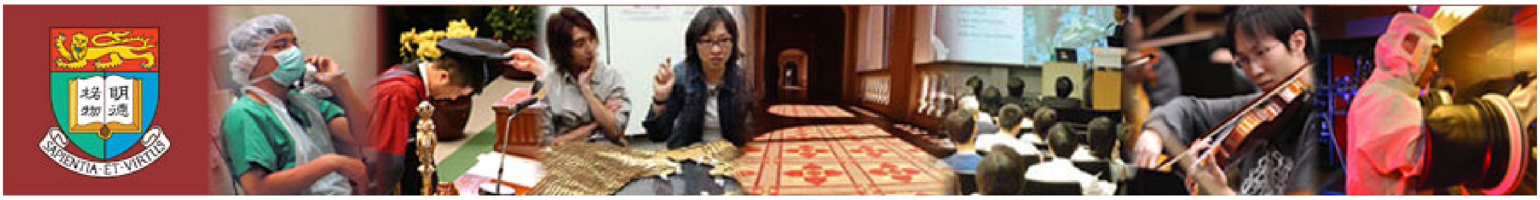

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Citation	Hong Kong Medical Journal = Xianggang Yi Xue Za Zhi / Hong Kong Academy Of Medicine, 2012, v. 18 Suppl 2, p. 8-11
Issued Date	2012
URL	http://hdl.handle.net/10722/145908
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Effect of influenza on cardiorespiratory and all-cause mortality in Hong Kong, Singapore and Guangzhou

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Key Messages

1. Using a common modelling approach, mortality attributable to influenza was higher in the two subtropical cities Guangzhou and Hong Kong than in the tropical city Singapore.
2. The virus activity appeared more synchronised in subtropical cities, whereas seasonality of influenza tended to be less marked in the tropical city.
3. High temperature was associated with increased mortality after influenza infection in Hong Kong, whereas relative humidity was an effect modifier for influenza in Guangzhou. No effect modification was found for Singapore.
4. Seasonal and environmental factors probably play a more important role than socioeconomic factors in regulating seasonality and disease burden of influenza. Further studies are needed in identifying the mechanism behind the regulatory role of environmental factors.

Hong Kong Med J 2012;18(Suppl 2):S8-11

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Introduction

Influenza has been associated with considerable mortality in temperate regions. The disease burden of influenza in subtropical and tropical regions are less known. Influenza viruses may exhibit various levels of virulence each year as a result of frequent antigenic drifts. There is disparity between geographical areas even in the same influenza season. Socioeconomic factors and circulating virus strains could play a role in determining the severity of influenza epidemics.[1] Several large-scale phylogenetic studies have postulated that novel influenza viruses first emerge in the East and Southeast Asia. It is therefore important to understand the seasonality and disease burden of influenza in these regions.

The same modelling methods were applied to three metropolitan cities: Guangzhou, Hong Kong, and Singapore. All have standardised influenza surveillance networks. Guangzhou and Hong Kong are subtropical cities, whereas Singapore is a tropical city. The similarity and differences between these cities in terms of socioeconomic status and environmental factors enable exploration of factors in terms of the disease burden of influenza.

Methods

This study was conducted from 1 July 2006 to 31 December 2008. All three cities have similarly designed surveillance networks for influenza, in which specimens are collected from both outpatients and inpatients throughout the year. Weekly data of virology surveillance, meteorology, and mortality from each city were obtained and aggregated. To reduce the bias introduced by unequal numbers of specimens taken each week, proportions of specimens positive for influenza were used as measures for influenza virus activity. Five causes of death were associated with influenza: cardiorespiratory diseases (CRD), pneumonia and influenza (P&I), chronic obstructive pulmonary diseases (COPD), ischaemic heart diseases (IHD), and all-cause deaths.

Poisson regression models were used to assess the percentage of excess mortality associated with increased influenza activity in the population.[2] This modelling method is well suited to the subtropics and tropics where influenza can be active throughout the year and usually without a clear pattern of epidemics. Briefly, weekly mortality, with the weekly proportions of specimens positive for each influenza type/subtype (named as virus activity) was used. Yearly dummy variables and the product terms between yearly dummies and virus activity were used as independent variables. Several confounders, including long-term trends and seasonal variations in mortality, weekly temperature and humidity, were simultaneously added into the models. The effects of influenza were estimated by the excess rates of mortality, which was calculated as the difference between the number of observed deaths and the estimated number under the assumption of no virus activity, and then divided by the total number of observed deaths.

To explore whether the regional heterogeneity of influenza-associated mortality was due to effect modification of temperature, the whole study period was divided into high, medium, and low temperature periods, with the first and third quartiles of weekly average temperatures as the cut-off points. Interaction models for all-cause, CRD and P&I mortality of each city were built, in which the product terms of virus activity and dummy variables for three temperature periods were added together with previously described confounders. The significance of effect modification by temperature was evaluated by the likelihood ratio tests between models with and without interaction terms. Based on the interaction models, the percentages of excess deaths among total observed deaths associated with each measure of observed virus activity for the high, medium, and low temperature periods were computed. Similar analyses were repeated for weekly average humidity, which was also stratified into the high, medium, and low humidity periods, with the first and third quartiles as cut-off points.

Results

Among the three cities, Singapore is hottest and most humid and its population is the youngest. The overall mortality rate of Guangzhou was highest. The average proportions of positive influenza isolates in all specimens, known as influenza virus activity, were lowest in Singapore. The dominant virus types/subtypes were consistent among three cities: A/H3N2 was dominant in year 2004 and 2005, whereas A/H1N1 and B were more prevalent in 2006.

During 2004-2006 for all-age groups in all three cities, influenza was significantly associated with all-cause mortality as well as mortality with underlying causes of CRD, P&I, COPD, and IHD ($P<0.05$), with the exceptions of P&I in Guangzhou, COPD in Singapore, and IHD in Hong Kong (Table 1). Among the three cities, Hong Kong had the highest excess mortality with underlying causes of P&I, COPD, and all causes, whereas influenza in Guangzhou was associated with most deaths caused by CRD and IHD. For the elderly aged ≥65 years, Guangzhou had the highest excess mortality for both all-cause and CRD mortality, and Singapore had the lowest rate. The year 2005 entailed the greatest disease burden of influenza for all three

Table 1. The annual excess mortality per 100 000 population associated with influenza in all-age groups

Cause of death	Annual excess mortality (95% CI)		
	Guangzhou	Hong Kong	Singapore
All causes			
2004	10.7 (-3.2, 25.2)	0.0 (-12.7, 12.7)	17.0 (7.2, 26.8)
2005	21.5 (-2.5, 43.7)	28.1 (17.1, 39.2)	5.7 (-3.4, 14.8)
2006	4.8 (-9.6, 18.0)	13.2 (-2.1, 27.4)	3.3 (-4.8, 11.1)
Overall	12.4 (1.2, 23.0)	13.9 (6.4, 20.9)	8.7 (3.0, 13.9)
Cardiorespiratory diseases			
2004	9.5 (-1.4, 20.5	2.1 (-5.9, 10.1)	7.5 (0.2, 14.8)
2005	18.8 (0.0, 36.3)	18.6 (11.6, 25.3)	5.6 (-1.2, 12.0)
2006	5.3 (-5.7, 15.4)	6.3 (-3.7, 15.5)	3.6 (-2.1, 9.3)
Overall	11.2 (2.4, 19.6)	9.1 (4.3, 13.6)	5.6 (1.6, 9.4)
Pneumonia and influenza			
2004	0.3 (-0.8, 1.4)	1.2 (-2.3, 4.4)	3.1 (-0.7, 6.7)
2005	1.4 (-0.5, 3.1)	8.8 (6.0, 11.6)	3.8 (0.3, 7.2)
2006	0.2 (-1.0, 1.3)	4.2 (0.0, 8.0)	1.8 (-1.3, 4.9)
Overall	0.6 (-0.3, 1.5)	4.7 (2.7, 6.7)	2.9 (0.8, 4.9)
Chronic obstructive pulmonary diseases			
2004	0.9 (-2.1, 3.7)	0.5 (-1.8, 2.7)	-1.3 (-3.6, 0.7)
2005	4.7 (0.1, 8.9)	5.4 (3.7, 7.0)	0.2 (-1.7, 1.9)
2006	1.2 (-1.5, 3.6)	1.5 (-0.9, 3.8)	-0.2 (-2.2, 1.1)
Overall	2.3 (0.0, 4.4)	2.5 (1.2, 3.7)	-0.5 (-1.7, 0.5)
Ischaemic heart diseases			
2004	2.2 (-0.9, 5.1)	2.1 (-1.1, 5.2)	2.9 (-1.5, 7.0)
2005	6.3 (1.3, 10.8)	2.3 (-0.2, 4.7)	3.9 (-0.2, 7.6)
2006	1.8 (-1.3, 4.6)	0.7 (-3.2, 4.3)	1.0 (-2.5, 4.3)
Overall	3.4 (1.0, 5.6)	1.7 (-0.2, 3.5)	2.6 (0.2, 4.7)

Table 2. The annual excess mortality per 100 000 population associated with influenza in the ≥65-year-old age group

Cause of death	Annual excess mortality (95% CI)		
	Guangzhou	Hong Kong	Singapore
All causes			
2004	108.9 (-14.8, 237.5)	10.3 (-86.0, 110.0)	202.3 (79.5, 325.1)
2005	212.5 (-4.9, 415.2)	211.4 (129.0, 293.8)	74.0 (-35.2, 183.3)
2006	60.1 (-69.4, 180.4)	73.7 (-40.2, 184.4)	13.5 (-81.0, 111.4)
Overall	130.6 (24.2, 227.4)	100.3 (44.9, 155.6)	94.5 (28.0, 161.0)
Cardiorespiratory diseases			
2004	100.3 (-3.2, 207.1)	27.9 (-36.6, 92.4)	91.4 (-4.4, 189.4)
2005	185.7 (6.3, 349.5)	148.1 (95.1, 201.1)	74.1 (-14.8, 156.8)
2006	58.8 (-44.8, 154.0)	46.9 (-28.5, 117.2)	15.9 (-57.6, 87.3)
Overall	116.3 (30.6, 195.9)	75.2 (38.5, 111.9)	58.5 (8.4, 110.8)

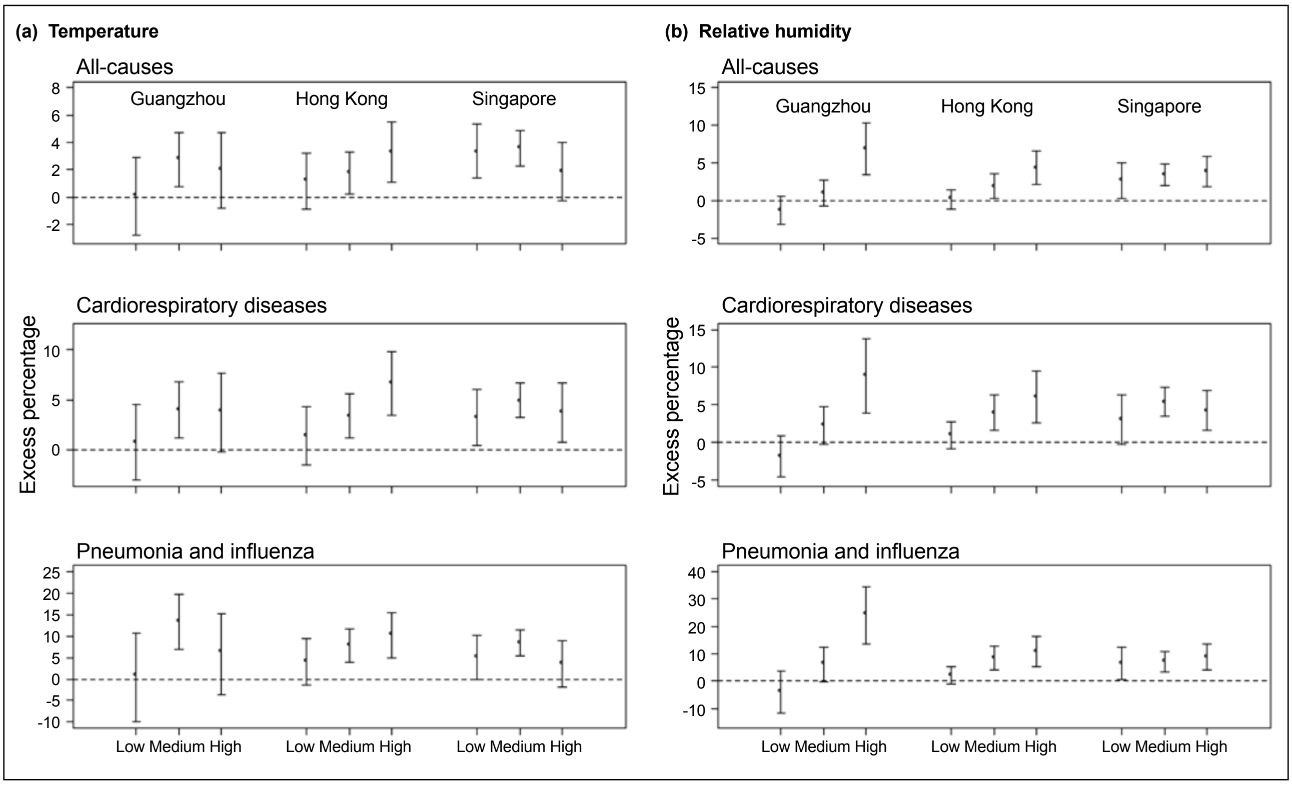

Fig. Excess percentages associated with influenza during the low, medium, and high periods stratified by weekly average (a) temperature and (b) relative humidity, for Guangzhou, Hong Kong, and Singapore

cities. The year entailed the lowest disease burden was 2006 for Guangzhou and Singapore, and 2004 for Hong Kong (Table 2).

Likelihood ratio tests between the interaction and main effect models showed that the difference between temperature periods was likely due to chance (P>0.05), except the CRD mortality in Hong Kong (P=0.006, Fig). The highest excess percentages were in medium temperature periods in both Guangzhou and Singapore, but were in high temperature periods in Hong Kong. The interaction of relative humidity and influenza was significant in the all-cause mortality in Hong Kong (P=0.006) and in all-cause and CRD mortality (P<0.001) in Guangzhou. Influenza accounted for more deaths during the high humidity periods in Guangzhou and Hong Kong, whereas influenza effects were similar across humidity strata in Singapore.

Discussion

This study systematically compared the influenza-associated disease burdens in three metropolitan cities in Asia. The surveillance networks for influenza in Guangzhou, Hong Kong, and Singapore were constructed under the World Health Organization Global Influenza Surveillance Network, which estimate disease burdens using a standardised procedure for comparison. Similar Poisson regression models were adopted to assess age- and disease-specific excess mortality associated with influenza, allowing for flexible adjustment of seasonal confounding factors. This model has been widely used in other disease burden studies and recommended for subtropical and tropical regions with unpredictable influenza seasonality.[3] However, this approach requires long-standing year-round surveillance that has not yet been established in many subtropical and tropical regions. Nevertheless, our study provides a good example for the future disease burden studies and for the development of more surveillance centres.

Influenza-associated mortality rates were comparable in Hong Kong and Singapore. Singapore even had a higher excess mortality for the elderly[2,4] However, slightly different models were used and different study periods were covered. In this study, the estimates of tropical Singapore remained lower than those of the other two subtropical cities for all the disease categories under study. Given the similar socioeconomic development levels in Hong Kong and Singapore, environmental and geographical factors may affect the severity of influenza to a greater extent than socioeconomic factors. The close geographical location of Guangzhou and Hong Kong may result in similar circulating influenza strains as well as pre-existing immunity in the population, but this hypothesis is not supported by our subtype-specific estimates, as a great heterogeneity could still be observed between the two cities. In future, a large-scale phylogenetic analysis for the circulating strains in these cities may provide information about this hypothesis.

Cold temperature and dry air facilitate the transmission of influenza virus and prolong their survival in the air.[5] Most studies were conducted at temperatures <30°C and relative humidity <80%. In our study, there was a significant linear trend for influenza-associated risks as temperature increased in Hong Kong, particularly for CRD deaths. This indicates that cold temperature may not increase the chances of deaths subsequent to influenza infections, although the possibility of increased transmission under low temperature could not be ruled out by our study. Such an effect modification by temperature may be due to widespread use of air conditioners in Hong Kong. The great difference between indoor and outdoor temperature could weaken the host immunity response against infection and the closed circulation of indoor air could facilitate virus transmission. Apparently in Guangzhou, humidity rather than temperature is the modifier for the effects of influenza, which exhibited a linear trend across three humidity strata for all-cause, CRD and P&I deaths. This could be explained by the higher annual variation of humidity in Guangzhou compared to the other two cities. Similarly, the absence of modification by temperature or humidity on influenza effects in Singapore could be due to its low variation of temperature and humidity throughout the year.

Our findings on regional heterogeneity of influenza disease burden and potential modification of environmental factors on influenza effects could shed more light on mechanisms of influenza seasonality and suggests a need to refine surveillance and control strategies against influenza specific to each region. In future, a multinational study involving more temperate and tropical, as well as developed and developing countries could provide more information about mechanisms and effect modifiers for the severity of influenza epidemics or pandemics.

Acknowledgements

This study was supported by the Research Fund for the Control of Infectious Diseases, Food and Health Bureau, Hong Kong SAR Government (#04050212) and the Area of Excellence Scheme of the University Grants Committee of the Hong Kong Special Administrative Region (AoE/M-12/06).

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