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Epidemiology of respiratory syncytial virus infection among paediatric patients in Hong Kong: seasonality and disease impact

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SUMMARY

In a 5-year retrospective survey of respiratory syncytial virus (RSV) infections among hospitalized children, 1340 cases were identified of which, 98·4% were children < 5 years old with a male : female ratio of 1·5 : 1. Most cases occurred from April to September showing a significant positive correlation with temperature and relative humidity. Community-acquired infections accounted for 92·5% of the cases with a mean hospital stay of 5 days. The estimated annual incidence of RSV infection requiring hospitalization was 2·5/1000 children < 5 years old with a mortality of 0·15% among hospitalized cases. On average, 248 children were admitted each year to the 1400-bed acute regional hospital accounting for an expenditure of HK $1.94 (~ US $0.25) million for hospitalization costs which equates to an annual cost in excess of HK $6.67 (~ US $0.86) million for the whole of Hong Kong. An RSV vaccine should be a priority.

INTRODUCTION

Acute respiratory infection is an important cause of morbidity and mortality in children world-wide. The World Health Organization has estimated that 25–33% of deaths in children under 5 years old are caused by acute lower respiratory infections [1, 2]. Among the respiratory pathogens, respiratory syncytial virus (RSV) remains the leading cause of hospitalization of infants and young children [3–6].

RSV is typically seasonal in its incidence and has been responsible for epidemics throughout the world. In temperate zones of the world, the infection peaks during late fall, winter or spring but not summer [7–9], while in tropical and semi-tropical countries, it mainly peaks during the rainy season [10, 11]. A correlation between the annual epidemic and meteorological factors has also been found in many studies [12, 13] although the correlation seems to vary in different countries.

While RSV continues to be an important pathogen in both the developed and developing countries, most epidemiological studies were carried out in an era when viral detection techniques were less sensitive. With the recent advances in RSV vaccine research, it is envisaged that an effective vaccine should soon become available. A precise assessment of the epidemiology as well as economic burden of the disease is crucial to determine the cost-effectiveness of such a potential vaccine [14]. Here we sought to elucidate the epidemiology of RSV in Hong Kong, a densely populated city, with emphasis on disease burden and the correlation with meteorological factors.

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MATERIALS AND METHODS

Study population

The retrospective study was conducted at the Prince of Wales Hospital (PWH), the teaching hospital of The Chinese University of Hong Kong. PWH is a 1400-bed acute regional hospital serving the Eastern and Northern New Territories and the outlying islands with a population of 1·3 million of which 7·6% are children aged less than 5 years. The catchment region constitutes about 29·1% of all children less than 5 years of age in Hong Kong [15–18].

Data on respiratory illness-associated admissions were retrieved from computerized clinical audit records maintained by the Department of Paediatrics. Patients with laboratory-confirmed RSV infection during the 5-year study period from 1 January 1993 to 31 December 1997 were identified through records of the virus laboratory. Data regarding time of RSV detection, length of hospital stay and outcome of illness were obtained from the Infection Control Unit of the hospital that documents all RSV infections for infection surveillance and control purposes.

Patients who were admitted with respiratory symptoms and from whom RSV was subsequently detected within 7 days of admission were classified as community-acquired cases, hence defined as RSV-attributed admissions. Otherwise, the positive cases were classified as hospital-acquired infections. The duration of hospitalization was determined from clinical records of all RSV-attributed admissions in 1997 when most comprehensive patients' data were available. Patients with concurrent illnesses were not included in this analysis so as to avoid the inclusion of hospital stay due to illnesses other than RSV infection. The epidemiological data observed in PWH were projected to the population of Hong Kong based on population census data to estimate the disease burden in the territory. Meteorological data were provided by the Hong Kong Royal Observatory.

Laboratory diagnosis

RSV was detected from patients' nasopharyngeal aspirates, bronchoaveolar lavages or endotracheal aspirates by direct immunofluorescent staining with RSV-specific monoclonal antibodies (Imagen, Dako, Cambs, UK), and in parallel by virus isolation using HEp-2 cells. Cell cultures were incubated for up to 2 weeks. RSV was identified by characteristic cytopathic effects and confirmed by staining with RSV-specific monoclonal antibodies (Imagen, Dako, Cambs, UK). When a throat swab was the only available specimen, virus isolation was used.

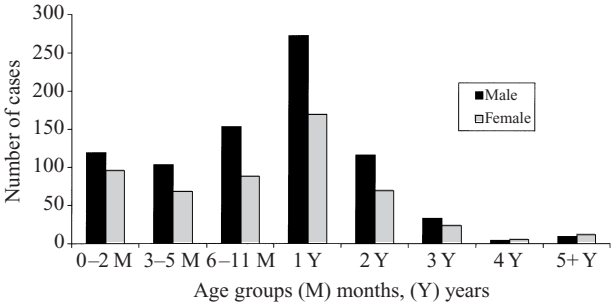

Fig. 1. Age and sex distribution of 1340 paediatric patients with respiratory syncytial virus infection hospitalized at the Prince of Wales Hospital, January 1993–December 1997.

Statistical analyses

All statistical analyses were done on a personal computer using SPSS/PC version 8.0.0, 1997 (SPSS Inc., Chicago, IL, USA). The distribution of all continuous variables was assessed by Levene's test. Normally distributed data were compared by the independent-samples' *t* test. Other data were compared by the Mann–Whitney–Wilcoxon test. The seasonal distribution of RSV infection was assessed by dividing each year into 3-month periods, and comparing the incidence at each period using the one-way ANOVA. When a difference was observed, the Bonferroni corrected *t* test was used to adjust for multiple comparisons. Univariate regression analysis with the Pearson correlation coefficient was used to analyse the relation between RSV incidence and meteorological factors, whereas independent associations were analysed by multiple linear regression using the forward stepwise method. All tests were two-tailed and *P*-values less than 0·05 were considered statistically significant.

RESULTS

During the 5-year study period from 1 January 1993 to 31 December 1997, a total of 9635 paediatric patients were admitted to PWH with clinical features of respiratory tract infections, of which 1340 (13·9%) were confirmed to be RSV infections. Among the RSV-positive cases, 989 (73·8%) were detected by both direct immunofluorescence test and virus isolation; 202 (15·1%) by virus isolation alone and 149 (11·1%) by direct immunofluorescence test alone.

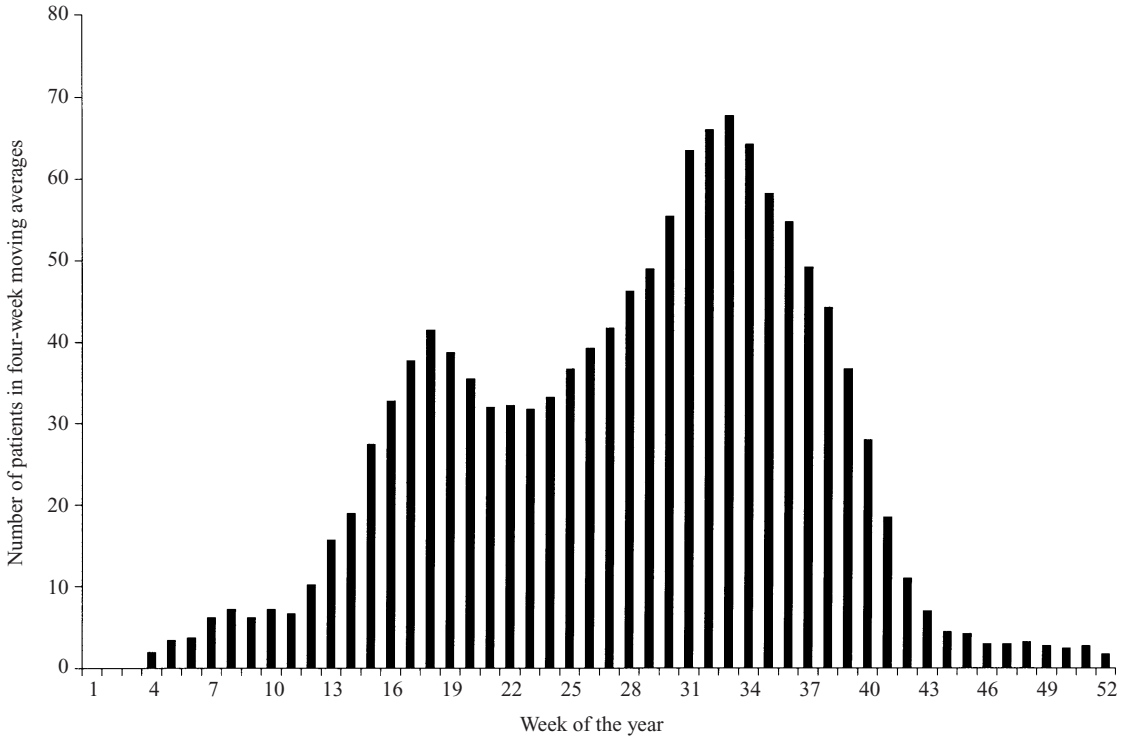

Fig. 2. Distribution by week of patients with respiratory syncytial virus infection hospitalized at the Prince of Wales Hospital, January 1993–December 1997.

Age and sex distribution

The age distribution of RSV-positive cases is shown in Figure 1 with children < 5 years old accounting for 98·4% of all the RSV-positive cases. The male : female ratio of these cases was 1·5 : 1.

Seasonal distribution and correlation with meteorological factors

A consistent seasonal distribution of RSV cases was observed in each year of the 5-year study period with the incidence starting to rise in April, reaching a peak in July and August, and then starting to decline in September (Fig. 2). When divided into periods of 3 months (January–March, April–June, July–September and October–December), the incidence rates of RSV infection at the periods of April–June (mean, 32·1 cases) and July–September (mean, 46·7 cases) were significantly higher than those of January–March (mean, 7·2 cases) and October–December (mean 3·3) ($P < 0{\cdot}05$ by Bonferroni corrected t test).

Univariate analysis showed that the monthly incidence of RSV infection was positively correlated with temperature, relative humidity and rainfall but not sunshine (Table 1). When the associations were further analysed by multivariate analysis, only temperature and relative humidity were found to be the independent associating factors (Table 1, Fig. 3).

Disease burden

Incidence

Of the 1340 cases of laboratory-confirmed RSV infection detected during the 5-year study period, 100 cases (7·5%) were classified as hospital-acquired infections while 1240 cases (92·5%) were community-acquired infections and hence referred to as RSV-attributed admissions. This figure represents an RSV-attributed admissions rate of 2·5/1000 children < 5 years old per year.

Hospital stay

There were 332 cases of laboratory-confirmed RSV infections admitted in 1997. Of these, 28 were hospital-acquired, 3 were community-acquired but had other underlying illnesses, 1 died while still on treatment for RSV. All these cases were excluded from the determination of duration of hospitalization. The average duration of hospital stay of the remaining 300 cases of RSV-attributed admissions was 5 days (range 1–16 days, S.D. 2·7 days). When analysed by age groups of 0–2, 3–5 and 6–11 months, 1, 2 and > 3

Table 1. *Correlation between RSV incidence and meteorological factors*

Meteorological factor	Mean	S.D.	Univariate regression analysis*		Multivariate regression analysis*	
			Pearson coefficient	*P*-value	Standardized beta coefficient	*P*-value
Temperature (°C)†	23·2	4·6	0·603	< 0·001	0·454	< 0·001
Relative humidity (%)†	78·1	5·9	0·532	< 0·001	0·324	0·005
Rainfall (mm)‡	223·6	280·2	0·500	< 0·001	0·07	0·615
Sunshine (h)‡	146·1	48·6	0·068	0·608	0·019	0·917

* RSV monthly incidence as dependent variable.
† Mean daily measurement of the month.
‡ Total measurement of the month.

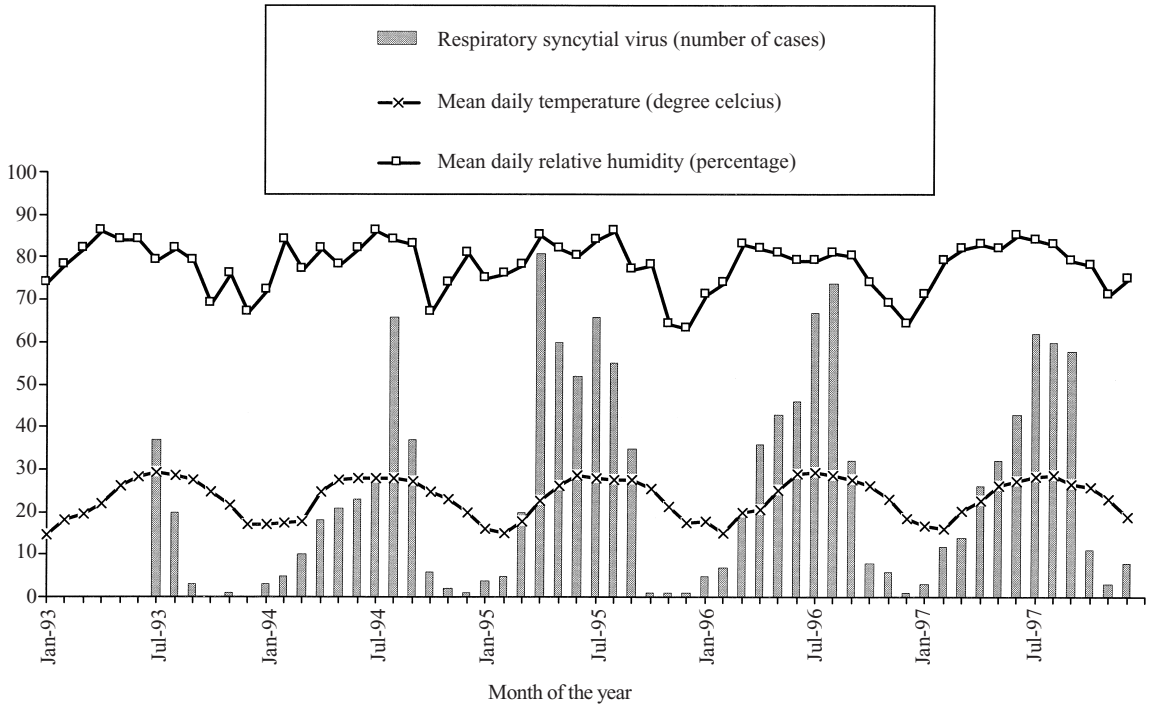

Fig. 3. Respiratory syncytial virus infection and meteorological variations, January 1993–December 1997.

years, no significant difference in duration of hospital stay was observed (mean range 4·4–5·7 days, $F = 1{\cdot}966$, $P = 0{\cdot}084$ by one-way ANOVA). There was also no significant difference in hospital stay between males and females (mean 5·1 *vs.* 4·7 days, $t = 1{\cdot}28$, 95% CI −0·215 to 1·015; $P = 0{\cdot}2$ by t test).

Mortality

Five deaths were recorded among confirmed cases of RSV infection over the 5-year study period. Three of them died of their underlying illnesses after recovering from an RSV infection (two from relapse of leukaemia, and the third had visceral myopathy and died of septicaemia). As for the remaining two deaths, causes other than severe RSV infection could not be identified. One was an 8-month-old girl with spinal muscular atrophy whose lung function deteriorated as a result of RSV infection, and died despite intensive care. The other was a 6-month-old boy who had immunodeficiency with hypoimmunoglobulinaemia, delayed development and cerebral palsy as a consequence of cerebral atrophy. He progressed to respiratory failure and died 5 days after admission. Therefore, the overall mortality among hospitalized cases of RSV infection was 0·15% (2/1340).

DISCUSSION

The present study confirms that RSV plays an important role in acute respiratory infection among children < 5 years old in Hong Kong. Over the 5-year

study period, community-acquired RSV infection accounted for 12·9% of all respiratory admissions, and during peak seasons it was responsible for over 90% of admissions classified as acute bronchiolitis or pneumonia. The incidence of RSV-associated admission among young children has been reported to be 1·5–14 per 1000 population, with a higher incidence in infants [13, 19]. A study conducted in Britain showed that the incidence was twice as higher in industrial areas than in urban and rural areas (14·1 and 4·4 per 1000 children of < 1 and < 5 years old, respectively) [19]. In addition, a positive correlation between RSV admission and air pollution has been reported [13]. The fact that our finding of a lower annual incidence of RSV-attributed admission (2·5/1000 children < 5 years old) than those reported may reflect a lower disease burden in this locality. Alternatively, the result may reflect a difference in availability of ambulatory out-patient services or differences in parents' threshold of taking their children into hospital. In addition, the utilization of private and adjacent public hospitals might have contributed to an underestimation. We did not have sufficient data to analyse the influence of living conditions and socio-economic status of our patients on the incidence of infection, these factors have previously been shown to affect the incidence of RSV infection requiring hospitalization [19, 20]. The male predominance in RSV disease was similar to that reported by others [21, 22] but there was no indication that the disease was significantly more severe in boys than in girls as their duration of hospital stay showed no significant difference.

A consistent seasonal variation of incidence of RSV has been observed world-wide. However, the correlation with climatic factors varies in different parts of the world. Studies in Europe showed a winter peak with negative correlation with daily temperature and hours of sunshine, but no correlation with rainfall/snow and humidity [12, 13]. De Silva and colleagues [21] also observed an RSV peak at mid-winter, but no significant correlation with climatic factors could be demonstrated. Our finding that RSV peaked in the middle of each year seems to be in line with observations made in tropical and semi-tropical countries were rainfall has been reported as the most consistent associating climatic factor [10, 11]. However, when subjected to statistical analyses, rainfall was not independently associated with the number of RSV infection in Hong Kong. In fact, each year, the number of RSV cases started to increase just before the onset of the rainy season. On the contrary, statistically significant independent positive correlation with temperature and with relative humidity was observed. The knowledge of local climatic factors together with the characteristic pattern of epidemics of RSV may help in predicting the beginning and end of epidemics, and thus also useful in the planning of preventive measures. This is particularly important in situations, like ours, where only limited side-rooms are available for cohort nursing of infectious patients.

It has been shown that the overall death rate among hospitalized children with RSV infection was 0·5–2·5% in 1970s. With the advent of modern intensive care, more recent estimates are lower, 0·3–1% [23, 24]. While the mortality associated with RSV is similarly low in the present study, disease burden in terms of hospitalization is tremendous. Annually, an average of 248 children were admitted for RSV infections and were hospitalized for a total of 1240 days costing around HK $1.94 million (US $ $\sim$ 0.25 million). This hospitalization cost for RSV accounted for 0·1% of the total hospital expenditure of PWH for 1996/7. When these figures are projected to the whole territory, the expenses on hospitalization for RSV infection alone would be in the region of HK $6.67 million (US $ $\sim$ 0.86 million). Our cost estimates reflect only part of the financial burden of RSV where the costs of ambulatory and out-patient care, parents' work time loss, and costs related to hospital-acquired RSV cases have not been included. Active immunization against RSV infection could eliminate a great part of this expenditure and should be a priority target as soon as it becomes available.

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