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Influenza associated mortality in the subtropics and tropics: Results from three Asian cities

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ABSTRACT

Influenza has been well documented to significantly contribute to winter increase of mortality in the temperate countries, but its severity in the subtropics and tropics was not recognized until recently and geographical variations of disease burden in these regions remain poorly understood. In this study, we applied a standardized modeling strategy to the mortality and virology data from three Asian cities: subtropical Guangzhou and Hong Kong, and tropical Singapore, to estimate the disease burden of influenza in these cities. We found that influenza was associated with 10.6, 13.4 and 8.3 deaths per 100,000 population in Guangzhou, Hong Kong and Singapore, respectively. The annual rates of excess deaths in the elders were estimated highest in Guangzhou and lowest in Singapore. The excess death rate attributable to A/H1N1 subtype was found slightly higher than the rates attributable to A/H3N2 during the study period of 2004–2006 based on the data from Hong Kong and Guangzhou. Our study revealed a geographical variation in the disease burden of influenza in these subtropical and tropical cities. These results highlight a need to explore the determinants for severity of seasonal influenza.

1. Introduction

Influenza is one of the respiratory pathogens that can cause serious health problems in both mortality and morbidity worldwide. However, unspecific presenting symptoms of influenza, absence of timely laboratory tests in clinical practice and frequent secondary bacterial pneumonia make it difficult to estimate the disease burden of influenza directly from the clinical diagnosed cases [1,2]. It is therefore necessary to assess influenza associated excess mortality or hospitalization by statistical modeling and use the estimate as a measurement for severity of influenza epidemics [3]. Some studies reported that the disease burden of influenza was nearly equivalent across some temperate countries [4], but others noticed that effects of influenza occasionally exhibited disparities between geographical areas even in the same influenza season [5]. It has been proposed that socioeconomic factors and various circulating virus strains could play an important role in determining the severity of influenza epidemics [5–7]. Some environmental factors that are critical for survival and transmission of viruses, such as temperature and humidity, could also be involved as effect modifiers [8]. However, geographical variations in influenza associated disease burden in the tropics and subtropics have not been explored.

A recent large-scale phylogenetic study postulated that novel influenza viruses first emerge in the tropics and subsequently spread into the temperate when environmental factors favor virus transmissions [9]. Particularly, East and Southeast Asian countries are proposed as the potential reservoirs for dormant influenza viruses, although the mechanism remains unclear [10]. Unfortunately, there are few disease burden studies in this region to provide the evidence for or against the postulation, largely due to a lack of data from well-designed long-standing surveillance. This situation was further complicated by the unpredictable influenza seasonality in these regions.

In this study we applied a standardized modeling strategy to three metropolitan cities in East and Southeast Asia: Guangzhou,

Abbreviations: ILI, influenza-like illness; ICD, International Classification of Diseases; CRD, cardiorespiratory diseases; P&I, pneumonia and influenza; COPD, chronic obstructive pulmonary diseases; IHD, ischemic heart diseases.

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Hong Kong and Singapore, all of which have well-organized surveillance networks for influenza for several years. Guangzhou and Hong Kong, both located at southern China, share a similar subtropical climate with a mean temperature around 23 °C, but the latter is more economically developed with a higher GDP per capita of $27,762 in Hong Kong as compared with that of $9235 in Guangzhou in 2006 [11,12]. Singapore is a tropical city with a higher mean temperature of 27.8 °C than Guangzhou and Hong Kong. The socioeconomic level of Singapore is comparable to Hong Kong, with a GDP per capita of $31,622 in 2006 [13]. The difference and similarity between these cities, in terms of socioeconomic status and environmental factors, provide us a good opportunity to explore the factors that may affect the disparity or similarity across geographical areas.

2. Methods

2.1. Influenza surveillance data

The influenza virology data in Guangzhou, Hong Kong and Singapore during 2004–2006 were obtained from the Guang Dong Provincial Center for Disease Control and Prevention (GDCDC), the Hong Kong Department of Health (DH) and the Singapore Ministry of Health (MOH), respectively. The nasopharyngeal aspirate specimens were collected from the outpatients or inpatients presenting influenza-like illness (ILI) symptoms of fever (≥38 °C), cough or sore throat and then were tested for influenza by direct immunofluorescence or cell culture. Positive samples were later typed or subtyped into A/H3N2, A/H1N1 and B by haemagglutination inhibition (HI) test with strain-specific antiserum provided by the World Health Organization (WHO).

2.2. Mortality and meteorology data

Mortality data for each city were obtained from Hong Kong Census and Statistics Department (coded according to the International Classification of Diseases Tenth Revision, ICD-10), Guangzhou Department of Health (coded in ICD-10) and Singapore Registry of Births and Deaths (coded in ICD-9), respectively. We aggregated the weekly numbers of deaths with underlying cause of cardiorespiratory diseases (CRD, ICD-9 390-519; ICD-10 I00-I99, J00-J99), pneumonia and influenza (P&I, ICD-9 480-487; ICD-10 J10-J18), chronic obstructive pulmonary diseases (COPD, ICD-9 490-496; ICD-10 J40-J47), ischemic heart diseases (IHD, ICD-9 410-414; ICD-10 I20-I25) and all causes (ICD-9 001-999; ICD-10 A00-T99). Two age groups were considered: all-ages and the elders aged 65 years or over. We obtained the weekly mean temperature and humidity for three cities, from the National Meteorological Information Center in China, Hong Kong Observatory and Singapore National Environment Agency, respectively.

2.3. Modeling influenza effects

We fitted a Poisson regression model to weekly numbers of mortality with the aim to assess the percentage of excess mortality associated with increased influenza activity in the population, as described in our previous studies [14,15]. Briefly, long-term trends and seasonal patterns of mortality counts, as well as weekly average temperature and relative humidity, were added as confounders into the core models with their natural cubic spline smoothing functions. Both temperature and humidity have been found to affect influenza virus transmission [8] and also been associated with mortality in previous studies [16,17]. A typical form of core model is

$$\log(Yt) = ns(t) + ns(temp_t) + ns(humd_t)$$

where Yt denotes the death numbers at week t; $ns(t)$, $ns(temp_t)$ and $ns(humd_t)$ denote the natural spline smoothing functions of time, temperature and relative humidity, respectively. Auto-regressive terms in the residuals may be added to remove significant autocorrelations of residuals in first four weeks, so that time varying confounding could be adequately controlled. The weekly proportions of specimens positive for specific influenza types/subtypes (named as influenza proportions, flu_t) were simultaneously entered into the core model, to estimate influenza effects:

$$\log(Yt) = ns(t) + ns(temp_t) + ns(humd_t) + flu_t$$

The annual effects of influenza on mortality for each year were measured by excess mortality associated with influenza, which is defined as the sum of differences between the observed and expected death numbers when influenza proportions were assumed to be zero during that entire year [14]. The 95% confidence intervals (CI) for estimates were derived by bootstrapping the scaled Pearson residuals for 1000 times. We further derived the excess death rates associated with influenza per 100,000 population to render influenza effects comparable between cities. The percentage of excess deaths was calculated as the excess deaths divided by the total number of observed deaths. All the analyses were performed using the mgcv package of R software (version 2.5.1.) [18].

3. Results

Two subtropical cities Guangzhou and Hong Kong shared similar meteorological conditions, while the tropical city Singapore tended to be hotter and more humid with much less variations in both temperature and humidity (Table 1). Among the three cities, Hong Kong had the largest population, while Singapore had the youngest (Table 1). The crude mortality rate of Guangzhou was slightly higher than that of Hong Kong and Singapore, respectively. More than 75% of deaths were in the 65 or older age group in Guangzhou and Hong Kong, whereas this number was only 66% in Singapore. CRD was the major cause of death in all three cities, but P&I mortality in Guangzhou and COPD in Singapore was the lowest among the three cities (Table 1).

The proportion of specimens positive for influenza A or B in Singapore had an average of 4.0%, which was lower than that in Guangzhou and Hong Kong (10.1% and 13.9%, respectively) (Table 2). This could be due to less stringent diagnosis criteria adopted by Singapore for recruitment of patients into its surveillance network, using the case definition of acute respiratory illness instead of ILI. Influenza seasonality was similar between Hong Kong and Guangzhou, but the winter peak was less pronounced in the latter. There were no clear epidemic periods in Singapore, despite one sharp spike around June of 2006 (Fig. 1). The dominant virus types/subtypes were consistent among three cities: A/H3N2 was dominant in year 2004 and 2005, while A/H1N1 and B were more prevalent in 2006.

Influenza was significantly ($p < 0.05$) associated with all-cause mortality as well as with underlying cause of CRD, P&I, COPD and IHD for the all-ages group in all three cities, with the exceptions of COPD in Guangzhou and Singapore, and IHD in Singapore (Table 3). During the study period of 2004–2006, Hong Kong had the highest percentages of excess deaths associated with influenza among the three cities, with the only exception of IHD deaths. For the all-ages group, Hong Kong had the highest excess deaths for all causes and for underlying causes of P&I and COPD, whereas Guangzhou had the highest excess deaths due to CRD and IHD. The excess death rates for the old population were highest in Guangzhou for all-cause and CRD death.

Table 1
Mean meteorology data, population and annual number of deaths in Guangzhou, Hong Kong and Singapore, 2004–2006.

	Guangzhou	Hong Kong	Singapore
Latitude	23°05′N	21°45′N	1°22′N
Temperature (°C) (SD)	23.0 (5.8)	23.4 (4.9)	27.8 (0.9)
Humidity (%) (SD)	70.0 (10.3)	78.9 (7.5)	83.6 (3.7)
Population (%)[a]			
All-ages	3,716,329 (100.0%)	6,817,933 (100.0%)	4,277,967 (100.0%)
65+	358,157 (9.6%)	835,267 (12.3%)	306,533 (7.2%)
Deaths (rate)[b]			
All-cause			
All-ages	23,084 (621)	36,525 (536)	16,093 (376)
65+	17,328 (4838)	28,877 (3457)	10,726 (3499)
CRD			
All-ages	12,585 (339)	16,264 (239)	8349 (195)
65+	10,961 (3060)	14,601 (1748)	6406 (2090)
P&I			
All-ages	522 (14)	4030 (59)	2298 (54)
65+	453 (126)	3792 (454)	1933 (631)
COPD			
All-ages	2355 (63)	2045 (30)	574 (13)
65+	2231 (623)	1921 (230)	476 (155)
IHD			
All-ages	2558 (69)	3789 (56)	2983 (70)
65+	2190 (611)	3313 (397)	2146 (700)

Note: SD, standard deviation.
[a] Proportion of each age group in total population.
[b] Death rate per 100,000 population.

Table 2
Annual sum of total specimens tested and specimens positive for influenza by subtypes in Guangzhou, Hong Kong and Singapore, 2004–2006.

Year	Virus type	Guangzhou	Hong Kong	Singapore[a]
2004	Test specimens	1895	28,345	7783
	A + B	117	4956	294
	A/H3N2	100 (85.5%)[b]	4605 (92.9%)	67 (38.7%)
	A/H1N1	0 (0.0%)	27 (0.5%)	9 (5.2%)
	B	17 (14.5%)	324 (6.5%)	97 (56.1%)
2005	Test specimens	1856	41,003	10,441
	A + B	266	5894	462
	A/H3N2	164 (61.7%)	4511 (76.5%)	75 (44.6%)
	A/H1N1	67 (25.2%)	429 (7.3%)	30 (17.9%)
	B	35 (13.2%)	954 (16.2%)	63 (37.5%)
2006	Test specimens	1865	36,419	11,105
	A + B	184	3881	535
	A/H3N2	1 (0.5%)	208 (5.4%)	33 (14.9%)
	A/H1N1	115 (62.5%)	2797 (72.1%)	44 (19.8%)
	B	68 (37.0%)	876 (22.6%)	145 (65.3%)
Total	Test specimens	5616	105,767	29,329
	A + B	567	14,731	1291
	A/H3N2	265 (46.7%)	9324 (63.3%)	175 (31.1%)
	A/H1N1	182 (32.1%)	3253 (22.1%)	83 (14.7%)
	B	120 (21.2%)	2154 (14.6%)	305 (54.2%)

[a] Sum of influenza subtypes for Singapore is not equal to A + B because the specimens for subtyping were different from those tested for A + B.
[b] Proportions of subtype in total positive specimens for influenza A + B.

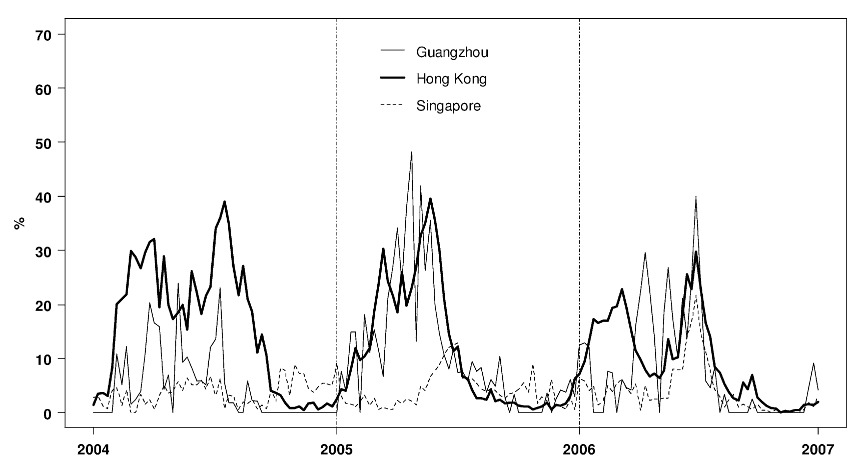

Fig. 1. Weekly proportions of specimens positive for influenza in Guangzhou, Hong Kong and Singapore, 2004–2006.

Table 3
The excess death percentage (Excess %) and excess death rate per 100,000 population (Excess rate) associated with influenza in the three cities Guangzhou, Hong Kong and Singapore.

Age	Disease	Guangzhou		Hong Kong		Singapore	
		Excess % (95% CI)	Excess rate (95% CI)	Excess % (95% CI)	Excess rate (95% CI)	Excess % (95% CI)	Excess rate (95% CI)
All-ages	All-cause	1.7 (0.1, 3.3)	10.6 (0.6, 20.5)	2.5 (1.0, 3.9)	13.4 (5.4, 20.9)	2.2 (0.8, 3.6)	8.3 (3.0, 13.5)
	CRD	2.9 (0.6, 5.2)	9.8 (2.0, 17.6)	4.0 (1.9, 6.1)	9.5 4.5, 14.6)	2.7 (0.9, 4.5)	5.3 (1.8, 8.8)
	P&I	6.8 (1.1, 12.2)	1.0 (0.2, 1.7)	7.8 (4.1, 11.3)	4.6 (2.4, 6.7)	5.2 (1.5, 8.7)	2.8 (0.8, 4.7)
	COPD	2.9 (−0.4, 6.1)	1.8 (−0.3, 3.9)	9.7 (5.7, 13.7)	2.9 (1.7, 4.1)	−1.3 (−8.8, 6.1)	−0.2 (−1.2, 0.8)
	IHD	4.5 (1.4, 7.5)	3.1 (1.0, 5.2)	3.5	1.9 (0.1, 3.8)	2.2 (−0.9, 5.3)	1.5 (−0.6, 3.7)
65+	All-cause	2.3 (0.4, 4.2)	111.3 (19.4, 203.2)	3.0 (1.3, 4.6)	103.7 (44.9, 159.0)	2.3 (0.5, 4.1)	80.5 (17.5, 143.5)
	CRD	3.4 (0.9, 5.8)	104.1 (27.5, 177.5)	4.5 (2.3, 6.7)	78.7 (40.2, 117.1)	2.2 (0.0, 4.5)	46.0 (0.0, 94.0)

Note: CI, confidence interval; CRD, cardiorespiratory diseases; P&I, pneumonia and influenza; COPD, chronic obstructive pulmonary diseases; IHD, ischemic heart diseases.

The annual death rates attributable to influenza revealed the greatest disease burden of influenza in the year 2005 for Guangzhou and Singapore, but in 2006 for Hong Kong. The year with the lowest disease burden was 2004 for Hong Kong and Singapore, and 2006 for Guangzhou (Fig. 2). In Guangzhou, an annual rate of 8.8 (95% CI 1.9–15.8), 17.7 (3.8–31.7) and 5.4 (−7.8 to 8.6) deaths per 100,000 population was estimated to occur in 2004, 2005 and 2006, respectively. The excess rates of deaths for Hong Kong were estimated to be 10.0 (0.5–20.1) in 2004, 12.7 (4.4–20.4) in 2005 and 16.9 (5.8–27.4) deaths per 100,000 population in 2006. Singapore observed 6.4 (1.1–12.1), 10.6 (5.7–15.6) and 7.4 (1.5–13.4) deaths per 100,000 population in 2004, 2005 and 2006, respectively.

Between the two types of influenza virus, influenza A accounted for the majority of excess deaths in all three cities (data not shown). As the denominator of subtype proportion of Singapore was not comparable with that of the other two cities, we only estimated deaths attributable to influenza A subtypes, A/H3N2 and A/H1N1, in Guangzhou and Hong Kong. Comparison between the two subtypes showed that A/H1N1 accounted for slightly more excess deaths in the all-ages group for all the disease categories under study in both Guangzhou and Hong Kong (Fig. 3). This pattern was also observed for the 65+ age group.

4. Discussion

To our best knowledge, this is the first comparative study between Asian subtropical and tropical cities for influenza disease burden. The surveillance networks for influenza in Guangzhou, Hong Kong and Singapore were established under the WHO Global Influenza Surveillance Network [19], which allowed us to estimate the disease burdens in a standardized procedure and to compare across cities. Here we adopted the Poisson regression models to assess the age-disease specific excess mortality rates associated with influenza. Allowing for flexible adjustment of seasonal factors, this Poisson model has been widely used in many other disease burdens studies and is recommended for the subtropical and tropical regions with unpredictable influenza seasonality in a recently published WHO guideline [20–24]. Our recent validation study using an empirical dataset of laboratory confirmed influenza cases demonstrated that this model was able to provide reliable estimates for disease burden of influenza [25]. Although this approach requires sufficient long-standing year-round surveillance data, such data have become available in many subtropical and tropical regions in recent years. Our study may serve as a good example for the disease burden studies across these regions.

Two previous studies found that the influenza associated mortality rates were nearly equivalent between Hong Kong and Singapore, and Singapore even had a higher excess rate for the older population [14,26]. However, these results need careful interpretation as these two studies differed in terms of statistical models, data aggregation and study periods covered. The present study adopted a standardized modeling approach to show that the overall influenza burden was comparable between the two subtropical cities Guangzhou and Hong Kong, but lower in the tropical Singapore. This geographical disparity was particularly evident in the elders, with the highest excess mortality rates associated with influenza found in Guangzhou, which has a smaller proportion of old population than Hong Kong but is the least developed among the three cities. Cohen et al. also found the mortality impact of seasonal influenza was higher in the elders of South Africa than in those of the United States and this difference did not diminish after adjustment for age structures [27]. Together with our findings, it seems that the socioeconomic factors may associate with the mortality burden of influenza, particularly for the elders. Another

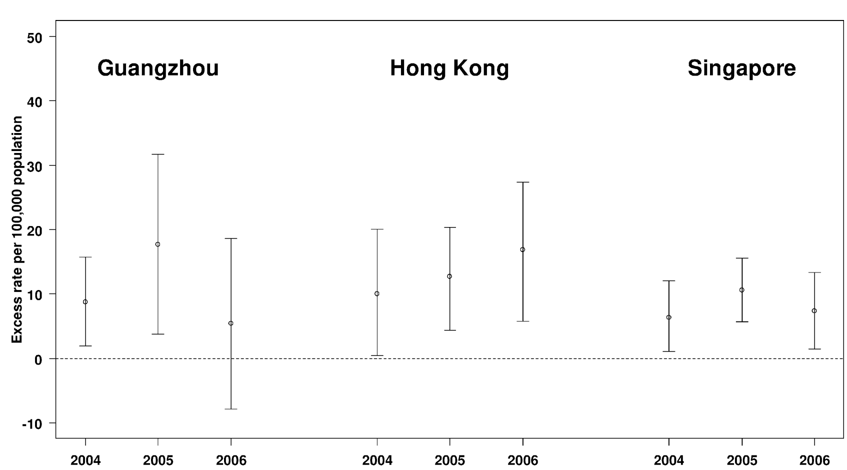

Fig. 2. Annual excess all-cause mortality rates associated with influenza (per 100,000 population) between Guangzhou, Hong Kong and Singapore, all-ages group.

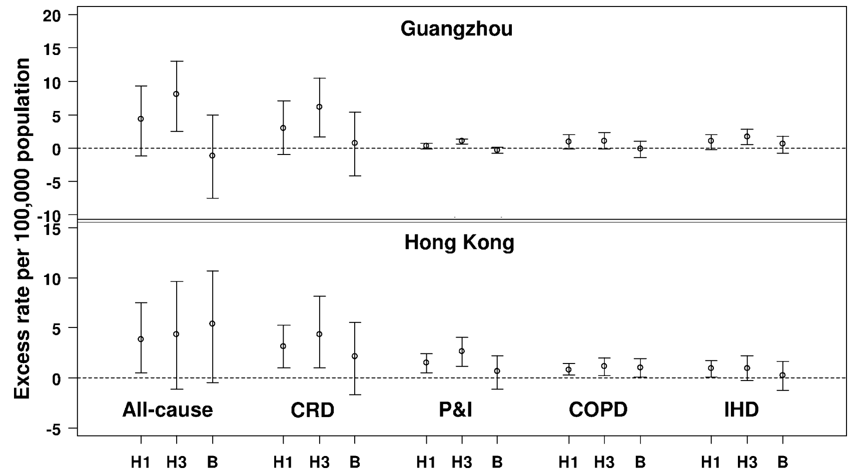

Fig. 3. The excess death rates per 100,000 population associated with A subtypes A/H1N1 (H1), A/H3N2 (H3) and type B influenza in Guangzhou and Hong Kong, all-ages group. *Note*: CRD, cardiorespiratory diseases; P&I, pneumonia and influenza; COPD, chronic obstructive pulmonary diseases; IHD, ischemic heart diseases.

important factor that needs to be considered in interpreting our results is the different underlying susceptibility of population to severe outcomes of influenza infection across three cities. For example, the lower overall impact of influenza in Singapore may not be due to its tropical climate, but partially due to its younger age structure. This heterogeneity of susceptibility could possibly been adjusted for by calculating age standardized excess mortality rates for each city, as the elders tend to be more fragile and have a higher mortality risk attributable to influenza. However, it is difficult to obtain reliable estimates for younger age groups due to small numbers of deaths. A future study with a longer study period shall be able to provide estimates with proper adjustment for age structures.

Singapore had the lowest disease burden from influenza among three cities, although fewer people in Singapore had received influenza vaccination annually. In 2003, 90 doses of influenza vaccine were distributed for every 1000 total population in Singapore [28], but a corresponding vaccination rate 191 doses/1000 total population was reported in Hong Kong [28] and 129 doses/1000 total population in Guangzhou (He JF, unpublished data). During 2004–2007 the annual distribution doses of seasonal influenza vaccines in Singapore were around 50 doses/1000 total population, less than half of those in Hong Kong [29]. However, the effectiveness of influenza vaccines is largely complicated by age structure of population and also by various levels of herd immunity. Moreover, the severity of infections could be aggravated by the environmental factors favoring virus transmission, such as air pollution [30].

It has been widely cited that the disease burden of influenza, in terms of excess P&I mortality and hospitalization, tended to be higher in the A/H3N2 dominant seasons than those with A/H1N1 and B as the dominant virus strains [31–33]. A/H3N2 is believed to transmit more efficiently in human population than A/H1N1 and antigenic drifts occurred more frequently in this subtype [8,34]. Surprisingly, we found that the disease burden attributable to A/H3N2 was slightly lower than the burden attributable to A/H1N1 in Guangzhou and Hong Kong. We noticed that after the outbreak of Severe Acute Respiratory Syndrome (SARS) viruses in 2003, all the three cities observed dramatically increased vaccination rates for influenza [29]. We compared the excess mortality attributable to each subtype during the pre-SARS period of 1998–2002 in Hong Kong, and the results showed that H3N2 were associated with significantly more deaths than H1N1 (data not shown). Although a new strain A/California/7/04-like gradually became prevalent in the late year of 2004, it did not dramatically increase the mortality risks associated with influenza according to our results. Some studies have shown that this novel strain mainly attacked the young adults and the vaccine recommended for the Northern Hemisphere during the 2003–2004 season was still able to provide cross-protection against it [35,36]. As a result, those susceptible people (the elders and chronic patients) might have still been benefited from increased vaccination and exempted from deaths. However, the disease burden of A/H1N1 may have long been neglected, probably owing to its less frequent antigenic drifts compared to A/H3N2 in the human community. Recent experimental studies have found that seasonal H1N1 strains can replicate as efficiently as pandemic H1N1 and avian H5N1 strains in *ex vivo*-infected lung tissues [37,38]. Further experimental studies on virulence of different subtypes circulating in 2004–2006 may help to solve this mystery. More epidemiology studies with longer time series data from different climates are also needed to compare the relative severity of A/H1N1 and A/H3N2 strains.

Our study has potential caveats. Firstly, these three cities vary in the organization of their influenza surveillance networks. Most specimens in Hong Kong were mainly from the inpatients and therefore more severe cases of influenza infections were recruited into the surveillance. The sentinel doctors of Guangzhou were all from the outpatient sectors, and the virology data exhibited greater variation than the other two cities due to limited numbers of samples taken each week. Singapore had the lowest positive rates of influenza specimens, probably due to the fact this city included a mixture of samples from both inpatient and outpatient settings. Nonetheless, we standardized the comparison procedure by using the age-specific excess mortality rate as measurement for influenza effects, which could at least partially exclude the bias introduced by different surveillance systems in these cities. Secondly, although we carefully controlled for the confounding seasonal factors by building core models *a priori*, it is possible that there are still many unmeasured confounding factors. Moreover, to what extent such confounding factors should be adjusted for was subject to personal judgement and over-fitting of core models cannot be completely avoided, as revealed by the negative estimates in some disease categories. Thirdly, all three cities in this study might be more socioeconomically developed than the rest of Asian cities; therefore, extra caution is needed to extrapolate our findings to the other cities/countries. Last but not least, we did not quantify the statistical significance of differences between the city specific estimates, because they were derived from different models. But their overlapping confidence intervals suggest that the differences might not be statistically significant.

In conclusion, by using a standardized modeling approach, we found a geographical disparity in mortality rates attributable to influenza, which could be partially explained by socioeconomic factors and age structure. In future, a multinational study comprising regions across temperate, subtropical and tropical countries like our present study could provide more information about mechanisms and severity of seasonal influenza and thereby help the policy makers to refine their regional specific control measures against influenza.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.vaccine.2011.09.071.

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