Severity profiles of respiratory viruses in children in Hong Kong: abridged secondary publication

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KEY MESSAGES

1. There was substantial respiratory disease burden associated with influenza, respiratory syncytial virus, parainfluenza, and adenovirus in children in Hong Kong, but virus-attributable deaths were rare.
2. Respiratory disease burden varies in young and old children.
3. Severity of infections with common respiratory viruses can be quantified using data collected from different sources.

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Introduction

Most respiratory virus infections lead to mild self-limiting illness, but on some occasions infection may lead to severe diseases such as viral pneumonia or secondary bacterial pneumonia. Considerable numbers of respiratory viruses have been detected from outpatients and inpatients with influenza-like illness or other respiratory infections.[1-3] Effects of respiratory viruses on population morbidity and mortality have been well studied,[4] no studies have systematically investigated the impact associated with common respiratory viruses and compared relative contributions from these viruses to disease burden. Therefore, we examined the impact of four common respiratory viruses in Hong Kong. We constructed an impact pyramid for each virus by estimating the number of symptomatic infections, medically attended infections, virus associated excess hospitalisations, intensive care unit (ICU) admissions, and deaths during 2009 and 2012.

Methods

Estimation of symptomatic infections

In 2008 to 2010, we conducted a randomised controlled trial to evaluate the direct and indirect benefits of influenza vaccination for children.[5,6] In October 2008 we began a pilot study in 119 households and in October 2009 we began a larger main trial in 796 households. One child in each household was randomised to receive influenza vaccination or placebo. Households were followed up for 1 year prospectively to identify illnesses, and nose and throat swabs were collected from ill children. We continued to follow up the subjects without administering any further vaccinations in 2010 to 2011 and 2011 to 2012. Nasal and throat swabs are routinely collected from symptomatic subjects reporting illness. Specimens collected from unvaccinated children were used in the present proposal to provide information on the incidence of symptomatic infections associated with various respiratory viruses. We tested 600 specimens from unvaccinated children 0-15 years for respiratory syncytial virus, parainfluenza and adenovirus by the xTAG multiplex array that permits testing of multiple respiratory viruses in a single sensitive assay.[7]

Incidence of medically attended infection

To estimate the probability of symptomatic cases seeking medical service, we conducted a population-based survey on patterns of health seeking behaviour among 1000 randomly selected parents with at least one child aged 0 to 15 years. Subjects were selected through household recruitment by random digital dialling of landline numbers. The recruited parents were asked about the intention to take their sick child to seek medical consultation if the child had acute respiratory symptoms, which were regarded as the driving factor for health-seeking behaviour by the parents. The information collected on the proportion of subjects with febrile respiratory infections seeking medical consultation were used to derive the probability of an infection leading to a medical consultation at a private general practitioner, a public general outpatient clinic, or a hospital emergency room for each virus of interest.

Incidence of hospitalisations, ICU admissions, and deaths

Weekly age-specific all-cause hospitalisations, ICU admissions, and deaths in Hong Kong between 2004 and 2012 were obtained from the Department of

Health and the Census and Statistics Department of the Government of the Hong Kong SAR. The public health laboratory in Hong Kong receives specimens for diagnostic and surveillance purposes from sentinel outpatient clinics and local hospitals, and reports the weekly proportions of specimens that tested positive for common respiratory viruses, including influenza (by type and subtype), respiratory syncytial virus, parainfluenza and adenovirus. The Centre for Health Protection reported weekly proportions of general practitioner consultations due to ILI. Weekly mean temperature and relative humidity were extracted from the published data from the Hong Kong Observatory. Age-specific population size from 2004 to 2012 was obtained from the Census and Statistics Department.

Statistical analyses

Using results from virological testing on the nasal and throat specimens collected from randomly selected household members in Hong Kong in the cohort study in 2009 to 2012, we were able to derive the proportion of infections with each virus among individuals in different age groups during the time period when the subjects were recruited and followed up. The number of individuals infected with each virus in Hong Kong during the same period as when the cohort study did was derived from the probability of infection by weighting the differences in age distribution between the cohort and general Hong Kong population.

We fitted weekly all-cause hospitalisation, ICU admissions, and death rates separately to multiple linear regression models that allow for adjustment of activities of different respiratory viruses, meteorological parameters, and temporal trends in weekly rates during the study period. The excess hospitalisations, ICU admissions and deaths associated with a respiratory virus were estimated as the difference between the predicted rates in the presence and in the absence of activities of the virus. These models were each run for age groups 1 (age 0-5 years) and 2 (age 6-15 years) using only respiratory causes of death (ICD-10 codes J00-99).

We estimated the number of cases for each severity level to derive the probability of medically attended symptomatic infection, the probability of hospitalisation among all medically attended symptomatic infections, the probability of being admitted to ICU after hospitalisation, and the probability of death after being admitted to ICU and to construct the impact pyramid for each common respiratory virus of interest applied a Bayesian evidence synthesis approach to integrate relevant information to derive the above parameters for each virus.[8,9] Information on the observed number of events in each level of the impact pyramid was used to derive the posterior distribution for each parameter. We used flat non-informative priors for each parameter. The model was fitted with Markov chain Monte Carlo to make inference on the parameters, with 100 000 iterations after burn-in. The advantage of this approach is that it maintains uncertainty from each data source through to the final estimates of the severity profile of each virus.

Results

During 2009 to 2012, influenza viruses caused three winter waves secondary to seasonal influenza A(H1N1) virus in 2009, the newly emerged influenza A(H1N1)pdm09 virus in 2011, and influenza B in 2012, and three summer waves associated with influenza A(H1N1)pdm09 virus in 2009 and influenza A(H3N2) in 2010 and 2012. No apparent seasonal patterns were suggested by virus activity data collected from the local sentinel surveillance system. Instead viruses were detected throughout the whole year except that a 3- to 4-year cyclic pattern was observed for adenovirus.

Respiratory symptomatic infections were estimated based on data collected from the prospective cohort. Viruses were more frequently detected in older children compared to the young counterparts. Among children who were testing positive for any of the six viruses, the distribution of acute respiratory symptoms varied substantially (data not shown). In the prospective cohort, we estimated that approximately 75% to 8% of healthy children aged 0 to 15 years would present acute respiratory symptoms associated with infection with influenza virus, syncytial virus, parainfluenza and adenovirus each year.

A telephone survey was conducted in order to collect information on health-seeking behaviour among children who presented acute respiratory symptoms in Hong Kong. In total, 1002 parents/guardians who were caring for at least one child aged 0 to 15 years were recruited for interview. Respondents recruited in the survey reported that >20% of their children showed at least one of the acute respiratory symptoms in the past months before the interview. Cough, running nose, and sore throat were the most frequent. We derived the probability for medical consultation for each symptom combination based on symptoms reported by each subject (data not shown).

We used linear regression models to fit weekly respiratory hospitalisation, ICU admission and death rates in 2009 to 2012, and estimated the excess respiratory hospitalisation, ICU and death associated with each of the six types/subtypes of respiratory viruses in children aged 0 to 5 years and 6 to 15 years between 2009 and 2012. The average annual excess hospitalisation admission rate was particularly high in respiratory infections associated with influenza and respiratory syncytial virus, 646

TABLE 1. Estimated annual rates (per 100 000) of symptomatic and medically attended symptomatic respiratory infections, excess hospitalisations, intensive-care-unit (ICU) admissions and deaths due to respiratory infections attributable to 7 types/subtypes of common respiratory viruses in children aged 0 to 5 years and 6 to 15 years between 2009 and 2012.

	Estimated annual rates (per 100 000) [95 % confidence interval]				
	Symptomatic*	**Medically attended***	**Excess hospitalisation**	**Excess ICU admission**	**Excess death**
Age 0-5 years					
All respiratory viruses	6847 (0-22709)	5432 (0-18368)	1491 (1359-1621)	27 (16-38)	-2.83 (-5.33 to -0.54)
All flu	2074 (0-8540)	1875 (0-7737)	646 (587-704)	0.8 (-2.6 to 4.1)	0.25 (-0.45 to 1.01)
A/h3	323 (0-1883)	300 (0-1748)	299 (270-328)	1.8 (0.3-3.3)	-0.06 (-0.40 to 0.27)
A/ph1	782 (0-2902)	703 (0-2609)	163 (155-172)	-0.3 (-0.7 to 0.2)	-0.21 (0.26 to -0.15)
B	970 (0-3756)	873 (0-3381)	119 (93-144)	-2.6 (-4.3 to -1.0)	0.05 (-0.31 to 0.41)
Respiratory syncytial virus	2538 (0-6961)	1716 (0-4706)	686 (623-747)	20 (17-23)	-0.47 (-1.22 to 0.26)
Parainfluenza	1705 (0-4915)	1415 (0-4078)	124 (63-185)	6.3 (0.4-12)	-0.85 (-2.20 to 0.42)
Adenovirus	528 (0-2293)	426 (0-1847)	35 (0-69)	-0.2 (-6.2 to 6.2)	-1.76 (-3.25 to -0.44)
Age 6-15 years					
All respiratory viruses	7570 (0-16205)	6230 (0-13256)	312 (264-359)	4.5 (1.3-7.7)	0.30 (0.00-1.15)
All flu	5208 (592-10602)	4426 (469-8909)	220 (205-235)	1.2 (0.2-2.1)	0.08 (0.00-0.83)
A/h3	931 (0-2086)	847 (0-1872)	48 (41-55)	-0.2 (-0.7 to 0.2)	-
A/ph1	1381 (0-2780)	1154 (0-2324)	107 (104-109)	1.2 (1.1-1.3)	0.11 (0.00-0.95)
B	2896 (832-5737)	2425 (684-4713)	89 (82-97)	0.6 (0.1-1.1)	0.05 (0.00-0.41)
Respiratory syncytial virus	853 (0-2069)	608 (0-1474)	8 (-7-23)	-0.1 (-1.0 to 0.8)	-
Parainfluenza	1079 (0-2367)	849 (0-1932)	37 (11-63)	1.2 (-0.6 to 3.1)	0.31 (0.00-1.16)
Adenovirus	430 (0-1167)	346 (0-940)	47 (22-72)	2.2 (0.2-4.1)	-

* Negative estimates of the lower bound of the 95% CIs were truncated to zero

and 686 per 100 000 population in children aged 0 to 5 years whereas parainfluenza caused a lower excess hospitalisation burden comparable to influenza A(H1N1)pdm09 or B viruses, and adenovirus was associated with the lowest excess hospitalisations in this age group (Table 1). In older children, most excess hospitalisations and ICU admissions associated with respiratory infections were likely to be caused by influenza, followed by adenovirus and parainfluenza. Among influenza viruses, influenza A(H1N1)pdm09 contributed a larger proportion of the excess hospitalisation burden than other types/subtypes. In general, no substantial excess deaths were estimated the excess ICU admissions were estimated to be considerably higher in younger than older children across different virus types/subtypes.

We estimated the severity of respiratory infections with seven types/subtypes of commonly reported respiratory viruses in Hong Kong from 2009 through 2012 using a Bayesian synthetic framework to incorporate information derived from different data sources. To estimate the proportion of symptomatic infections seeking health care, progressing to being hospitalised, ICU admission or death, the number of patients in each level of the severity pyramid was estimated (Fig). We estimated the proportion of respiratory deaths, ICU admissions, and hospitalisations among symptomatic and medically-attended symptomatic infections with influenza A(H1N1)pdm09, A(H3N2), B, respiratory syncytial virus, parainfluenza, and adenovirus (Table 2).

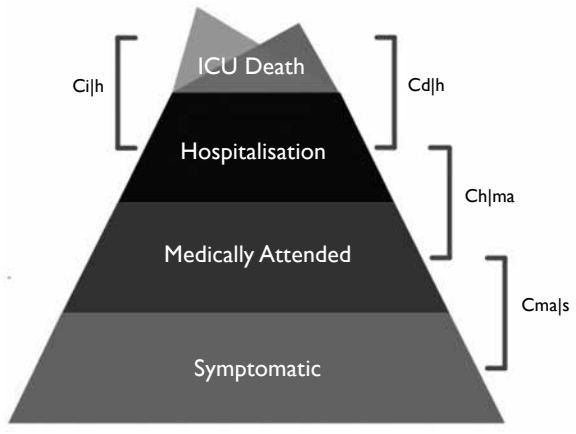

FIG. Schematic illustration of severity pyramid of infections with respiratory viruses.

TABLE 2. Estimated ratios of respiratory death, intensive care unit (ICU) admission and hospital admission among symptomatic or medically attended symptomatic infections with six common respiratory virus types/subtypes in children aged 0 to 5 years and 6 to 15 years.

	Estimated ratio (95 % confidence interval)						
	Symptomatic: medically-attended	**Hospitalised: medically-attended**	**ICU admitted: hospitalised**	**Fatal: hospitalised**	**Hospitalised: symptomatic**	**ICU admitted: symptomatic**	**Fatal: symptomatic**
Age 0-5 years							
All viruses	0.79 (0.762-0.793)	0.27 (0.259-0.288)	0.02 (0.014-0.028)	-	0.22 (0.207-0.230)	0.004 (0.003-0.007)	-
All flu	0.90 (0.849-0.910)	0.34 (0.313-0.375)	0.001 (0.000-0.005)*	0.0004 (0.0000-0.0015)	0.31 (0.283-0.337)	0.0004 (0.000-0.002)*	0.0001 (0.0000-0.0015)
A/h3	0.91 (0.833-0.992)	0.99 (0.825-1.000)	0.006 (0.000-0.011)*	-	0.93 (0.773-1.058)	0.006 (0.003-0.028)	-
A/ph1	0.90 (0.821-0.922)	0.23 (0.195-0.275)	-	-	0.21 (0.174-0.245)	-	-
B	0.90 (0.864-0.957)	0.14 (0.108-0.160)	-	0.0004 (0.0000-0.0278)	0.12 (0.095-0.141)	-	0.0004 (0.0000-0.0031)
Respiratory syncytial virus	0.75 (0.721-0.771)	0.40 (0.364-0.433)	0.03 (0.018-0.044)	-	0.27 (0.243-0.287)	0.008 (0.007-0.015)	-
Parainfluenza	0.83 (0.817-0.883)	0.09 (0.068-0.100)	0.05 (0.017-0.102)	-	0.07 (0.056-0.082)	0.004 (0.002-0.009)	-
Adenovirus	-	0.08 (0.046-0.096)	-	-	0.07 (0.037-0.078)	-	-
Age 6-15 years							
All viruses	0.82 (0.810-0.839)	0.05 (0.042-0.054)	0.01 (0.003-0.026)	0.001 (0.0000-0.0103)	0.04 (0.035-0.044)	0.0006 (0.0001-0.001)	0.00004 (0.00000-0.00040)
All flu	0.85 (0.829-0.869)	0.05 (0.042-0.056)	0.006 (0.000-0.024)*	0.0004 (0.0000-0.0154)	0.04 (0.036-0.047)	0.0002 (0.000-0.001)*	0.00002 (0.00000-0.00059)
A/h3	0.91 (0.853-0.944)	0.06 (0.042-0.077)	-	-	0.05 (0.039-0.070)	-	-
A/ph1	0.84 (0.798-0.871)	0.09 (0.073-0.111)	0.01 (0.000-0.045)*	0.001 (0.0000-0.0357)	0.08 (0.062-0.093)	0.0009 (0.000-0.005)*	0.00008 (0.00000-0.00217)
B	0.84 (0.802-0.851)	0.04 (0.029-0.046)	0.007 (0.000-0.041)*	0.0006 (0.0000-0.0500)	0.03 (0.024-0.037)	0.0002 (0.000-0.001)*	0.00002 (0.000000-0.00104)
Respiratory syncytial virus	0.71 (0.618-0.761)	0.01 (0.002-0.016)	-	-	0.01 (0.001-0.011)	-	-
Parainfluenza	0.79 (0.762-0.839)	0.04 (0.033-0.065)	0.03 (0.000-0.178)*	0.008 (0.0000-0.1334)	0.03 (0.027-0.051)	0.001 (0.000-0.005)*	0.0003 (0.00000-0.00465)
Adenovirus	0.81 (0.69-0.911)	0.14 (0.098-0.183)	0.05 (0.000-0.132)*	-	0.11 (0.079-0.145)	0.005 (0.000-0.015)*	-

* The negative lower bound of the 95% confidence intervals was truncated to zero. The numerator and/or denominator used to calculate the proportion were/was negative

Discussion

There was a substantial burden of symptomatic respiratory infections associated with influenza, respiratory syncytial virus, parainfluenza, and adenovirus each year in children aged 0 to 15 years in Hong Kong. Among those presenting with acute respiratory symptoms, approximately 70% to 90% of patients choose to seek a medical consultation either through government-supported public clinics/hospitals or general practitioners/private hospitals. No major differences were observed between young and older children. During 2009 to 2012, the annual excess hospitalisation rate was different for each respiratory virus of interest, whereas the excess burden of ICU admission and death associated with respiratory infections of the virus was generally low or rare in both younger and older children, consistent with previous findings.[10] Therefore, severity of respiratory infection measured by the risk of ICU admission and death was extremely low among sick children having symptomatic infections with the six types/subtypes of respiratory viruses in Hong Kong.

Our study indicated that it was possible to quantitatively measure the severity of infections with respiratory viruses using data collected from the sentinel surveillance system, community-based cohort and population morbidity and mortality statistics. Previously published studies to measure

population burden of infections associated with respiratory infection largely relied on outpatient data collected from outpatient clinics or one cohort of subjects (patients or non-patients) in which it was therefore difficult to determine the population denominator for estimation of the severity profile, or used rate difference statistical models which would sometimes fail to estimate virus-specific burden when there was co-circulation of viruses during the study period.[10]

Conclusion

Considerable respiratory morbidity burden was caused by common respiratory viruses in Hong Kong children, and severity of infection varied across different viruses in young and old children. Influenza viruses generally contributed to the highest disease burden in both young and old children. Respiratory syncytial virus was associated with the highest risk of hospitalisation among laboratory-confirmed symptomatic infections in children aged 0 to 5 years.

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Disclosure

The results of this research have been previously published in:
(1) Wu P, Presanis AM, Bond HS, Lau EHY, Fang VJ, Cowling BJ. A joint analysis of influenza-associated hospitalizations and mortality in Hong Kong, 1998–2013. Sci Rep 2017;7:929.

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