of hospitalized cases without ICU stay was US$ 800 per infection while that of hospitalized cases with ICU care was a much higher US$ 5313 per infection. The medical cost per infection of those with underlying diseases was significantly higher than those without (US$ 1256 vs 675, p<0.001). The total medical cost was US$ 250,000 annually in our hospital. Since our study involved mainly inpatients and payments covered by the Bureau of National Health Insurance, the actual disease burden, including non-medical costs, was much higher than estimated.

Discussion

RSV infections can be detected using the rapid antigen test by direct immunofluorescence assays or conventional virus cultures. Although the sensitivity and specificity of the 2 methods are different, they peaked in the same seasons in our study (data not shown).

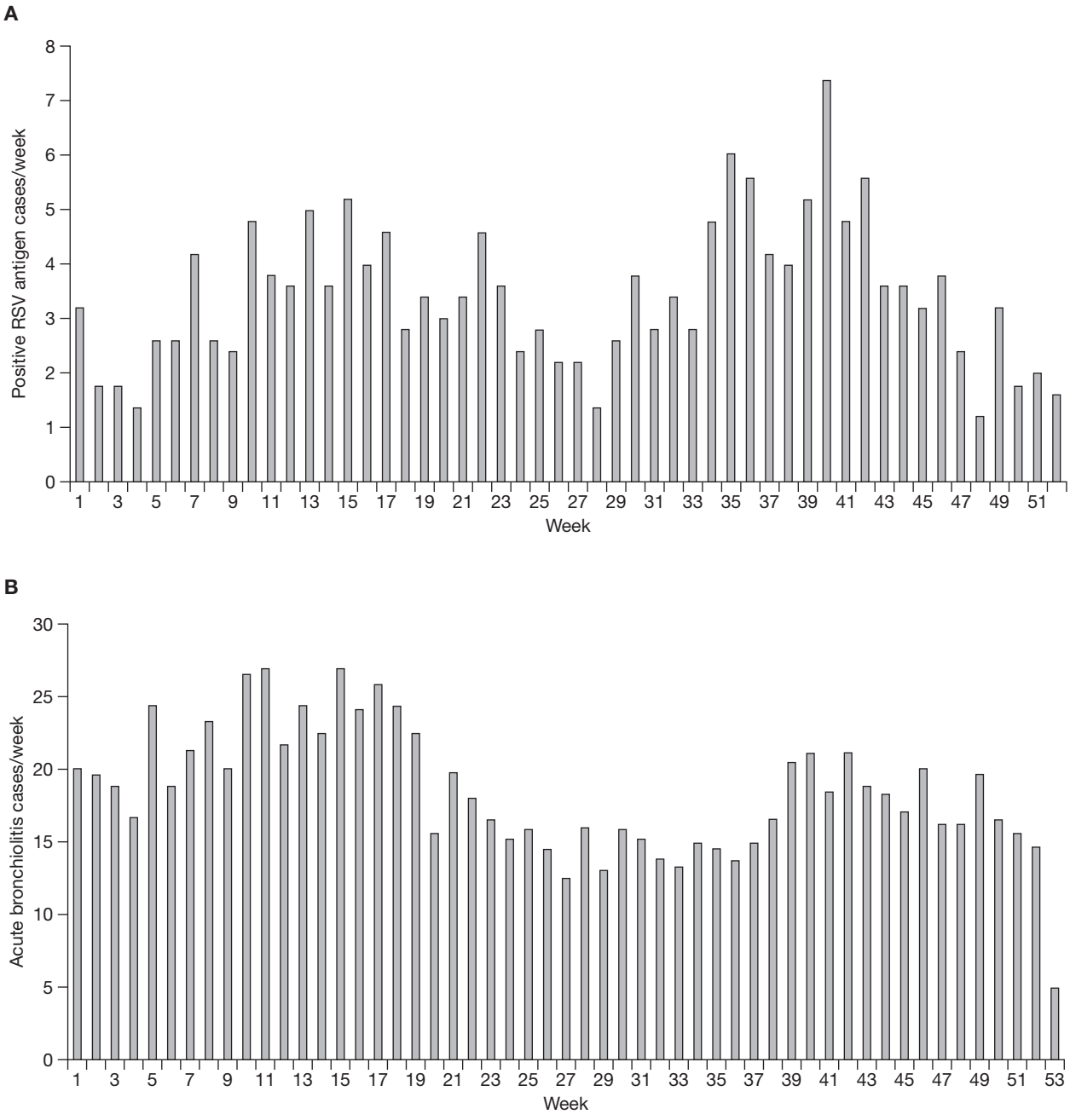

Fig. 1. Composite weekly rates show a biennial pattern with peaks in spring and fall for (A) positive respiratory syncytial virus (RSV) antigen; and (B) acute bronchiolitis.

The severity score of RSV infections in children with underlying diseases cannot be assessed easily and may be affected by underlying conditions. Our analysis selected the final outcome (humidified oxygen use, ICU stay, endotracheal intubation, use of antibiotics, and medical cost) to be the indicator of disease severity. Children with underlying diseases suffered from significant morbidity, and even mortality, and carried a heavy disease burden.

RSV infections requiring endotracheal intubation were associated with underlying diseases, including chronic lung disease, congenital heart disease, either cyanotic or acyanotic, and neurological disorders. Premature infants, one-third of whom developed chronic lung disease in our study, were not associated with increased endotracheal intubation after RSV infections. Selection bias due to exclusion of outpatients was considered. Family history of respiratory illness was

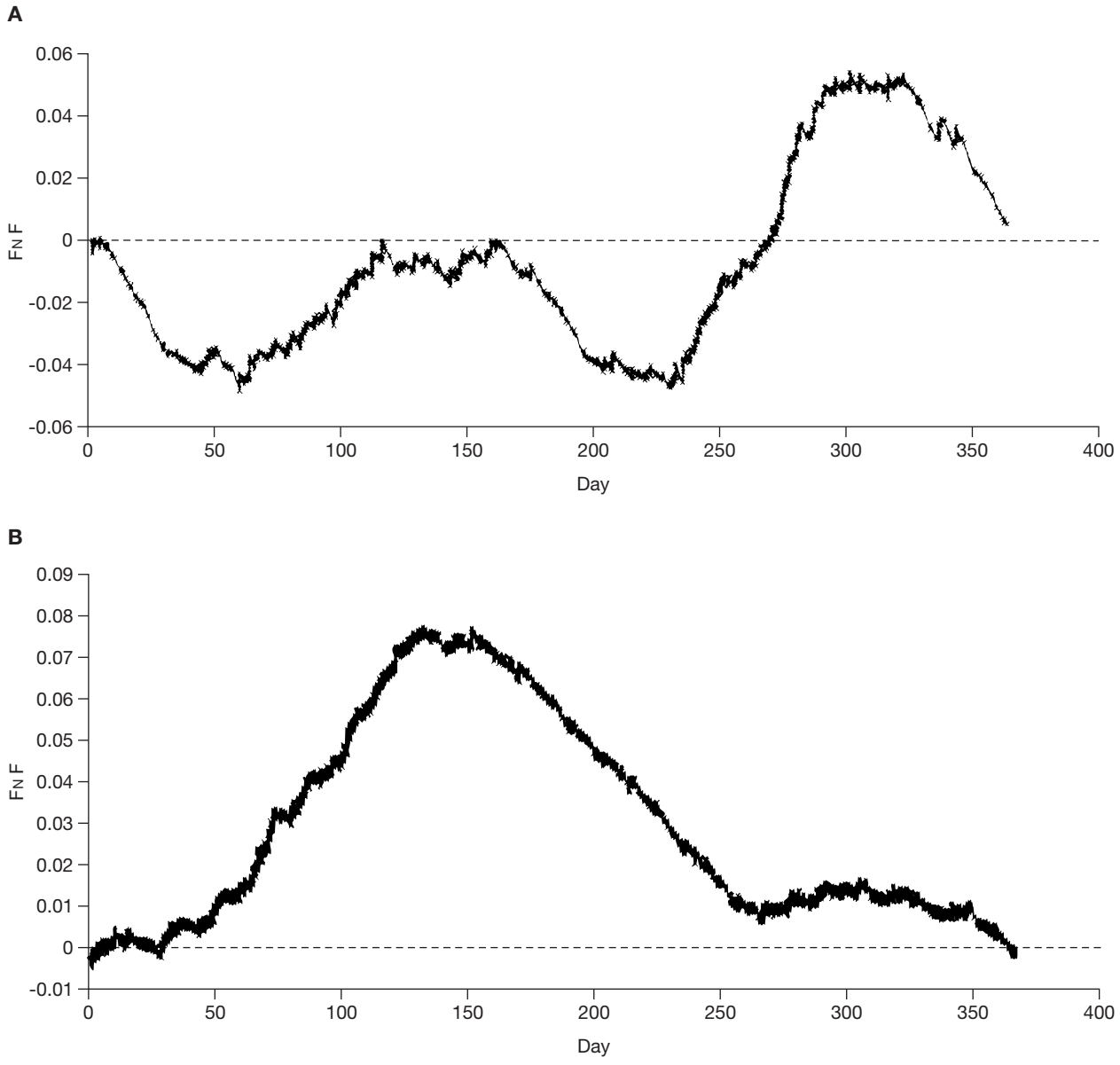

Fig. 2. Difference between sampling distribution (F_N) and cumulative distribution (F) confirms seasonal variation of (A) positive respiratory syncytial virus antigen; and (B) acute bronchiolitis. $p<0.01$ in both (A) and (B).

significantly less common in those with endotracheal intubation than those without (10.3% vs 33.0%, $p<0.001$). This may be explained by a higher percentage (80.9% vs 25.1%, $p<0.001$) of cases with underlying disease in the group with endotracheal intubation. Patients with underlying diseases had a lower incidence of family history of respiratory disease (22.0% vs 35.0%, $p<0.001$) and a higher rate of nosocomial RSV infection (24.8% vs 1.0%, $p<0.001$) than those without underlying diseases.

The severity scores of RSV infections among infants below and over 6 months of age were not significantly different. The much lower percentage of cases of onset and duration of fever in infants below 6 months of age may be explained by the partial protective effects of maternally-derived serum antibodies against RSV. However, younger infants stayed more frequently in ICUs than their older counterparts (22.3% vs 3.2%, $p<0.001$). More vacant beds in the ICUs and parental anxiety may be the cause. Fewer histories of respiratory illness were found in the families of older infants and children, who mainly acquired the infection from day-care units or kindergartens; for infants, older siblings were the most likely source of the virus [8].

Among the identified risk factors, children with cyanotic congenital heart disease and chronic lung disease were particularly prone to develop serious illness following RSV infections. CPB was associated with lung injury [9]. The time interval between CPB and RSV infection seems crucial. The underlying mechanism of CPB-related lung injury is still unclear, but surfactant deficiency may play a role.

Reinfection and rehospitalization in this series indicated the partial and short-term character of RSV immunity. Reinfection illnesses are generally mild [10], but can be detrimental in the immunocompromised. Earlier reports have suggested that normal infants shed RSV for 21 days [11], but RSV shedding could be as long as 199 days in human immunodeficiency virus-infected children [12]. In our cohort, 1 healthy, 5-month-old boy shed virus for at least 33 days in an episode of hospitalization. Based on the rapid antigen test, 2 cases of cerebral palsy with rehospitalization shed virus for up to 66-110 days. The duration of virus shedding and route of transmission are key issues for the control of nosocomial RSV infections. Eye and nose were proven to be equally common routes of transmission [13]. Medical personnel should wear gloves, gowns, and goggles to protect themselves against infectious secretions and stop their further spreading. Strict washing of hands and cohort care also reduce infection risk. In our hospital, contact isolation was employed for RSV infections. However, shortage of nursing staff at wards with high patient turnover rates, lack of isolation facilities, and delays in the reports of rapid antigen tests all contributed to the high nosocomial infection rate.

The different major peaks between the positive RSV antigen and acute bronchiolitis may indicate that pathogens other than RSV are responsible for acute bronchiolitis in the spring. These unspecified pathogenic agents behind the spring episodes of acute bronchiolitis in Taiwan may merit further studies.

Although the seasonality of RSV infection in our series showed a biennial pattern, it represented only a single institute in northern Taiwan. Huang et al showed that RSV circulated year-round with a peak between July and October in northern Taiwan [3]. Nevertheless, great variations in the year-to-year patterns make it difficult to define specific epidemic seasons in Taiwan. Passive immunization, using high-titer RSV immunoglobulin or humanized monoclonal antibody against RSV, will remain the mainstay for the prophylaxis of the disease until a more effective vaccine for RSV becomes available. However, the potency of antibody prophylaxis would be considerably lower in Taiwan in the absence of constant seasonal peaks in RSV infections.

There were 2 major limitations in our studies. Firstly, this retrospective study focused mainly on inpatients. We need prospective surveillance to monitor the epidemiology of RSV infections in the community, as RSV is an emerging nosocomial pathogen both in the elderly and in the immunocompromised [14,15]. Secondly, this study represents only the results of a tertiary care medical center in northern Taiwan. A comprehensive study collaborating local clinics, regional hospitals, and medical centers will provide more details of RSV infections in Taiwan.

In conclusion, RSV is the most important viral pathogen in infants and children below the age of 2 years. In chidren with underlying diseases, RSV infection is associated with significant morbidity and even mortality. Nosocomial infections appear to be an important cause of RSV transmission. The seasonality of RSV infections in Taiwan showed a biennial pattern with peaks in the spring and fall.

Acknowledgment

We thank the Department of Medical Affairs, National Taiwan University Hospital, for their help in the calculation of medical costs.

References

1. Meert K, Heidemann S, Abella B, Sarnaik A. Does prematurity alter the course of respiratory syncytial virus infection? Crit Care Med. 1990;18:1357-9.
2. American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn. Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. Pediatrics. 2003;112: 1442-6.
3. Huang YC, Lin TY, Chang LY, Wong KS, Ning SC. Epidemiology of respiratory syncytial virus infection among paediatric inpatients in northern Taiwan. Eur J Pediatr. 2001;160:581-2.
4. Chen CJ, Jeng MJ, Yuan HC, Wu KG, Soong WJ, Hwang B. Epidemiology of respiratory syncytial virus in children with lower respiratory tract infection. Acta Paediatr Taiwan. 2005; 46:72-6.
5. Wainwright C, Altamirano L, Cheney M, Cheney J, Barber S, Price D, et al. A multicenter, randomized, double-blind, controlled trial of nebulized epinephrine in infants with acute

bronchiolitis. N Engl J Med. 2003;349:27-35.
6. Rusconi F, Castagneto M, Gagliardi L, Leo G, Pellegatta A, Porta N, et al. Reference values for respiratory rate in the first 3 years of life. Pediatrics. 1994;94:350-5.
7. Freedman LS. The use of a Kolmogorov-Smirnov type statistic in testing hypotheses about seasonal variation. J Epidemiol Community Health. 1979;33:223-8.
8. Hall CB, Geiman JM, Biggar R, Kotok DI, Hogan PM, Douglas GR Jr. Respiratory syncytial virus infections within families. N Engl J Med. 1976;294:414-9.
9. McGowan FX, Ikegami M, del Nido PJ, Motoyama EK, Kurland G, Davis PJ, et al. Cardiopulmonary bypass significantly reduces surfactant activity in children. J Thorac Cardiovasc Surg. 1993;106:968-77.
10. Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. Am J Dis Child. 1986;140:543-6.
11. Hall CB, Douglas RG, Geiman JM. Respiratory syncytial virus infections in infants: quantitation and duration of shedding. J Pediatr. 1976;89:11-5.
12. King JC, Burke AR, Clemens JD, Nair P, Farley JJ, Vink PE, et al. Respiratory syncytial virus illnesses in human immunodeficiency virus- and noninfected children. Pediatr Infect Dis J. 1993;12:733-9.
13. Hall CB, Douglas RG Jr, Schnabel KC, Geiman JM. Infectivity of respiratory syncytial virus by various routes of inoculation. Infect Immun. 1981;33:779-83.
14. Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. N Engl J Med. 2005;352:1749-59.
15. Jones BL, Clark S, Curran ET, McNamee S, Horne G, Thakker B, et al. Control of an outbreak of respiratory syncytial virus infection in immunocompromised adults. J Hosp Infect. 2000; 44:53-7.

