HK J Paediatr (new series) 2007;**12**:15-21

Respiratory Syncytial Virus and Influenza Infections among Children ≤3 Years of Age with Acute Respiratory Infections in a Regional Hospital in Hong Kong

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Abstract

Objective: To study the demographic features, clinical manifestations, and hospitalisation rate in children ≤3 years of age with respiratory syncytial virus (RSV) and influenza infections. ***Method:*** Retrospective review of case records of children ≤3 years admitted to paediatric department of a regional hospital in Hong Kong with RSV or influenza infection from 1st January 2004 to 31st December 2004. ***Results:*** During the 1-year study period, 561 children ≤3 years of age were admitted with acute respiratory infection, which accounted for 32.3% of total acute admissions in this age group. Ninety (16.0%) and sixty five (11.6%) of them were infected with influenza and RSV respectively. The majority of children with RSV infection presented with cough (98.5%), wheezing (56.9%) and crepitation (67.7%). When compared with those with influenza infection, children with RSV were younger (12.05 ± 10.07 vs. 18.43 ± 10.67 months, p=0.001), and more commonly hospitalised for acute bronchiolitis (52.3% vs. 5.6%, p<0.05). Chest X-ray abnormalities were more often detected in RSV infection (53.1% vs. 16.7%, p<0.05). Children infected with influenza had higher temperature (39.44 ± 0.73°C vs. 39.16 ± 0.6°C, p=0.046), and longer duration of fever (4.06 ± 2.37 days vs. 2.77 ± 2.69 days, p<0.05) than those with RSV. Four patients (6.2%) with RSV infection were admitted to PICU and none in the influenza group. There was no fatality. Sixteen (16/155, 10%) ex-premature infants or children were admitted for respiratory tract infection. Fourteen and two were infected with RSV and influenza, respectively. ***Conclusion:*** In our locality, children ≤3 years of age with acute respiratory tract infection requiring hospitalisation is mainly due to RSV and influenza virus. The PICU admission and mortality rates were low among these children.

Key words Acute Respiratory Infections; Influenza; Respiratory Syncytial Virus

Introduction

During the past 40 years, overall mortality among children younger than five years of age in Hong Kong has declined greatly, from 43 per 1000 to 4 per 1000.[1] Nevertheless, an increase in many childhood respiratory infections, in particular croup and bronchiolitis, is seen over the years.[2] A recent retrospective population-based study found that influenza had been the leading cause of children hospitalisation in Hong Kong. The estimates of influenza-related hospitalisation ranged from 2,882 per 100,000 in children <1 year of age to 773 per 100,000 children 2-5 years of age.[3] For respiratory syncytial virus (RSV), the estimated annual incidence of hospitalisation in Hong Kong is 2.5/1000 children <5-year-old with a mortality of 0.15% among hospitalised cases.[4] Community-acquired RSV infection accounts for 12.9% of all respiratory admissions in children and it is responsible for over 90% admissions during the peak seasons.[4]

The aims of the current report are to determine the incidence of hospitalisation of infants or children under 3 years of age with RSV or influenza infection within the

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Received August 30, 2006

1 year study period and to examine socio-demographic, clinical features and radiographic characteristics among these infected children.

Materials and Methods

Sample Selection

We searched the Clinical Data Analysis and Reporting System (CDARS) using diagnostic codes 487 (Influenza), 079.6 (RSV), 466.11 (acute bronchiolitis due to RSV), and 480.1 (pneumonia due to RSV) of the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) AND discharge date between 1st January 2004 and 31st December 2004 AND age ≤3 years. Patient name list was generated. Every patient's medical record was traced and completely reviewed from admission to discharge. We also obtained from CDARS the following diagnostic codes for the numbers of acute general admissions of patients ≤18 years of age and children ≤3 years of age with acute respiratory illnesses between 1st January 2004 and 31st December 2004: ICD-9-CM codes 460 to 466 (acute upper respiratory infections), and ICD-9-CM codes 480 to 487 (pneumonia).

Data Collection

Information on birth weight, age at admission, admission date, sex, gestational age, race, clinical findings, investigation results, medical diagnoses, medical procedures, and duration of hospitalisation was obtained from medical record reviews and entered into a computerised database.

Viral Diagnosis

Nasopharyngeal aspirate (NPA) was routinely collected for viral investigation from all children hospitalised with acute respiratory disease. A catheter was inserted into the nasopharynx via each nostril in turn, and secretions were aspirated. The catheter containing nasal secretion was then dipped into the virus transport medium (Earle's balanced salt solution with bovine serum albumin and antibiotics) and approximately 2 ml was aspirated to wash the secretions from the catheter into the mucus extractor. The specimens were collected at the time of admission and transported to the laboratory at ambient temperature immediately. The duration of exposure to ambient temperature should not exceed 3 hours at maximum. Specimens collected were held at 4°C in the refrigerator if immediate transportation to the laboratory was not feasible.[5]

Aliquot of the nasopharyngeal aspirate suspension was tested by Directigen Flu A+B assay in our hospital microbiology laboratory. Additional aliquots were sent to Government Virus Unit, Department of Health for immunofluorescent antigen detection of respiratory viruses and for viral culture.

Directigen Flu A+B. The Directigen Flu A+B assay was carried out according to the manufacturer's instructions. 200 µl NPA was mixed with 8 drops extraction buffer into the tube provided. Four drops of the specimen extract was then added to each well of the test device. Subsequently, specific conjugate, washing buffer, and substrate solution were added within a 10-min period. The results were read at 5 minute, the stop solution was added, and the test result was read again. The control dot needed to be visible for a valid test, and if absent, the result was regarded as indeterminate. A purple triangle was required for a positive result.[6]

Immunofluorescence (IF) and viral culture. The direct immunofluorescent antigen (DFA) of NPA specimens was carried out as previously described.[7] The DARKO (K6102), a commercial direct IF test kit was used. In brief, the specimen was washed in phosphate buffered saline and was centrifuged for 10 minutes at 380 g, after which the sediment was smeared onto a glass slide and fixed with acetone. Fluorescein isothiocyanate (FITC) conjugated murine monoclonal antibodies against RSV were then added. After 15 minutes of incubation at 37°C followed by washing, the slide was examined under the fluorescence microscope to detect yellowish green fluorescent intracellular cytoplasmic granules indicative of RSV infection. For influenza virus isolation and identification, NPA specimen was inoculated into the test tubes containing Madin-Darby canine kidney (MDCK) cells and maintenance medium, which was changed every 2 days. The cultures were incubated at temperatures of 33-34°C on a roller drum at 12 rpm. The tubes were observed daily for cytopathic effect (CPE) or hemadsorption activity with guinea pig red blood cells, as appropriate for 10 to 14 days.[8]

Statistical Analysis

The differences of clinical characteristics between children with RSV and influenza virus infections were analysed statistically. We used Fisher's exact test for

categorical comparisons of data. Differences in the means of continuous measurements were tested by the Student's t-test or the Mann-Whitney U test. A *P* value of <0.05 signified statistical significance. All statistical analyses were performed on a personal computer with the statistical package SPSS for Windows (Version 13, SPSS).

Results

During the study period, a total of 561 children ≤3 years of age were hospitalised with an acute respiratory infection and the total number of acute admissions in this age group was 1735. Therefore these children accounted for 32.3% of total acute admissions in children aged ≤3 years. Sixty-five (11.6%) children were diagnosed to have RSV infection by NPA immunofluorescence. In one child a concomitant infection with Haemophilus Influenzae was present. Ninety children (16.0%) were infected with influenza virus. Although Directigen A+B was negative in twelve of them, the diagnosis was all confirmed by viral culture. Eighty-eight children had influenza A/H3N2 infection. The other two children had influenza B and C infections, respectively. Children with RSV ranged from 17 days to 35 months of age (mean 12.05 months, SD 10.1) and were younger than those with influenza infection (mean 18.43 months, SD 10.7; p=0.001). There was a preponderance of males (M:F 1.3:1) with influenza while the sex ratio for RSV group was 1:1. In children ≤3 years of age, influenza and RSV contributed to 5.2% and 3.7% of total acute paediatric admissions, respectively.

The seasonal pattern of influenza and RSV infections was shown in Figure 1. The clinical features and diagnoses of patients with RSV were compared with those children with influenza (Tables 1 and 2). Children infected with influenza tended to have higher temperature (39.44 ± 0.73°C vs. 39.16 ± 0.6°C, p=0.046), and longer duration of fever (4.06 ± 2.37 days vs. 2.77 ± 2.69 days, p<0.05) than those with RSV. Congested throat (61.1%) was commonly seen in children having influenza. However, RSV infections were more likely to be associated with cough (98.5%), wheezing (56.9%), and crepitations (67.7%) than were influenza infections. URTI accounted for 80% of hospital admissions of influenza-infected children but only 23.1% in RSV-infected children. In contrast to influenza infection, the cause of hospital admission in RSV infection was often acute bronchiolitis rather than URTI (Table 3). 26.8% children with influenza

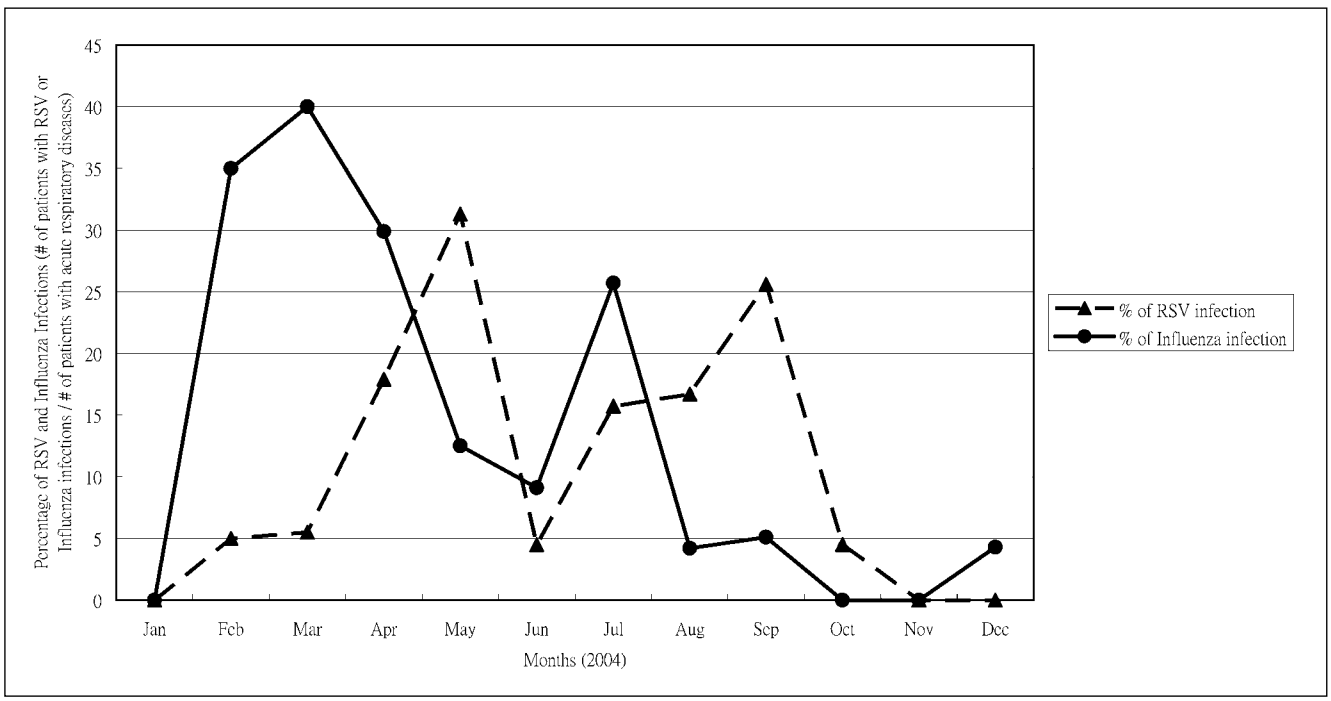

Figure 1 The percentage of RSV and Influenza infections diagnosed from January to December 2004.

Table 1 Clinical features of 90 children admitted with influenza infection compared with 65 children with RSV infection

	Influenza No. positive/total (%)	RSV[a] No. positive/total (%)	p value[b] Influenza vs. RSV
Mean age (months)[c]	18.43	12.05	0.001
Prematurity	2/90 (2.2)	14/65 (21.5)	<0.05
Cough	81/90 (90)	64/65 (98.5)	0.046
Running nose	76/90 (84.4)	55/65 84.6)	1.000
Congested pharynx	55/90 (61.1)	27/65 (41.5)	0.022
Vomiting	25/90 (27.8)	22/65 (33.8)	0.480
Febrile seizures	16/90 (17.8)	6/65 (9.2)	0.165
Crepitations	15/90 (16.7)	44/65 (67.7)	<0.05
Rash	11/90 (12.2)	27/65 (41.5)	0.275
Wheezing	9/90 (10)	37/65 (56.9)	<0.05
Diarrhoea	8/90 (8.9)	8/65 (12.3)	0.595
Conjunctivitis	3/90 (3.3)	0/65 (0)	0.265

[a] RSV, respiratory syncytial virus; ALT, alanine aminotransferase; [b] p values performed using Fisher's exact test except the "age"; [c] p values performed using Mann-Whitney U test.

Table 2 Diagnoses of 90 children admitted with influenza infection compared with 65 children with RSV infection

Clinical diagnoses	Influenza No. positive/total (%)	RSV[a] No. positive/total (%)	p value[b] Influenza vs. RSV
Upper respiratory tract infection	72/90 (80)	15/65 (23.1)	<0.05
Pneumonia	10/90 (11.1)	14/65 (21.5)	0.114
Acute bronchiolitis	5/90 (5.6)	34/65 (52.3)	<0.05
Otitis media	3/90 (3.3)	0/65 (0)	0.265
Asthma exacerbation	2/90 (2.2)	5/65 (7.8)	0.131
Croup	2/90 (2.2)	0/65 (0)	
Gastroenteritis	2/90 (2.2)	0/65 (0)	

[a] RSV, respiratory syncytial virus; ALT, alanine aminotransferase; [b] p values performed using Fisher's exact test.

Table 3 Fever, laboratory findings and duration of hospitalisation of 90 children admitted with influenza infection compared with 65 children with RSV

Characteristics	Influenza Mean (SD)	RSV[a] Mean (SD)	p value
Highest temperature in hospital (°C)[b]	39.44 (0.73)	39.16 (0.60)	0.046
Duration of fever[c] (days)	4.06 (2.37)	2.77 (2.69)	<0.05
White blood cell count[c] (10^9/L)	9.33 (3.48)	12.00 (5.65)	0.004
Neutrophil count[c] (10^9/L)	5.20 (3.12)	6.06 (4.24)	0.523
Lymphocyte count[c] (10^9/L)	3.11 (1.99)	4.81 (2.48)	<0.05
Number of patients with neutropenia[d] (ANC<1 x 10^9/L)	1/82 (1.2)	5/51 (9.8)	0.071
Number of patients with lymphopenia[d] (≤1.5 x 10^9/L)	22/82 (26.8)	4/51 (7.8)	0.007
C-reactive protein[c] (mg/L)	27.05 (57.79)	36.98 (61.77)	0.775
ALT[ac] (IU/L)	23.11 (12.36)	21.61 (9.83)	0.520
Number of patient with elevated ALT[ad] (>30 IU/L)	11/64 (17.2)	4/31 (12.9)	0.767
Number of patients with bacteraemia[d]	0/82 (0)	0/51 (0)	
Antibiotic use[d]	43/90 (47.8)	30/65 (46.2)	0.872
Abnormal chest X-ray[d]	15/90 (16.7)	34/64 (53.1)	<0.05
Duration of hospitalisation[c] (days)	4.39 (1.74)	6.08 (3.06)	<0.05

[a] RSV, respiratory syncytial virus; ALT, alanine aminotransferase; [b] p values performed using student t-test. Children who were afebrile in the hospital were excluded: eight children with influenza, and twenty-eight with RSV; [c] p values performed using Mann-Whitney U test; [d] p values performed using Fisher's exact test.

had lymphopenia (≤1.5 x 10^9/L) compared to 7.8% in children with RSV. Nearly all patients with acute respiratory illness had chest X-ray evaluation. Attending paediatricians detected more chest X-ray abnormalities in children with RSV infections (53.1%) than those with influenza (16.7%). In children with RSV infections, perihilar peribronchial thickening, perihilar patchy opacities, or both were found in 15 patients. Hyperinflation was seen in 12 children. One child has lobar consolidation. Blood cultures were negative in all patients infected with RSV or influenza virus.

Antibiotic was administrated to 73 children with the diagnosis of pneumonia or acute otitis media on admission. It was subsequently discontinued in 26 patients once the NPA results of influenza directigen and RSV immuno-fluorescence were known (usually one day after the admission). Thus, in 155 patients with known RSV or influenza infection, 47 (30%) patients were given a course of antibiotics.

Four patients (6.2%) with RSV infection were admitted to PICU. They spent an average 8.75 days in PICU. Supplemental oxygen was given to 12 patients (18.5%) with RSV infection. None of our patients with influenza was admitted to PICU and only one of them required oxygen. There was no fatal case.

Sixteen ex-premature (≤36 weeks of gestation) infants or children were admitted for respiratory tract infection during the study period. Fourteen of them were infected with RSV. One (7.1%) was admitted to PICU and two (14%) required oxygen therapy.

Discussion

Sixty percent of RSV infections occurred in patients under 1 year of age in this study. This rate is consistent with those observed in other Asian countries.[9,10] In China, Zhaori et al observed a remarkable high incidence of 70% in the first six months of age.[11] Our report also described the seasonal variation of RSV and influenza infection in Hong Kong. The pattern of influenza occurrence in this study is similar to that described in previous Hong Kong Influenza Surveillance System (HKISS) report. Although the data from the HKISS was collected mainly from outpatient clinic and private practitioners, it demonstrated a clear seasonal periodicity with influenza isolation peaking in March and July in 3 consecutive years (1998 to 2000).[12] We reported that the incidence of RSV infection was higher in March and September than any other months of the year. In a previous local study, Sung et al observed a similar seasonal periodicity but the peak incidence was in July and August instead. The reason for the seasonal pattern remained unknown but Sung et al postulated that the rain and heat in summer might discourage people going outdoors, and crowded indoor living conditions might also facilitate RSV transmission.[13]

From this study, both RSV and influenza are important respiratory pathogens in young children, accounting for 8.9% (155/1735) of total acute admissions and 27.6% (155/561) of all respiratory infections in children ≤3 years of age. When compared to children infected with influenza, a greater proportion of children with RSV had lower respiratory tract involvement and chest X-ray abnormalities. Influenza had been previously reported to be a major cause of febrile seizures.[14] However, febrile seizures could also occur in children with RSV infection as shown in the current case series. Our results demonstrate that the risk of serious bacterial infections is low in children with influenza or RSV infection. This finding was supported by Bloomfield's study showing that 0.6% of 1795 patients with RSV infection had concurrent bacteraemia.[15] Nevertheless, our children with uncomplicated RSV and influenza infection were often treated with antibiotics. This is consistent with similar studies from developed countries which also showed high rates of antibiotics use in RSV infection.[16,17] Antibiotics were continued in around one third of our patients after positive RSV or influenza result was known. The clinical indications for antibiotics were difficult to evaluate retrospectively, but it seemed likely that antibiotics could have been stopped in most if not all the patients in whom they were continued. This confirmed that antibiotics were generally overused for children with RSV and influenza infections in our hospital as they were in other hospitals.[16,17] Our data suggest that full septic evaluations and antibiotics are not necessary in nontoxic-appearing infants with a positive influenza or RSV test.

This study showed that high-risk infants contributed to a small proportion of RSV- or influenza-related hospitalisations. The incidence of RSV related hospitalisations among the high-risk infants in our study was lower than those recently reported from US and European countries. These studies, mainly population-based, reported that RSV-related hospitalisation rates were 2-13% in infants born at gestational age ≤32 weeks,[18-21] 15-39% in infants with chronic lung diseases (CLD),[21-24] and 9.2-14% in infants with congenital heart diseases (CHD).[20,23,25] Infants born at a gestational age of <28 weeks

and preterm infants with concomitant CLD accounted for 7-16% and 30% of RSV-related hospitalisations.[24,26] In addition, the rate of ICU admission in our children was substantially lower than those reported in the US high risk infants (6.2% vs. 32-37% for ICU admission).[27] Our study also showed no fatality as compared with other centres in which the fatality rate could be up to 0.15%.[4] Navas et al, demonstrated that the mortality rate in patients with underlying conditions hospitalised with RSV illness ranged from 0% for premature infants to 3.5% in children with chronic lung disease.[28] Overall RSV-related mortality rates in the US were estimated to be 7.3 per 100,000 infants, but it increased to 61.8 per 100,000 in infants born at ≤35 weeks gestation who were <2.5 kg birth weight and had co-morbidities.[29]

There are several limitations to our study. Firstly, our clinical information was obtained only from children admitted to one hospital, and rates of hospitalisation among such children may not be generalisable to the entire population in our region. Secondly, many parents in this region only had temporary residence in Hong Kong. They usually brought their children back to China when their visa permit expired. Hence, the incidence of RSV related hospitalisations might have been underestimated. Lastly, we reported data from only one RSV and influenza season. It is difficult to determine the accurate periodicity of disease from a short study period.

The current study concludes that among children less than 3 years of age in our locality, with or without underlying medical conditions, RSV and influenza are two main respiratory viruses causing hospitalisation and PICU admission and mortality rates from RSV or influenza disease were low.

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