Contents lists available at ScienceDirect

Journal of the Formosan Medical Association

Journal homepage: http://www.jfma-online.com

ELSEVIER

Original Article

Epidemiological Study of Hospitalization Associated With Respiratory Syncytial Virus Infection in Taiwanese Children Between 2004 and 2007

Hsin Chi,[1,4,5] I-Shou Chang,[2] Fang-Yu Tsai,[2] Li-Min Huang,[3,5]* Pei-Lan Shao,[3,5]
Nan-Chang Chiu,[1,4] Luan-Yin Chang,[3,5]* Fu-Yuan Huang[1]

Background/Purpose: Respiratory Syncytial Virus (RSV) is the leading cause of hospitalization in young children. The population-based burden of RSV hospitalization and the effect of potential risk factors on the severity of illness were evaluated in Taiwanese children.

Methods: We analyzed the annual population-based incidence, underlying diseases and characteristics of hospitalizations due to RSV in Taiwanese children under 5 years of age from 2004 to 2007 by using Taiwan's National Health Insurance database.

Results: A total of 11,081 children with RSV-associated hospitalization were studied. Average annual population-based hospitalization incidence was 1,077 and 232 per 100,000 children-year in children under 6 months and under 5 years of age, respectively. The peak incidence occurred between 1 and 2 months of age. The male-to-female incidence risk ratio was 1.4:1 ($p < 0.001$). There was a significant seasonal distribution with consistent peaks in the spring and autumn every year ($p < 0.001$). A total of 373 patients (3.3%) had repeated RSV infection. The 943 children (8.5%) with underlying diseases were older ($p = 0.001$), required longer intensive care unit (ICU) stays ($p < 0.001$), had a higher rate of endotracheal intubation ($p < 0.05$), and incurred higher medical costs ($p < 0.001$). A total of 888 patients (8%) required ICU care. Younger age ($p < 0.001$), prematurity ($p < 0.001$), cerebral palsy ($p < 0.001$) and congenital heart disease ($p < 0.001$) were independent predictors of requiring ICU care.

Conclusion: RSV infection occurs biennially with peaks in spring and fall in Taiwan. Patients with underlying diseases need longer hospital and ICU stays and incur higher medical costs. Younger age, prematurity, congenital heart disease and cerebral palsy are predictors of ICU care.

Key Words: hospitalizations, respiratory syncytial virus, underlying diseases

[1]Department of Pediatrics, Mackay Memorial Hospital, [3]Department of Pediatrics, National Taiwan University Hospital, [4]Mackay Medicine, Nursing and Management College, [5]Graduate Institute of Clinical Medicine, National Taiwan University College of Medicine, Taipei, and [2]Division of Biostatistics and Bioinformatics, National Health Research Institutes, Miaoli, Taiwan.

*Correspondence to: Dr Luan-Yin Chang, Department of Pediatrics, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, Taiwan 100.
E-mail: ly7077@tpts6.seed.net.tw, lychang@ntu.edu.tw
OR
Professor Li-Min Huang, Department of Pediatrics, National Taiwan University Hospital, 7 Chung-Shan South Road, Taipei, Taiwan 100.
E-mail: lmhuang@ntu.edu.tw

Lower respiratory tract infection due to respiratory syncytial virus (RSV) is a major cause of morbidity in infants and young children.[1] Almost all children are infected by RSV at least once by 2 years of age, and approximately 1–2% of infants require hospitalization for RSV-associated lower respiratory tract infection.[2,3] The peak incidence of RSV infection and hospitalization is between the second and the sixth month of age.[4,5] In high-risk groups, such as preterm infants, younger chronological age, young children with chronic lung disease, immunodeficient patients and infants with congenital heart disease, RSV infections can cause considerable morbidity and death.[6–9] Hospitalization rate and mortality rate in these higher risk groups are approximately 10% and 3%, respectively.[10] RSV epidemics depend on geographic location, and cluster during the autumn and last until spring in temperate climates and generally coincide with the rainy season in tropical areas.[11–14] Treatment of RSV respiratory illness is mainly supportive, with ribavirin remaining the specific treatment.[15] Monthly palivizumab is currently recommended in high-risk children as prophylaxis for RSV infection during winter,[16] however, this medication is still very expensive and in limited supply in Taiwan.[17]

Nationwide epidemiologic data concerning RSV is limited and the total burden of RSV infection remains undefined in Taiwan.[18–20] Therefore, the aims of this population-based study were to determine severity, risk factors, seasonality, and medical cost of RSV-associated hospitalization in Taiwan.

Materials and Methods

Taiwan's National Health Insurance (NHI) system implemented in March 1995, covers over 96% of the Taiwanese population. Through the NHI database, we collected hospital healthcare records from 2004 to 2007 for hospitalized children below the age of 5 diagnosed with RSV-associated International Classification of Diseases, Ninth Revision, and Clinical Modification (ICD-9 CM) codes.

These codes included RSV bronchiolitis (ICD-9 CM Code 466.11), viral pneumonia due to RSV (ICD-9 CM 480.1) and RSV infection (ICD-9 CM 079.6). The underlying diseases were also collected based on the ICD-9 CM: prematurity (ICD-9 CM Code 765.10–765.19); congenital heart disease (ICD-9 CM Code 745.0–747.4); chronic lung disease (ICD-9 CM code 770.7); cerebral palsy (ICD-9 CM code 343.9) and hematologic diseases (ICD-9 CM code 200.2–205.9). We also collected data on whether the above patients were treated with intubation of the respiratory tract (ICD-9 procedure code 96.5) or continuous mechanical ventilation (96.7). Chronic lung disease in premature infants was defined as a persistent need for supplemental oxygen at a gestational age of 36 weeks and characteristic findings in the chest radiography. Hospitalizations were stratified by patient age: younger than 1 month, 1 to 2 months, 3 to 6 months, 7 to 12 months, 13 to 24 months, or 25 to 60 months.

We analyzed the RSV-associated hospitalization by year, age group, gender, and season. To calculate the annual population-based incidence of RSV-associated hospitalization, the annual episodes were divided by the same age-specific, midyear gender-specific population of children as reported between 2004 and 2007 from the Taiwan census data. We also analyzed the rate of receiving intensive care unit (ICU) care and compared length of stay with and without specified underlying diseases.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and were compared using Student t test. Categorical variables were expressed as absolute and relative frequencies and were compared using the χ^2 or Fisher's exact test. We then performed simple and multiple logistic regression analyses to identify independent predictors of the need of ICU care. Variables were selected for entry into the regression model if the variables were significantly associated with the need for ICU care ($p < 0.1$) in the univariate analysis. A p value of < 0.05 was considered significant.

Results

Annual incidence

11,081 hospitalizations identified using the RSV specific ICD codes in children up to 5 years of age were reported during the 4-year study period: 2,788 in 2004; 2,795 in 2005; 2,607 in 2006; and 2,891 in 2007. No statistically significant difference was observed in different years. A total of 370 patients (3.3%) had repeated RSV infection. 276 episodes per 100,000 children-year for boys and 194 episodes per 100,000 children-years for girls were identified. The male-to-female incidence risk ratio was 1.4:1 ($p < 0.001$). The average annual population-based incidence of RSV-associated hospitalization was 232 episodes per 100,000 for all children under the age of 5 years (Table 1). The average annual incidence peaked in children between 1 and 2 months of age with 1637 episodes

Figure 1. Annual incidence of RSV-associated hospitalization in children under 5 years of age from 2004 to 2007 in Taiwan.

per 100,000 children-year, which was 7-fold greater than the overall incidence under 5 years of age. The average annual incidence of children less than 1 year of age was 930 episodes per 100,000 children-years. About 70% of RSV-related hospitalizations occurred in infants. The annual incidence of RSV-associated hospitalization was highest in children under 6 months of age in different years (Figure 1).

Seasonality

RSV-associated hospitalization occurred year-round in Taiwan. An analysis of seasonal distribution of hospitalization due to RSV (Figure 2) showed a significant seasonal distribution with a consistent biennial pattern, with yearly peaks in the spring and autumn ($p < 0.001$).

Underlying diseases

Among all the 11,081 RSV-associated inpatients, one or more underlying diseases were present in 943 (8.5%) children. Among these children, 602 (64%) were premature, 468 (50%) had congenital heart disease, 59 (6.3%) had chronic lung disease, 30 (3.2%) had cerebral palsy, 14 (1.5%) had Down syndrome and 10 (1.1%) had hematologic diseases. The children with underlying diseases were older ($p = 0.001$), required longer ICU stays ($p < 0.001$), needed a higher rate of endotracheal intubations ($p < 0.05$), were administered ribavirin ($p < 0.05$) and incurred higher medical costs ($p < 0.001$). Comparisons between patients with
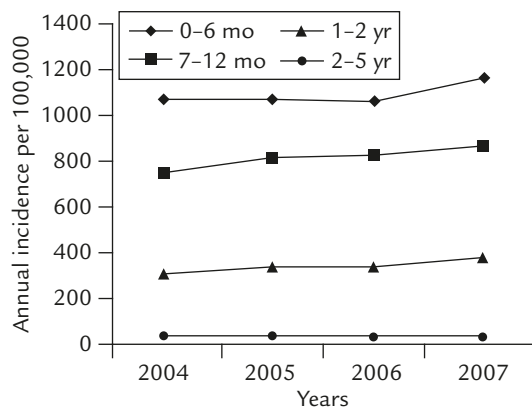
| Table 1.	The annual population-based rate of RSV-associated hospitalization in children under 5 years of age[a]				
Year	2004	2005	2006	2007	Average
Sex					
Boy	255	269	274	307	276
Girl	180	190	185	223	194
Age (mo)					
0–1	437	400	437	446	430
1–2	1608	1491	1569	1879	1637
3–6	1068	1121	1063	1146	1099
7–12	716	781	797	839	783
13–24	250	279	272	328	282
25–60	33	33	25	33	31

[a]*Incidence = episodes per 100,000 children.*
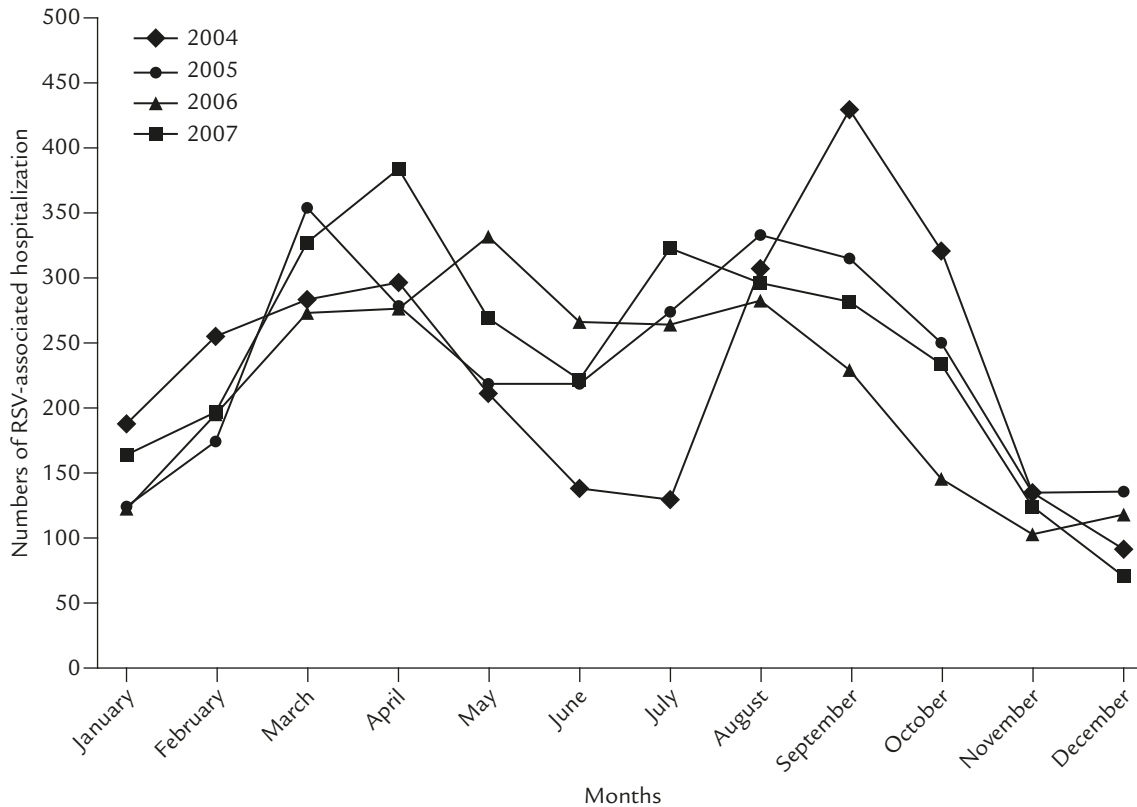
Figure 2. Monthly distribution of RSV-associated hospitalization in children under 5 years of age from 2004 to 2007.

and without underlying diseases of RSV-associated hospitalization are listed in Table 2. The seasonal occurrence of RSV-associated hospitalization in the premature and in patients with congenital heart diseases also peaks in the spring and autumn (Figure 3).

Risk factors associated with the need for ICU care, ribavirin and endotracheal intubation

Ninety-two percent of patients were managed exclusively on a general pediatric ward. Compared with patients managed exclusively in a general pediatric ward, patients requiring ICU care were more likely to be younger ($p < 0.001$), to have higher rates of underlying diseases ($p < 0.05$) and higher mortality rates ($p < 0.05$). One or more risk factors were present in 7.3% of patients managed exclusively in a general pediatric ward compared with 22.5% of patients requiring ICU care ($p < 0.05$).

Ribavirin was prescribed in 0.1% of patients managed exclusively on a general pediatric ward, while 32.1% of patients admitted to the ICU

($p < 0.05$) were treated with this medication. Patients needing ICU care had longer hospital stays (12.0 ± 9.6 vs. 5.9 ± 4.1, $p < 0.001$) and higher mortality rates (0.9% vs. 0.05%, $p < 0.05$). The risk factors associated with the need of ICU care are listed in Table 3. Multivariate analyses showed that age [odds ratio (OR), 0.94; 95% confidence interval (CI), 0.93–0.95, $p < 0.001$], prematurity (OR, 1.78; 95% CI, 1.38–2.29, $p < 0.001$), cerebral palsy (OR, 15.06; 95% CI, 6.48–33.60, $p < 0.001$) and congenital heart disease (OR, 4.50; 95% CI, 3.06–5.78, $p < 0.001$) were independent predictors of the need for ICU care.

Medical cost

The annual mean cost of hospitalization for RSV-associated hospitalization ranged between 84.2 and 93.4 million New Taiwan dollars (NT$) per year. One hospitalization cost an average of NT$32,300. The cost per hospitalization was much higher in patients having underlying disease (72,672 vs. 28,562, $p < 0.001$).

Table 2. Demographic data and management of RSV-associated hospitalization patients with and without underlying diseases[a]

	Underlying diseases		p
	Yes (n = 943)	No (n = 10,138)	
Age (mo)	12.6 ± 10.7	10.4 ± 10.2	0.001
Gender (male)	521 (55.2)	6225 (61.4)	< 0.001
O_2 use	581 (61.6)	5419 (53.5)	< 0.05
ICU care	200 (21.2)	688 (6.8)	< 0.05
Ribavirin use	68 (7.2)	223 (2.2)	< 0.05
Endotracheal intubation	57 (6.0)	79 (0.8)	< 0.05
CPAP	46 (4.9)	111 (1.1)	< 0.05
Transfusion	7 (0.8)	17 (0.16)	NS
Mortality rate	11 (1.2)	2 (0.02)	< 0.01
ICU stay (d)	9.27 ± 8.86	5.70 ± 6.07	< 0.001
Hospital stay (d)	9.9 ± 10.6	6.1 ± 4.00	< 0.001
Medical cost (NT$)	72,672 ± 133,213	28,562 ± 42,551	< 0.001
Medical cost (US$)	2076 ± 3806	816 ± 1216	< 0.001

[a]Data are presented as mean ± SD or n (%). ICU = intensive care unit; CPAP = continuous positive airway pressure; NT$ = New Taiwan dollar; US$ = United States dollar; NS = not significant.
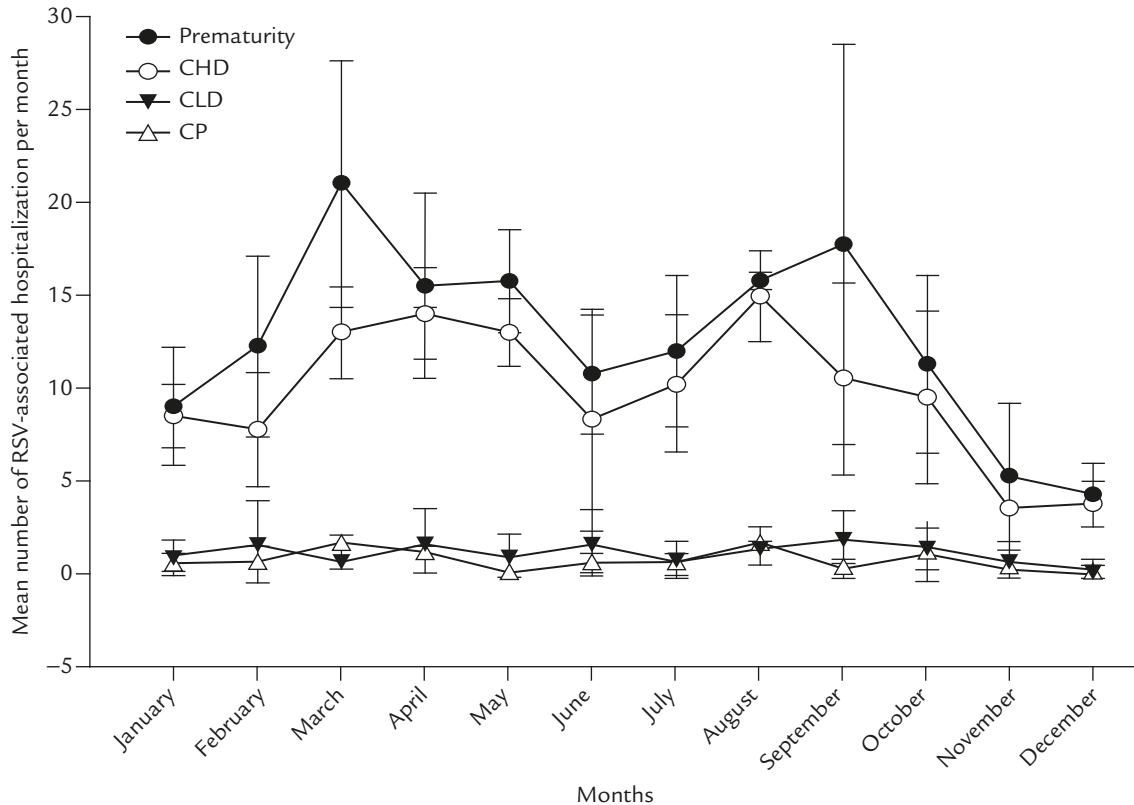

Figure 3. Monthly distribution of RSV-associated hospitalization in children with underlying diseases under 5 years of age from 2004 to 2007. CHD = congenital heart disease; CLD = chronic lung disease; CP = cerebral palsy.

Table 3. Analysis of risk factors associated with patients hospitalized with respiratory syncytial virus, with and without intensive care unit care[a]

	ICU (n=888)	No ICU (n=10,193)	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI)	p
Age (mo)	7.4±8.8	10.9±10.3		<0.001	0.94 (0.93–0.95)	<0.001
Gender (male)	545 (61.4)	6201 (60.8)	1.02 (0.89–1.18)	0.75		
Underlying disease	200 (22.5)	743 (7.3)	3.70 (3.14–4.36)	<0.001		
Prematurity	103 (11.6)	499 (4.9)	2.85 (2.27–3.54)	<0.001	1.78 (1.38–2.29)	<0.001
CHD	127 (14.3)	341 (3.4)	4.82 (3.96–5.88)	<0.001	4.50 (3.06–5.78)	<0.001
Acyanotic	117 (13.2)	309 (3.0)	4.85 (3.95–5.96)	<0.001		
Cyanotic	2 (0.2)	6 (0.1)	3.83 (0.87–16.96)	0.08		
With CLD	8 (0.9)	26 (0.26)	3.55 (1.69–7.49)	<0.001		
CLD	16 (1.8)	43 (0.4)	4.33 (2.43–7.72)	<0.001		
Cerebral palsy	14 (1.6)	16 (0.2)	10.19 (5.69–18.25)	<0.001	15.06 (6.48–33.60)	<0.001
Hematologic diseases	1 (0.1)	9 (0.1)	1.28 (0.16–10.03)	0.82		

[a]Data are presented as mean±SD, n (%) or OR (95% CI). CHD = congenital heart disease; CLD = chronic lung disease; CI = confidence interval.

Discussion

Our findings from the National Health Insurance (NHI) system provide a comprehensive view of the RSV burden among Taiwanese children. Almost 70% of the patients with RSV-associated hospitalization are under 12 months of age. Children with underlying diseases suffered from significant morbidity and mortality. The seasonal distribution had a biennial pattern with peaks in the spring and autumn every year.

The average annual hospitalization rates under 5 years of age were 3 per 1000 children in the United States and 293 per 100,000 children in rural Kenya.[21,22] The average annual hospitalization incidence in Taiwan is lower than the previous report from the USA and in rural Kenya.[21,22] According to the previous studies showing that the hospitalization rate of RSV infection was around 1–2%,[2,3] the total disease burden of RSV infection would be estimated at about 46,500 to 93,000 per 100,000 children per year in the first year of life in Taiwan. This is compatible with previous serologic studies that indicate half of the children are infected during the first year and nearly all children have antibodies against RSV by the end of the second year of life.[1,2] The incidence of RSV-related hospitalizations is highest among young infants 2–6 months of age,[5,23] whereas the incidence peaked among 1–2 months of age in our study. Furthermore, we found the same result that the younger the age, the higher the incidence of RSV-associated hospitalization. In addition to the small size of the conducting airways and incomplete development of the lung structure, the less efficient immune response may explain why an age of less than 6 months at the time of hospitalization is associated with a higher likelihood of being hospitalized due to RSV infection.[9]

Most children with RSV infection who were hospitalized had no coexisting medical conditions or characteristics that significantly identified them as being at greater risk for severe RSV disease, except for being under 2 years of age.[21] Like other previous studies,[21,24] the vast majority of children hospitalized for this condition in our study are

previously normal babies. Although RSV may cause severe infections in healthy young children, the infections are more severe in premature children, in those with immune deficiency, and in those with a subjacent illness, such as chronic lung disease or congenital heart disease.[24–26] In previous analyses, RSV infection is the single most common principal diagnosis leading to rehospitalization of premature infants.[27] Our findings suggested that the patients who had underlying diseases needed longer hospital stay, ICU stay, and incurred higher medical costs.

The risks of severe complications of RSV-associated hospitalization are increased in prematurely born infants with chronic lung disease and in children with unstable hemodynamic congenital heart disease, as well as with severe neuromuscular impairment.[28–31] Of all risk factors assessed, the following were found to be independent risk factors for the development of severe RSV infection: male gender, young age, birth in the first half of the RSV season, day-care attendance, crowding in the home and siblings.[32] In this study, we found younger age and prematurity, congenital heart disease and cerebral palsy were independent predictors of ICU care. We suggested that these findings might be attributed not only to RSV infection, but also to underlying diseases, for example the impaired function of sputum clearance in patients with cerebral palsy might result in respiratory failure and the subsequent need for ICU care. Also, Chan et al assessed the effect of having a combination of risk factors on disease course, and reported that children under 24 months of age with both a history of prematurity and failure to thrive were more likely to develop respiratory failure.[33] However, we demonstrated that a great proportion of our children had no underlying diseases predisposing to admission to the ICU and endotracheal tube intubation. This finding was consistent with data published by other groups.[10,34]

RSV infection occurs mainly during fall and winter in temperate countries,[14] and during the hot months and the rainy season in tropical climates.[11,35] A biennial pattern with peaks in spring and fall occurs in northern Taiwan[20,36] but without

significant seasonality in southern Taiwan.[18] Monthly intramuscular injection of palivizumab in winter is currently recommended to high-risk children as a prophylaxis for reducing the incidence of hospitalization due to RSV infection.[16,30,37] We found a biennial pattern with peaks in spring and fall of RSV associated hospitalizations in this study, which was also seen in the premature and in patients with congenital heart diseases. Cost effectiveness of RSV prophylaxis tended to be more favorable in specific populations, including premature infants born before 32 weeks gestational age, and infants or children aged < 2 years with chronic lung disease or congenital heart disease.[38] In our study, we found prematurity and congenital heart diseases are the independent risk factors of severe RSV infection and these patients might be the candidates for the palivizumab prophylaxis. However, the cost effectiveness of RSV prophylaxis in Taiwan might need further study as the biennial pattern the "RSV season" makes the timing of prophylaxis different from other countries.

One major limitation of this investigation is that this retrospective study focused mainly on reported data, and the true cases of RSV infections might be underestimated. To our knowledge, RSV infection is detected by using the rapid antigen test or conventional virus cultures; however, these detection methods are not available in all hospitals in Taiwan. Besides, not all of the hospitalizations caused by RSV infections were well examined and coded as RSV infections, because the results may have been pending before discharge, or due to indiscretion. Most probably, these patients might be tested for the possibility of RSV infection only when they had severe symptoms and treatment in medical centers. We need prospective surveillance to monitor the epidemiology of RSV infections in the community; collaboration of local clinics, regional hospitals, and medical centers will provide more details of RSV infections in Taiwan.

In summary, RSV infection is an important health issue in children that occurs biennially in Taiwan, with peaks in spring and fall. Patients with underlying diseases needed longer hospital stay,

ICU stay and incurred higher medical costs. We found younger age, prematurity, congenital heart disease and cerebral palsy were independent predictors of ICU care in Taiwanese children below the age of 5 years. Public health goals could be advocated to reduce and prevent RSV disease burden from children with underlying diseases and risks.

Acknowledgments

References

1. Hall CB, McCarthy CA. Respiratory syncytial virus. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and practice of infectious disease*, 6th edition. New York: Churchill Livingstone Inc, 2005:2008–26.

2. Howard TS, Hoffman LH, Stang PE, et al. Respiratory syncytial virus pneumonia in the hospital setting: length of stay, charges, and mortality. *J Pediatr* 2000;137:227–32.

3. Behrendt CE, Decker MD, Burch DJ, et al. International variation in the management of infants hospitalized with respiratory syncytial virus. International RSV Study Group. *Eur J Pediatr* 1998;157:215–20.

4. Hall CB. Respiratory syncytial virus and parainfluenza virus. *N Engl J Med* 2001;344:1917–28.

5. Simoes EA. Respiratory syncytial virus infection. *Lancet* 1999;354:847–52.

6. Meissner HC, Welliver RC, Chartrand SA, et al. Immunoprophylaxis with palivizumab, a humanized respiratory syncytial virus monoclonal antibody, for prevention of respiratory syncytial virus infection in high risk infants: a consensus opinion. *Pediatr Infect Dis J* 1999;18:223–31.

7. Baker KA, Ryan ME. RSV infection in infants and young children. What's new in diagnosis, treatment, and prevention? *Postgrad Med* 1999;106:97–9, 103–4, 7–8 passim.

8. Krilov LR. Respiratory syncytial virus: update on infection, treatment, and prevention. *Curr Infect Dis Rep* 2001;3: 242–6.

9. Rossi GA, Medici MC, Arcangeletti MC, et al. Risk factors for severe RSV-induced lower respiratory tract infection over four consecutive epidemics. *Eur J Pediatr* 2007;166: 1267–72.

10. Wang EE, Law BJ, Stephens D. Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) prospective study of risk factors and outcomes in patients hospitalized with respiratory syncytial viral lower respiratory tract infection. *J Pediatr* 1995;126:212–9.

11. Loscertales MP, Roca A, Ventura PJ, et al. Epidemiology and clinical presentation of respiratory syncytial virus infection in a rural area of southern Mozambique. *Pediatr Infect Dis J* 2002;21:148–55.

12. Stensballe LG, Devasundaram JK, Simoes EA. Respiratory syncytial virus epidemics: the ups and downs of a seasonal virus. *Pediatr Infect Dis J* 2003;22:S21–32.

13. Meissner HC, Anderson LJ, Pickering LK. Annual variation in respiratory syncytial virus season and decisions regarding immunoprophylaxis with palivizumab. *Pediatrics* 2004;114: 1082–4.

14. Handforth J, Friedland JS, Sharland M. Basic epidemiology and immunopathology of RSV in children. *Paediatr Respir Rev* 2000;1:210–4.

15. Ventre K, Randolph A. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children. *Cochrane Database Syst Rev* 2004: CD000181.

16. The IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics* 1998;102:531–7.

17. Weckx LY, Fernandes MM, Monteiro AI, et al. Optimization strategy to minimize wastage of palivizumab during the 2008 RSV season in Sao Paulo, Brazil. *J Trop Pediatr* 2009;55:341–2.

18. Tsai HP, Kuo PH, Liu CC, et al. Respiratory viral infections among pediatric inpatients and outpatients in Taiwan from 1997 to 1999. *J Clin Microbiol* 2001;39:111–8.

19. Huang YC, Lin TY, Chang LY, et al. Epidemiology of respiratory syncytial virus infection among paediatric inpatients in northern Taiwan. *Eur J Pediatr* 2001;160:581–2.

20. Lee JT, Chang LY, Wang LC, et al. Epidemiology of respiratory syncytial virus infection in northern Taiwan, 2001–2005—seasonality, clinical characteristics, and disease burden. *J Microbiol Immunol Infect* 2007;40:293–301.

21. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. *N Engl J Med* 2009;360:588–98.

22. Nokes DJ, Ngama M, Bett A, et al. Incidence and severity of respiratory syncytial virus pneumonia in rural Kenyan children identified through hospital surveillance. *Clin Infect Dis* 2009;49:1341–9.

23. Glezen WP, Taber LH, Frank AL, et al. Risk of primary infection and reinfection with respiratory syncytial virus. *Am J Dis Child* 1986;140:543–6.

24. Weisman LE. Populations at risk for developing respiratory syncytial virus and risk factors for respiratory syncytial virus severity: infants with predisposing conditions. *Pediatr Infect Dis J* 2003;22:S33–7; discussion S7–9.

25. Figueras-Aloy J, Carbonell-Estrany X, Quero J. Case-control study of the risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born at a gestational age of 33–35 weeks in Spain. *Pediatr Infect Dis J* 2004;23:815–20.

26. Heikkinen T, Valkonen H, Lehtonen L, et al. Hospital admission of high risk infants for respiratory syncytial virus infection: implications for palivizumab prophylaxis. *Arch Dis Child Fetal Neonatal Ed* 2005;90:F64–8.

27. Underwood MA, Danielsen B, Gilbert WM. Cost, causes and rates of rehospitalization of preterm infants. *J Perinatol* 2007;27:614–9.

28. Purcell K, Fergie J. Driscoll Children's Hospital respiratory syncytial virus database: risk factors, treatment and hospital course in 3308 infants and young children, 1991 to 2002. *Pediatr Infect Dis J* 2004;23:418–23.

29. Law BJ, Langley JM, Allen U, et al. The Pediatric Investigators Collaborative Network on Infections in Canada study of predictors of hospitalization for respiratory syncytial virus infection for infants born at 33 through 35 completed weeks of gestation. *Pediatr Infect Dis J* 2004;23:806–14.

30. Meissner HC, Long SS. Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. *Pediatrics* 2003;112:1447–52.

31. Feltes TF, Cabalka AK, Meissner HC, et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. *J Pediatr* 2003;143: 532–40.

32. Simoes EA. Environmental and demographic risk factors for respiratory syncytial virus lower respiratory tract disease. *J Pediatr* 2003;143:S118–26.

33. Chan PW, Lok FY, Khatijah SB. Risk factors for hypoxemia and respiratory failure in respiratory syncytial virus bronchiolitis. *Southeast Asian J Trop Med Public Health* 2002; 33:806–10.

34. Lanari M, Giovannini M, Giuffre L, et al. Prevalence of respiratory syncytial virus infection in Italian infants hospitalized for acute lower respiratory tract infections, and association between respiratory syncytial virus infection risk factors and disease severity. *Pediatr Pulmonol* 2002;33:458–65.

35. Law BJ, Carbonell-Estrany X, Simoes EA. An update on respiratory syncytial virus epidemiology: a developed country perspective. *Respir Med* 2002;96 (Suppl B):S1–7.

36. Chen CJ, Jeng MJ, Yuan HC, et al. Epidemiology of respiratory syncytial virus in children with lower respiratory tract infection. *Acta Paediatr Taiwan* 2005;46:72–6.

37. 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.

38. Prescott WA Jr, Doloresco F, Brown J, et al. Cost effectiveness of respiratory syncytial virus prophylaxis: a critical and systematic review. *Pharmacoeconomics* 2010;28: 279–93.