Influenza-like illness and viral aetiology in Hong Kong children

BJ Cowling *, KH Chan, JSM Peiris

KEY MESSAGES

1. Respiratory viruses are frequently detected in paediatric outpatients in Hong Kong, and non-influenza viruses appear to be associated with a much greater burden on ambulatory care than influenza A and B viruses do.
2. Increased detection of respiratory syncytial virus, parainfluenza, adenovirus, and bocavirus among inpatients suggest that these viruses may be associated with more severe illnesses than influenza and rhinovirus are, particularly in younger children.
3. Given the substantial burden of respiratory viruses other than influenza, more attention should be given to potential measures to control these diseases in Hong Kong.

Hong Kong Med J 2018;24(Suppl 6):S12-5
RFCID project number: 10091272

[1] BJ Cowling, [2] KH Chan, [1,3] JSM Peiris

The University of Hong Kong:
[1] *School of Public Health*
[2] *Department of Microbiology*
[3] *Centre for Influenza Research*

* Principal applicant and corresponding author: bcowling@hku.hk

Introduction

Respiratory viruses are responsible for a large proportion of infections, hospitalisations, and deaths every year in Hong Kong.[1,2] The most severe infections are usually due to respiratory syncytial virus (RSV) in infants and influenza in all ages. The burden of other common respiratory viruses including parainfluenza, adenovirus, metapneumovirus, coronavirus, and rhinovirus are also considerable.[1-4] These viruses often result in a broad and overlapping spectrum of symptoms commonly called the 'common cold'. Only a few of the most severe infections result in hospitalisation. Previous studies have focused mainly on infections among hospitalised patients.[1-4] Nonetheless, some community-based studies of respiratory viral infections were conducted prior to the availability of molecular diagnostics and the discovery of certain respiratory pathogens such as human metapneumovirus, coronaviruses NL-63 and HKU1, and bocavirus. Limited data specific to the community viral burden in Hong Kong are available, except for those about influenza virus, for which good local surveillance data exist.

This study aimed to characterise the incidence of common respiratory viruses in children that lead to influenza-like illness and compare paediatric outpatient with inpatient data.

Methods

The study protocol was approved by the Institutional Review Board of the University of Hong Kong. Proxy written consent from parents or legal guardians was obtained for participants aged 16 years and younger, with additional written assent from those aged 8 to 16 years.

We conducted a large field study of influenza transmission within households in the years 2007-2010.[5-7] The inclusion criteria were (1) Hong Kong residents, (2) presenting two or more symptoms of acute respiratory illness, including body temperature of ≥37.8°C, headache, cough, sore throat, myalgia, runny nose, or phlegm, (3) onset of symptoms within the preceding 48 hours, (4) living in a household with at least two other people, and (5) all household members, except for the index subject, being free from acute respiratory illness in the past 2 weeks.

Patients were asked to complete a short data collection from. A combined nasal and throat swab was then collected and tested with the QuickVue Influenza A+B rapid diagnostic test (Quidel, San Diego, California). The household contacts of patients with positive results received further follow-up. In the present analysis, we focus only on the specimens collected from patients at the clinic. While waiting for the rapid test result (5-10 minutes), an additional nasal and throat swab specimen was collected and stored immediately in a viral transport medium for subsequent virological testing.

We compared our results with those of another study in which paediatric inpatients were recruited from two public hospitals (Pamela Youde Nethersole Eastern Hospital and Queen Mary Hospital) from January to September of 2008 to 2010.[8] Nasopharyngeal aspirates were obtained and tested by the same xTAG assay for respiratory viruses as the outpatient specimens were.

The primary outcome measure was respiratory

virus infection in participants, indicated by positive multiplex assay results from the combined nasal and throat swab. The secondary outcome measure was presentation of influenza-like-illness-related symptoms (body temperature ≥37.8°C, headache, sore throat, cough, runny nose, myalgia, and phlegm).

Each specimen was stored in viral transport medium (5% bovine serum albumin in Earle's balanced salt solution with antibiotic) and kept at 2-8°C immediately after collection, then cryopreserved at –70°C within 36 hours. The specimens were tested for 18 respiratory viruses (influenza A and B, RSV A and B, parainfluenza types 1-4, metapneumovirus, enterovirus/rhinovirus, adenovirus, bocavirus, coronavirus types NL63, HKU1, 229E, and OC43) by the xTAG RVP FAST multiplex assay followed by product detection and identification using a Luminex suspension microarray. Total nucleic acids were extracted from the clinical specimens using NucliSens easyMAG extraction system (bioMerieux, Netherlands) according to the manufacturer's instructions. The extracted nucleic acids were tested for respiratory viruses.

Detection frequencies in children aged 0-5 and 6-16 years were compared using Chi-squared tests, with 95% confidence intervals obtained using the exact binomial method. Associations between individual respiratory viruses and clinical symptoms were determined by cross-tabulating the proportion of influenza-like-illness-related symptoms presented with each type of virus detected. The differences between certain symptom onset rates were compared among viruses using Chi-squared tests. For virus detection frequencies, outpatient data were compared with inpatient data using Chi-squared tests, with 95% confidence intervals obtained using the exact binomial method.

Results

Of the 2700 children recruited between 2007 and 2010, 2090 (77%) provided specimens that were extracted and tested for respiratory viruses. Children recruited in each year had similar baseline characteristics (data not shown). Of the 2090 specimens, 1343 (64%) were positive for at least one respiratory virus, among which 81 (6%) were positive for more than one respiratory virus (Table 1). The most common viruses detected were entero/rhinovirus and influenza A virus. In the 81 specimens with co-detection, many were positive for entero/rhinovirus. One notable co-detection was coronavirus and influenza A. Two specimens had three viruses detected: one with entero/rhinovirus, metapneumovirus, and RSV B and another with entero/rhinovirus, parainfluenza type 4, and RSV A.

Influenza A and B viruses were significantly more frequently detected in children aged 6-16 years, whereas rhinovirus, metapneumovirus, RSV, parainfluenza, adenovirus, and bocavirus were more frequently detected in children aged 0-5 years (Table 2). Nonetheless, we could not identify consistent seasonal patterns for any of the respiratory viruses across the 4 study years (data not shown). Many of the viruses appeared in epidemics (including influenza A and B and parainfluenza), but the timing of the epidemics differed from year to year. Other viruses (including entero/rhinovirus, metapneumovirus, and coronavirus) appeared throughout most years.

Both younger and older children infected with influenza A, influenza B, or adenovirus had a significantly higher chance of presenting with fever, whereas those infected with metapneumovirus or RSV had a significantly higher chance of presenting with coughing (Table 3). Among children infected with influenza A or B, 70% to 80% presented with both fever and cough or sore throat, compared with 50% among children infected with other viruses.

Our study's outpatient data were compared

TABLE 1. Detection of respiratory viruses among 2090 paediatric outpatients

Virus type	Detection rate (95% confidence interval)	Co-infection rate among positive detection (95% confidence interval)
Entero/rhinovirus	23.4 (21.6-25.3)	12.7 (9.8-15.9)
Influenza A	19.6 (17.9-21.3)	8.8 (6.2-12.0)
Influenza B	6.3 (5.3-7.4)	6.1 (2.7-11.6)
Metapneumovirus	5.3 (4.4-6.4)	7.2 (3.2-13.7)
Respiratory syncytial virus A and B	4.9 (4.0-5.9)	19.4 (12.3-28.4)
Parainfluenza types 1-4	3.0 (2.3-3.8)	9.5 (3.6-19.6)
Coronavirus	2.8 (2.2-3.6)	22.0 (12.3-34.7)
Adenovirus	2.5 (1.9-3.3)	11.3 (4.3-23.0)
Bocavirus	0.3 (0.1-0.6)	83.3 (35.9-99.6)

TABLE 2. Comparison of virus detection between children aged 0-5 years and 6-16 years

Virus type	Detection rate (95% confidence interval)		P value
	Age 0-5 years (n=822)	Age 6-16 years (n=1268)	
Entero/rhinovirus	28.5 (25.4-31.7)	20.2 (18.0-22.5)	<0.01
Influenza A virus	14.5 (12.1-17.1)	22.9 (20.6-25.3)	<0.01
Influenza B virus	3.8 (2.6-5.3)	8.0 (6.5-9.6)	<0.01
Metapneumovirus	8.4 (6.6-10.5)	3.3 (2.4-4.5)	<0.01
Respiratory syncytial virus A and B	10.9 (8.9-13.3)	1.0 (0.5-1.7)	<0.01
Parainfluenza	5.1 (3.7-6.8)	1.7 (1.0-2.5)	<0.01
Coronavirus	2.3 (1.4-3.6)	3.2 (2.3-4.3)	0.32
Adenovirus	3.5 (2.4-5.0)	1.9 (1.2-2.8)	0.03
Bocavirus	0.7 (0.3-1.6)	0.0 (0.0-0.3)	0.01

TABLE 3. Association between individual respiratory viruses and clinical symptoms by age group

Symptoms	Proportion									P value
	Entero/ rhinovirus	Influenza A	Influenza B	Metapneu-movirus	Respiratory syncytial virus A and B	Para-influenza	Corona virus	Adeno-virus	Boca-virus	
Age 0-5 years, n	234	119	31	69	90	42	19	29	6	
Body temperature ≥37.8°C	0.44	0.83	0.81	0.52	0.48	0.62	0.47	0.83	0.50	<0.01
Headache	0.09	0.15	0.26	0.06	0.10	0.12	0.05	0.24	0.17	0.02
Sore throat	0.32	0.42	0.29	0.28	0.30	0.36	0.37	0.48	0.33	0.34
Cough	0.84	0.85	0.74	1.00	0.97	0.76	0.63	0.59	1.00	<0.01
Myalgia	0.09	0.15	0.16	0.09	0.07	0.07	0.05	0.14	0.00	0.37
Runny nose	0.90	0.81	0.84	0.74	0.86	0.74	0.84	0.69	0.83	0.01
Phlegm	0.46	0.49	0.35	0.55	0.72	0.36	0.32	0.34	0.67	<0.01
Age 6-16 years, n	256	290	101	42	13	21	40	24	0	
Body temperature ≥37.8°C	0.38	0.80	0.82	0.43	0.46	0.57	0.50	0.75	-	<0.01
Headache	0.38	0.45	0.59	0.33	0.15	0.38	0.48	0.50	-	<0.01
Sore throat	0.61	0.65	0.50	0.52	0.62	0.67	0.72	0.54	-	0.11
Cough	0.74	0.86	0.81	0.98	0.85	0.71	0.80	0.54	-	<0.01
Myalgia	0.22	0.31	0.39	0.19	0.00	0.19	0.30	0.25	-	<0.01
Runny nose	0.86	0.82	0.87	0.76	0.92	0.76	0.82	0.67	-	0.27
Phlegm	0.52	0.64	0.63	0.81	0.69	0.48	0.65	0.33	-	<0.01

with inpatient data from two public hospitals from January to September of 2008 to 2010. Among both younger and older children, inpatients had a significantly higher chance of RSV A and B detection than outpatients had. Among children aged 0-5 years, inpatients had a significantly higher chance of parainfluenza, adenovirus, and bocavirus detection than outpatients had (data not shown).

Discussion

Many studies have confirmed the substantial morbidity and mortality burden associated with influenza virus. Nonetheless, studies of respiratory viruses such as rhinovirus, parainfluenza, adenovirus, and RSV are limited. These viruses are also associated with a substantial burden perhaps exceeding that of the influenza virus in certain age groups.[8] Influenza vaccination is effective at preventing influenza virus infection and associated morbidity in most age groups. Nonetheless, no licensed vaccines are available for these other respiratory viruses.

In our study, among children aged 6-16 years, entero/rhinoviruses and influenza A were the most common causes of outpatient visits for acute respiratory illness. Among younger children, there was a broader range of common viral aetiologies. Overall, we identified at least one respiratory virus in 64% of specimens. Almost all specimens were collected within 48 hours of illness onset, so it is unlikely that the patients had ceased virus shedding. However, it is possible that the xTAG assay used had imperfect sensitivity for some respiratory viruses. It is unclear how the 6% prevalence of co-infections, which may have special epidemiological significance, should be interpreted.

In our study, we did not have an estimate of the underlying population from which the outpatients came, and therefore, the population-based incidence of various viral infections cannot be estimated. Among outpatients and inpatients aged 0-5 years, RSV, parainfluenza, adenovirus, and bocavirus were more frequently detected among inpatients than outpatients. This suggests that these viruses may lead to more severe illnesses than other respiratory viruses. Previous studies have also identified similar patterns for RSV and influenza in children in Taiwan[9] and the United States.[10]

Influenza-like illness is defined as fever plus cough or sore throat. Nonetheless, this case definition lacks sensitivity and specificity for influenza. We could not identify any differences between the various respiratory viruses. Influenza A and B and adenovirus infections were more likely to cause febrile illness (Table 3).

Influenza has a seasonal pattern with activity peaks in the winter and summer in most years, whereas RSV tends to occur in the summer months. Nonetheless, we could not identify any consistent seasonal pattern. Another study with a longer timeframe reported consistent patterns in RSV and parainfluenza activity in Hong Kong prior to the 2009 influenza pandemic and noted that the seasonal

patterns of respiratory viruses were disrupted after 2009.[11]

One study has reported detection of respiratory viruses in the respiratory tracts of children who were not ill and questioned the role of some respiratory viruses in causing disease.[12] Further studies are needed to determine the pathogenicity of viruses that are not known to be pathogenic. In our other study, we commonly detected respiratory viruses in children with acute respiratory illness, but we rarely detected respiratory viruses in children who were not ill.[13] Preliminary results provide indirect evidence that virus detection in children with medically attended acute respiratory illness is consistent with the pathogenicity of the viruses detected. A limitation of our study is that detailed clinical data were not accessed for either outpatients or inpatients.

In terms of disease control, improved control of respiratory virus transmission in schools and increased frequency of disinfection of common surfaces in public areas are suggested. Our findings on the substantial outpatient burden of RSV and data on the burden of hospitalisations and deaths associated with RSV are useful for calculating the cost-effectiveness of an RSV vaccine. Treatment for acute respiratory illnesses is largely empirical and focused on management of specific symptoms. An understanding of viral aetiology may be used in campaigns to reduce antiviral prescription rates and preserve antibiotics.

Conclusions

The RSV was frequently detected in inpatients and outpatients with acute respiratory illness. The symptoms of parainfluenza and adenovirus infections were generally more severe than those of influenza virus and rhinovirus infections. Further studies are needed to clarify the annual burden of these viruses across the full spectrum of disease, including ambulatory care, inpatient care, intensive care, and mortality.

Acknowledgements

This study was supported by the Research Fund for the Control of Infectious Diseases, Food and Health Bureau, Hong Kong SAR Government (#10091272). The authors thank Dr Susan Chiu from the Department of Paediatrics and Adolescent Medicine at The University of Hong Kong for sharing inpatient laboratory results for comparison with our outpatient data.

References

1. Cheuk DK, Tang IW, Chan KH, Woo PC, Peiris MJ, Chiu SS. Rhinovirus infection in hospitalized children in Hong Kong: a prospective study. Pediatr Infect Dis J 2007;26:995-1000.
2. Chiu SS, Lau YL, Chan KH, Wong WH, Peiris JS. Influenza-related hospitalizations among children in Hong Kong. N Engl J Med 2002;347:2097-103.
3. Chan PK, Sung RY, Fung KS, et al. Epidemiology of respiratory syncytial virus infection among paediatric patients in Hong Kong: seasonality and disease impact. Epidemiol Infect 1999;123:257-62.
4. Peiris JS, Tang WH, Chan KH, et al. Children with respiratory disease associated with metapneumovirus in Hong Kong. Emerg Infect Dis 2003;9:628-33.
5. Cowling BJ, Fung RO, Cheng CK, et al. Preliminary findings of a randomized trial of non-pharmaceutical interventions to prevent influenza transmission in households. PLoS One 2008;3:e2101.
6. Cowling BJ, Chan KH, Fang VJ, et al. Facemasks and hand hygiene to prevent influenza transmission in households: a cluster randomized trial. Ann Intern Med 2009;151:437-46.
7. Cowling BJ, Chan KH, Fang VJ, et al. Comparative epidemiology of pandemic and seasonal influenza A in households. N Engl J Med 2010;362:2175-84.
8. Chiu SS, Chan KH, Chen H, et al. Virologically confirmed population-based burden of hospitalization caused by respiratory syncytial virus, adenovirus, and parainfluenza viruses in children in Hong Kong. Pediatr Infect Dis J 2010;29:1088-92.
9. Tsai HP, Kuo PH, Liu CC, Wang JR. Respiratory viral infections among pediatric inpatients and outpatients in Taiwan from 1997 to 1999. J Clin Microbiol 2001;39:111-8.
10. 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.
11. Mak GC, Wong AH, Ho WY, Lim W. The impact of pandemic influenza A (H1N1) 2009 on the circulation of respiratory viruses 2009-2011. Influenza Other Respir Viruses 2012;6:e6-10.
12. Advani S, Sengupta A, Forman M, Valsamakis A, Milstone AM. Detecting respiratory viruses in asymptomatic children. Pediatr Infect Dis J 2012;31:1221-6.
13. Cowling BJ, Fang VJ, Nishiura H, et al. Increased risk of noninfluenza respiratory virus infections associated with receipt of inactivated influenza vaccine. Clin Infect Dis 2012;54:1778-83.