



## Respiratory Viral Infections in Hong Kong Children---What is New?

**Dr. Susan Chiu** MD, FAAP

Department of Paediatrics & Adolescent Medicine  
The University of Hong Kong  
Queen Mary Hospital



Dr. Susan Chiu

*This article has been selected by the Editorial Board of the Hong Kong Medical Diary for participants in the CME programme of the Medical Council of Hong Kong (MCHK) to complete the following self-assessment questions in order to be awarded one CME credit under the programme upon returning the completed answer sheet to the Federation Secretariat on or before 30 November 2004.*

Acute viral respiratory tract infections remain a leading cause of morbidity in both developing and industrialized countries, particularly in young children as well as the elderly. It is the leading cause of acute hospitalization in children. In Queen Mary Hospital, it accounts for 70-75% of the annual acute paediatric admissions. With good virologic support, there have been some new understanding of the clinical manifestation and impact of respiratory viruses in Hong Kong children.

There had been little data on influenza disease burden in tropical and subtropical regions.<sup>1</sup> Hong Kong is situated within the hypothetical pandemic influenza epicentre and serves as a sentinel post for the region. While the H5N1 incident in 1997 made an impact on the professional and public consciousness, the annual epidemics of influenza are generally believed to be clinically insignificant, a perception common to many other tropical and subtropical regions.<sup>2-4</sup> Earlier reports pertaining to influenza disease burden in HKSAR documented few influenza-attributed hospital admissions and no associated deaths.<sup>5,6</sup>

In temperate regions, influenza affects 30 to 40 percent of children during epidemics. While the impact of influenza on children with underlying conditions is well-recognized, its impact on healthy children is less clear.<sup>7</sup> In the United States, respiratory syncytial virus (RSV) co-circulates with influenza during winter, making it difficult to separate their clinical impact at population-level. In Hong Kong, RSV is a summer infection while the seasonality of influenza varies from year to year. In some years influenza overlaps with RSV while in others it has a sharper spring peak separate from RSV. Hospitals within the Hospital Authority (HA) of HKSAR account for 90 percent of all hospitalization in Hong Kong. Therefore, Hong Kong provides a unique opportunity for documenting the impact of influenza in a well-defined population, separate from the confounding influence of RSV.

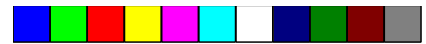
We performed a retrospective population-based study of children  $\leq 15$  years old to determine rates of hospitalization for acute respiratory disease (ARD) associated with influenza.<sup>8</sup> To calculate the morbidity attributable to influenza, we compared mean

hospitalization rates during periods of high influenza and low RSV activity ("influenza predominance") with periods when both influenza and RSV activity were low ("baseline"). For each age group, we calculated the excess rates of hospitalization attributable to influenza virus by subtracting the rates of hospitalization during baseline periods from that during influenza predominance. A similar analysis was carried out for Queen Mary Hospital where all children admitted with respiratory tract infection are virologically investigated. The estimated excess influenza-associated hospital admissions were compared with virologically confirmed influenza diagnosis. The extent of under-estimation inherent to the excess hospitalization model was defined and the appropriate correction was then applied to the data from the whole of Hong Kong to derive adjusted age-specific hospitalization rates.

In 1998 and 1999, peaks of ARD hospitalization clearly coincided with peaks of influenza activity. This relationship is discernible in all age groups up to 10 years. We found that the excess rates of hospitalization for ARD documented for the <1 year and 1-<2 year old groups (124.8/10,000 and 90/10,000 per year, respectively) were about 6 fold greater than that reported from the States (14.4-18.7/10,000 population between 0 and 23 months of age). The difference was even greater for the older age groups: 33.0/10,000 vs. 0-2.5/10,000 for 2-4 years, 3.0-9.5/10,000 for 5 to 15 years vs. 0.8-1.2/10,000 for 5-17 years, respectively.<sup>9-10</sup>

This study contributes to the ongoing discussion on the cost-benefit of universal vaccination of children. In Hong Kong, the use of influenza vaccine is very limited. It has been recommended for use for institutionalized elderly since 1997, and in children with chronic lung disease (excluding asthma), congenital heart disease or those hospitalized receiving aspirin therapy since November 2000. Around the world, there is increasing awareness of the impact of influenza on healthy young children, leading to recommendation for vaccination in this group: the American Academy of Pediatrics and the Advisory Committee on Immunization Practices in the US recommend vaccination for all healthy children aged 6-23m this 2004 season; the Korean Pediatric Society and Korean CDC recommend universal influenza vaccination





for children aged 6-35m; Taiwan will implement free vaccination for all children aged 6-23m beginning this 2004 season and the Philippine Pediatric Societies and the Philippine Foundation for Vaccination recommend universal vaccination of children aged 6-23m. This year, in Hong Kong, the Scientific Committee on Vaccine Preventable Diseases also recommends vaccination for children of this age group.

In addition to causing respiratory illness, we also documented that influenza A is an important cause of febrile seizures in children.<sup>11</sup> Febrile seizures are defined as an event in infancy or childhood, usually occurring between 6 months and 5 years of age, associated with fever but without evidence of intracranial infection or other definable causes. Seizures with fever in children who have suffered a previous afebrile seizure are excluded.

Of children hospitalized for influenza A in 1998 and 1997, 54/272 (19.9%) and 27/144 (18.8%) had febrile seizures, respectively ( $P=0.9$ ). The overall incidence of febrile seizures associated with influenza A (19.5%) was higher than that in children hospitalized for parainfluenza (18/148; 12.2%) and adenovirus (18/199; 9%) infection, respectively ( $P=0.0004$ ). In children who had febrile seizures, repeated seizures were more commonly associated with influenza A infection than with parainfluenza or adenovirus infection [23/81 (28%) vs. 3/36 (8.3%),  $P=0.02$ ; OR 4.3, 95% CI: 1.2 to 15.4]. Alternatively, children with influenza A infection had a higher incidence (23/416, 5.5%) of multiple seizures during the same illness than those with adenovirus or parainfluenza infection (3/347, 0.86%), ( $P=0.0004$ , OR=6.7, 95% CI: 2 to 22.5.) The increased incidence of febrile seizures associated with influenza A was not attributable to differences in age, gender or family history of febrile seizure. Multivariate analysis, adjusted for peak temperature and duration of fever, showed that hospitalized children infected with infection A had a higher risk of febrile seizures than those who were infected with parainfluenza or adenovirus. ( $P=0.0005$ , OR 1.97). The pathogenesis of these observations warrants further studies. Complex febrile seizures, particularly multiple febrile seizures at the time of presentation have been thought to carry an adverse long term prognosis because of its association with a higher incidence of epilepsy. Repeated febrile seizures alone, particularly if associated with influenza A infection, may not be as worrisome as children with complex febrile seizures due to other etiology. This finding may subsequently have an impact on reducing the burden of evaluation in a subset of children with complex febrile seizures.

While paediatricians have known for a long time that the majority of acute bronchiolitis is caused by RSV, there still remains a significant proportion of acute bronchiolitis that tests negative for RSV. In June 2001, van den Hoogen et al. from the Netherlands reported the discovery of a respiratory virus in 28 nasopharyngeal aspirate (NPA) samples of children with respiratory tract infections.<sup>12</sup> The new virus was named Human metapneumovirus (hMPV). HMPV belongs to the family Paramyxoviridae<sup>13,14</sup> whose clinical significance is still being defined. Following its initial discovery in the Netherlands, HMPV has been detected in respiratory specimens from patients of all ages in a number of countries, eg. Canada, Australia, the United

Kingdom and Finland<sup>15-20</sup>. In children, it has been reported to cause disease similar to that of RSV, with presentation ranging from severe cough to bronchiolitis and pneumonia. We conducted a 13-month study to systematically investigate children hospitalized with respiratory infection.<sup>21</sup> Five hundred eighty-seven children were included and 32 (5.5%) children had HMPV detected in the nasopharyngeal aspirates by RT-PCR. HMPV infection was associated with clinical diagnoses of pneumonia (36%), asthma exacerbation (23%) or acute bronchiolitis (10%). The most common presentation in children with HMPV was fever (100%) and cough with sputum in 28 (90%) The attending paediatricians diagnosed bacterial pneumonia in 4, atypical pneumonia in 5 and viral pneumonia in 3 children, respectively. Perihilar peribronchial thickening and/or perihilar patchy consolidation suggestive of a viral infection was found in 14, viral or atypical pneumonia diagnosed in one, and viral or bacterial pneumonia in two. Hyperinflation was seen in 5 children. No child had lobar consolidation. Two children with HMPV had hoarseness without stridor. Five (16.1%) children presented with febrile seizures - 2 of them had 3 seizures each. When compared to those with RSV infection, children with HMPV infection were older and wheezing was more likely to represent asthma exacerbation rather than acute bronchiolitis. Asthma exacerbation accounted for 66.7% of the wheezing of HMPV-infected children but only 16.7% in RSV-infected children. HMPV viral activity peaked during the spring-summer period in Hong Kong. Phylogenetically, all the HMPV virus strains from Hong Kong belonged to one of the two genetic lineages previously described. It was estimated that HMPV contributed to 441.6 hospital admissions per 100,000 population  $\leq 6$  years of age. All in all, HMPV is an important cause of childhood respiratory disease, contributing to significant morbidity and hospitalization in childhood in Hong Kong.

Coronaviruses are a genus of enveloped RNA viruses and are subdivided into 3 groups based on antigenic and genetic differences. Human coronavirus 229E (HCoV 229E) and human coronavirus OC43 (HCoV OC43) have been recognized since the mid 1960's as causes of upper respiratory disease including the common cold and are classified as group 1 and group 2 coronaviruses, respectively. In 2003, a novel coronavirus (SARS CoV) was identified as the causative agent of the severe acute respiratory syndrome (SARS). Recently, two research groups independently reported another group 1 human coronavirus, HCoV NL 63<sup>22-24</sup>. In one report, 8 adults and children with HCoV-NL-63 virus were documented with 3 patients having lower respiratory tract infection, 2 patients with unknown clinical presentation and the others having upper respiratory tract infection. A second report from the Netherlands documented the same coronavirus in an 8 month old boy with pneumonia. After screening 139 other children and adults with respiratory tract infections negative for known viral pathogens, the virus was found in 4 more children. We have also conducted a study of coronavirus infections in Hong Kong children. Preliminary results showed that the newly discovered HCoV NL63 also circulates in Hong Kong and is a cause of respiratory infections in children.





References

- 1) Anon. Adoption of Global Agenda on Influenza - part II. *Weekly Epid Rec.* 2002; **23**: 191-5.
- 2) Yuen KY, Chan PKS, Peiris M. et al. Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. *Lancet* 1998; **351**:467-71.
- 3) Center for Disease Control and Prevention: Isolation of avian influenza A (H5N1) viruses from humans-Hong Kong, May-December 1997. *MMWR* 1997; **46**: 1204-07.
- 4) Fitzner KA, Shortridge KF, McGhee SM, Hedley AJ. Cost-effectiveness study on influenza prevention in Hong Kong. *Health Policy* 2001; **56**: 215-34.
- 5) Hong Kong Coroners Report. Hong Kong Government, Hong Kong Government Printer, Hong Kong, 1993.
- 6) Hong Kong Coroners Report. Hong Kong Government, Hong Kong Government Printer, Hong Kong, 1994.
- 7) Prevention and Control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP) *MMWR* 2001; **50**(RR-4):1-44.
- 8) Chiu SS, Lau YL, Chan KH, Wong WHS, Peiris JSM. A population-based study defining influenza-related hospitalization in children in Hong Kong. *N Engl J Med* 2002; **347**:2097-2103.
- 9) Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Engl J Med* 2000; **342**:232-9.
- 10) Neuzil KM, Mellen BG, Wright PF, Mitchel EF, Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. *N Engl J Med* 2000; **342**:225-31.
- 11) Chiu SS, Tse CYC, Lau YL, Peiris M. Influenza A Infection Is an Important Cause of Febrile Seizures. *Pediatrics* 2001; **108**(4):e63
- 12) van den Hoogen BG, de Jong JC, Groen J, Kuiken T, de Groot R, Fouchier RA, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. *Nat Med* 2001; **7**(6): 719-24.
- 13) van den Hoogen BG, van Doornum GJ, Fockens JC, Cornelissen JJ, Beyer WE, de Groot R, et al. Prevalence and clinical symptoms of human metapneumovirus infection in hospitalized patients. *J Infect Dis* 2003; **188**(10):1571-7.
- 14) Pelletier G, Dery P, Abed Y, Boivin G. Respiratory tract reinfections by the new human Metapneumovirus in an immunocompromised child. *Emerg Infect Dis* 2002; **8**(9):976-8.
- 15) Peret TC, Boivin G, Li Y, Couillard M, Humphrey C, Osterhaus AD, et al. Characterization of human metapneumoviruses isolated from patients in North America. *J Infect Dis* 2002; **185**(11):1660-3.
- 16) Stockton J, Stephenson I, Fleming D, Zambon M. Human metapneumovirus as a cause of community-acquired respiratory illness. *Emerg Infect Dis* 2002; **8**(9):897-901.
- 17) Nissen MD, Siebert DJ, Mackay IM, Sloots TP, Withers SJ. Evidence of human metapneumovirus in Australian children. *Med J Aust* 2002; **176** (4):188.
- 18) Freymouth F, Vabret A, Legrand L, Eterradosi N, Lafay-Delaire F, Brouard J, et al. Presence of the new human metapneumovirus in French children with bronchiolitis. *Pediatr Infect Dis J* 2003; **22**(1):92-4.
- 19) Jartti T, van den Hoogen B, Garofalo RP, Osterhaus AD, Ruuskanen O. Metapneumovirus and acute wheezing in children. *Lancet* 2002; **360** (9343):1393-4.
- 20) Esper F, Boucher D, Weibel C, Martinello RA, Kahn JS. Human metapneumovirus infection in the United States: clinical manifestations associated with a newly emerging respiratory infection in children. *Pediatrics* 2003; **111**(6 Pt 1):1407-10.
- 21) Peiris JS, Tang WH, Chan KH, Khong PL, Guan Y, Lau YL, et al. Children with respiratory disease associated with metapneumovirus in Hong Kong. *Emerg Infect Dis* 2003; **9**(6):628-33.
- 22) Gorbalenya AE, Snijder EJ and Spaan WJ. Severe acute respiratory syndrome coronavirus phylogeny: toward consensus. *J Virol* 2004; **78**: 7863-6
- 23) Fouchier RA, Hartwig NG, Bestebroer TM, et al. A previously undescribed coronavirus associated with respiratory disease in humans. *Proc Natl Acad Sci U S A* 2004; **101**:6212-6
- 24) van der Hoek L, Pyrc K, Jebbink MF, et al. Identification of a new human coronavirus. *Nat Med* 2004; **10**:368-73

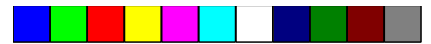
MCHK CME Programme Self-assessment Questions

Please read the article entitled "Respiratory Viral Infections in Hong Kong Children - What is New?" by Dr. Susan CHIU and complete the following self-assessment questions. Participants in the MCHK CME Programme will be awarded 1 CME credit under the Programme for returning completed answer sheet via fax (2865 0345) or by mail to the Federation Secretariat on or before 30 November 2004. Answers to questions will be provided in the next issue of The Hong Kong Medical Diary.

Questions 1-5: Please select one best answer. Questions 6-10: Please answer T(True) or F(False).

1. Which of the following viral agent(s) has/have been associated with respiratory viral infections in Hong Kong children:
  - a) Respiratory syncytial virus (RSV)
  - b) Influenza A virus
  - c) Parainfluenza virus
  - d) Adenovirus
  - e) All of the above
2. In Queen Mary Hospital, acute viral respiratory tract infections account for what percentage of annual acute paediatric admissions?
  - a) 10-15%
  - b) 20-25%
  - c) 30-35%
  - d) 55-60%
  - e) 70-75%
3. Which of the following viral agents is associated with the highest incidence of febrile seizures in children?
  - a) Respiratory syncytial virus (RSV)
  - b) Influenza A virus
  - c) Parainfluenza virus
  - d) Adenovirus
  - e) Coronavirus





4. Majority of acute bronchiolitis in children is caused by:
  - a) Respiratory syncytial virus (RSV)
  - b) Influenza A virus
  - c) Parainfluenza virus
  - d) Adenovirus
  - e) None of the above
5. The most common presentation in children affected by the new virus HMPV (Human Metapneumovirus) is:
  - a) Hemoptysis
  - b) Non productive cough
  - c) Stridor
  - d) Fever
  - e) Lobar Consolidation

**Which of the following concerning respiratory viral infections in Hong Kong children is true?**

6. In 1998 and 1999, the excess rates of hospitalization for acute respiratory disease (ARD) in Hong Kong children under 2 years old were about 6 fold greater than that reported from United States.
7. The excess rates of hospitalization for acute respiratory disease (ARD) in older Hong Kong children (2-15 years old) were lower than that reported from United States.
8. In 2004, the Hong Kong Scientific Committee on Vaccine Preventable Diseases recommended influenza vaccine for children aged 6-23 months.
9. Influenza vaccine is also recommended for institutionalized elderly, children with chronic lung disease (excluding asthma), congenital heart disease or those hospitalized receiving aspirin therapy.
10. The new virus HMPV (Human Metapneumovirus) is not an important cause of acute respiratory disease in children under 6 years old.

### ANSWER SHEET FOR NOVEMBER 2004

Please return the completed answer sheet to the Federation Secretariat on or before 30 November 2004 for documentation. 1 CME point will be awarded for answering the MCHK CME programme (for non-specialists) self-assessment questions.

**Respiratory Viral Infections in Hong Kong Children - What is New?**

Dr. Susan CHIU, MD, FAAP

Department of Paediatrics & Adolescent Medicine, The University of Hong Kong, Queen Mary Hospital

1  2  3  4  5  6  7  8  9  10

Name: \_\_\_\_\_ HKID No. \_\_\_\_\_ - \_\_\_\_\_ X X (x)

Signature: \_\_\_\_\_ Contact Tel No.: \_\_\_\_\_

### Special Announcement

It has come to our attention that a communications agency named Aktiv Health recently wrote to individual doctors to seek their consent of publishing their personal data in the "Medical Directory of Hong Kong 2005". We would like to draw your attention that this *Medical Directory of Hong Kong 2005* is NOT the 8<sup>th</sup> Edition of *The Medical & Dental Directory of Hong Kong*, the official publication of Federation that we plan to publish. If you have received their fax, please reply to them, should you do not wish to have your name listed in that Directory. Otherwise, they may assume your consent and proceed to publish your data.

