# Different Responses of Influenza Epidemic to Weather Factors among Shanghai, Hong Kong and British Columbia

Xi-Ling Wang[1,©], Lin Yang[2,©], Dai-Hai He[3], Alice PY Chiu[3], Kwok-Hung Chan[4], King-Pan Chan[5], Qing Guo[6], Maigeng Zhou[7], Chit-Ming Wong[5], Wenbiao Hu[1,8,*]

1. Department of Biostatistics, School of Public Health and Key Laboratory of Public Health Safety, Fudan University, Shanghai, People's Republic of China; 2. School of Nursing, The Hong Kong Polytechnic University, Hong Kong SAR, People's Republic of China; 3. Department of Applied Mathematics, The Hong Kong Polytechnic University, Hong Kong SAR, People's Republic of China; 4. Department of Microbiology, The University of Hong Kong, Hong Kong SAR, People's Republic of China; 5. School of Public Health, The University of Hong Kong, Hong Kong SAR, People's Republic of China; 6. Center for Public Health Surveillance and Information Service, Chinese Center for Disease Control and Prevention, Beijing, China; 7. National Center for Chronic and Noncommunicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, People's Republic of China; 8. School of Public Health and Social Work, Queensland University of Technology, Brisbane, Australia.

©These authors contributed equally to the work.

*Correspondence: Dr. Wenbiao Hu, School of Public Health and Social Work, Queensland University of Technology, Kelvin Grove, Brisbane, Queensland 4059, Australia. Email: w2.hu@qut.edu.au; Tel: +61 7 3138 5724.

**Running head:** Associations of influenza and weather factors

**Abstract**

**Background** Understanding of weather factors that drive influenza circulation is useful to recognize how influenza dynamics will be affected at regional levels by global climate change. As influenza peaks coincide with both high and low temperature in subtropical cities, weather factors may nonlinearly or interactively affect influenza activity.

**Objectives** This study aims to compare the similarities and differences in the responses of influenza epidemic to weather factors and assess the nonlinear relationships and their interactive effects of weather factors with influenza activity in two subtropical regions of Southern China (Shanghai and Hong Kong) and one temperate province of Canada (British Columbia).

**Methods** Weekly data on influenza activity and weather factors (i.e. mean temperature and relative humidity (RH)) were obtained from pertinent government departments for the three regions. Absolute humidity (AH) was measured by actual vapor pressure (VP), which could be converted from temperature and RH. Generalized additive Poisson models were used to assess the exposure response relationship between weather factors and influenza virus activity. Interactions of weather factors were further assessed by bivariate response model and stratification analyses.

**Results** The exposure response curves of temperature and VP, but not RH, were consistent among three regions/cities. Bivariate response model revealed a significant interactive effect between temperature (or VP) and RH ($P<0.05$). Influenza peaked at low temperature or high temperature with high RH.

**Conclusion** Temperature and VP is useful in constructing a universal model to explain the seasonal outbreaks of influenza epidemics. However, further research is needed to

review the association between weather factors and influenza activity in a wider context of social and environmental conditions.

**Keywords:** Influenza; Seasonality; Meteorology; Interaction.

## Introduction

Influenza used to be considered as a "cold" disease as it usually returns every cold winter in temperate countries. However, accumulating studies have shown that influenza can be active throughout the year in the warm tropics and subtropics where the disease burden of influenza was comparable to that in the temperate (Chow et al. 2006; Viboud et al. 2006; Wong et al. 2004; Wong et al. 2006; Yang et al. 2012). The investigation of underlying drivers for various seasonal patterns of influenza outbreaks has long been a research topic. Understanding of the weather factors that drive influenza circulation may be especially useful to recognize how influenza dynamics will be affected at regional levels by global climate change.

Previous studies have proposed several seasonal factors, among which weather factors (particularly temperature and humidity) have been most thoroughly explored by laboratory and epidemiological studies. Absolute humidity (AH) measures the actual mass of water vapor in a particular volume of air and is highly correlated with temperature, whereas relative humidity (RH) is the ratio of the partial pressure of water vapor to the saturated pressure of water vapor at a given temperature. Previous laboratory studies reported that low RH and cold temperature increased the survival of aerosolized influenza virus (Harper 1961; Hemmes et al. 1960) as well as virus transmission in animal models (Lowen et al. 2007; Schulman and Kilbourne 1962). Recent laboratory and simulation studies have proposed AH as an important seasonal factor that drives influenza seasonality (Shaman and Kohn 2009; Shaman et al. 2010; Shamanna and Bosch 2011). However, most of the findings so far could well explain the single winter peak of

4

influenza in temperate climates, but could barely be applied to the subtropics and tropics where influenza can still be active under a hot and humid weather. Moreover, given the fact that the influenza peaks coincide with both high and low temperature in subtropical cities (Yang et al. 2008; Yu et al. 2013), it is unlikely that these weather factors independently affect the influenza seasonality in a linear manner. Nonlinear relationships between weather factors and influenza activity, as well as interactive effects between weather factors, shall be further assessed by more sophisticated statistical models.

Shanghai and Hong Kong are developed subtropical cities located in eastern and southern China, respectively. Although seasonal pattern of influenza are not well-defined for both cities, Shanghai is likely to be dominated by a semi-annual influenza periodicity (Yu et al. 2013) while Hong Kong experiences one or two peaks of influenza irregularly in one epidemic year (Yang et al. 2008). Whether warmer and more humid climate in Hong Kong than that in Shanghai contributes to different influenza seasonality of these two subtropical cities remains unclear. We also include British Columbia, a province located on the west coast of Canada, as a comparison region. British Columbia has a typical temperate climate with a single influenza peak in winter. Therefore, this study aims to assess the associations of weather factors with influenza seasonality and compare the similarities and differences in the responses of influenza epidemic to weather factors in two subtropical cities of Southern China (Shanghai and Hong Kong) and one temperate region of Canada (British Columbia).

**Methods**

*Data*

Weekly notified numbers of influenza for Shanghai from 2007–2011 were obtained from Chinese Center for Disease Control and Prevention. Influenza surveillance data for Hong Kong were obtained from The Microbiology Laboratory of Queen Mary Hospital. Queen Mary Hospital is the largest public hospital located in Hong Kong Island. Nasopharyngeal aspirates or swabs were collected from the patients with influenza-like symptoms and tested for influenza infection by immunofluorescence tests (Chan et al. 2002). Influenza virology data of this single laboratory have been demonstrated representative of the virus activity in the entirety of Hong Kong (Wong et al. 2006). Weekly notified numbers of influenza for British Columbia were downloaded from the open-access website of British Columbia Center for Disease Control (http://www.bccdc.ca/dis-cond/DiseaseStatsReports/influSurveillanceReports.htm).

Weather data of weekly mean temperature, RH and total amount of rainfall for Shanghai and Hong Kong were derived from Shanghai Weather Bureau and Hong Kong Observatory, respectively. Weather data for Vancouver were downloaded from an open-access website of Environment Canada (http://ec.gc.ca/meteo-weather/default.asp?lang=En&n=FDF98F96-1). We used the Vancouver climate date to represent the climate in British Columbia as more than 50% of British Columbia population was in Greater Vancouver. Vapor pressure (VP) was calculated from temperature and RH, and was regarded as a measurement for AH (Basu et al. 2008). During the study period, Hong Kong had the highest mean temperature (23.35℃) among

the three cities, followed by Shanghai (17.50℃) and British Columbia (10.23℃) (Table 1). The order of VP was in accordance with the order of temperature, which was not surprising considering VP and temperature were highly correlated in three regions. RH was generally comparable among the three regions ranging from 69.20% to 77.36% (Table 1).

The total resident populations by the mid of 2011 in Shanghai, Hong Kong and British Columbia were 14.2, 7.1 and 4.5 million, respectively. The population age structure were in general comparable in the three cities. In Shanghai, the proportions of population aged 0–17, 18–64 and 65 or older were 10%, 73% and 17%, respectively (Shanghai Statistical Bureau 2012). The proportions of population aged 0-14, 15-64 and 65 or older in Hong Kong were 12%, 75% and 13% (Census and Statistics Department 2012) while the numbers for British Columbia were 15%, 69% and 16% (Statistics Canada 2012).

*Independent exposure-response model*
For each city/region, the independent exposure-response relationships between environmental factors and virus activity were assessed by Poisson generalized additive models (GAM) with a logarithm link. This model used the nonparametric smoothing functions to explore the linear and nonlinear association between explanatory and outcome variables. Because VP and temperature were highly correlated (Spearman correlation ranges from 0.95 to 0.98 in the three regions), separate models were built by including either VP or RH to avoid the collinearity problem. A typical form of model with temperature as covariate is as follows:

$$E(flu_t) = \alpha + s(t) + s(temp_t) + s(RH_t) + s(rain_t) + offset(\log(population_t)) + pandemic_t \quad (I)$$

where E(*flu_t*) denotes the expected notified number of influenza at week *t*; here

t=1,2,..,260. *s(t)*, *s(temp_t)*, *s(RH_t)*, *s(rain_t)* and *s(VP_t)* denote the thin plate smoothing

functions of time trend, temperature, RH, rainfall and VP, respectively. Here the

smoothing function of time trend was used as adjustment for confounding of unmeasured

seasonal factors. An offset of total resident population by year (*offset*

*(log(population_t)*) )was added to adjust for temporal variation of population. *pandemic_t*

was a dummy variable to adjust for the 2009 H1N1 pandemic period from the week of 11

June 2009 to the week of 10 August 2010. The combination of degrees of freedom (*df*)

for these smoothing functions was chosen to minimize the Generalized Cross Validation

(GCV) scores of the model (Hastie and Tibshirani 1990). A model was also developed

for VP by replacing *s(temp_t)* with *s(VP_t)* in Model I, in order to assess the effect of VP.


*Bivariate surface model*

Given the previous findings that temperature, VP and RH were consistently found

associated with influenza seasonality, we only assessed the interaction between

temperature and RH, or between VP and RH in the subsequent analysis. We adopted a

bivariate surface model under the same assumption of Model I (Hastie and Tibshirani

1990). By adding a bivariate smoothing function, this model avoids artificial definition of

exposure categories, and allows the assessment of joint effects of these two factors on

virus activity without a strong assumption of linearity (Daniels et al. 2000; Greenland

1993). This modeling approach allows more flexibility in assessing the interaction of

environmental factors. A typical form of bivariate surface model is as follows:

$$E(flu_t) = \alpha + s(t) + s(temp_t, RH_t) + s(rain_t) + offset(\log(population_t)) + pandemic_t \quad (II)$$

where $s(temp_t, RH_t)$ represents a bivariate spline smoothing function of weekly average

temperature and RH. The *df* of smoothing functions were fixed to 5 for temperature, RH

and VP. The *df* for time trend and rainfall were the same as model I. We then drew the

bivariate exposure response surface plots derived from the above model to examine the

interaction between temperature and RH. A model was also developed for VP by

replacing $s(temp_t, RH_t)$ with $s(vp_t, RH_t)$ in Model II, in order to assess the interactive

effect of VP and RH.


*Stratification model*

Because the bivariate surface model (model II) was unable to provide the effect estimates

and their statistical significance, we adopted an alternative method to assess the

interaction between temperature and RH, as well as between VP and RH. Stratification

models were developed by adding the interaction terms of weekly average temperature

(or VP) and three dummy variables for the periods with high, medium and low RH. The

first and third quartiles of city/region-specific RH were defined as cutoff points for these

periods. A typical model for interaction of temperature and RH is as follows:

$$E(flu_t) = \alpha + s(t) + \beta_1 temp_t + \beta_2 temp_t * RH.m_t + \beta_3 temp_t * RH.h_t$$
$$+ \beta_4 RH.m_t + \beta_5 RH.h_t + \beta_6 RH_t + \beta_7 rain_t + offset(\log(population_t)) + pandemic_t \quad (III)$$

where $RH.m_t$ and $RH.h_t$ denote the dummy variables for the periods with medium and

high RH levels. The statistical significance of the interaction terms between temperature

and RH was assessed by the likelihood ratio test of full model (model III) and a partial

model without the interaction term (model I). We did not add the linear interaction term

9

$temp_t*RH_t$ (or $vp_t*RH_t$ ) into the model as the results from model II suggested a nonlinear

interaction between temperature and RH (or VP and RH) on influenza seasonality. The

above analysis was repeated by replacing temperature with VP, to investigate the

interaction effect of VP with RH.

*Sensitivity analysis*

The lag effects of weather factors were also assessed through adding into the models the

weather variables up to 3 weeks before the present week. Sensitivity analyses by

excluding the pandemic period from 11 June 2009 to 10 August 2010 were conducted to

examine the robustness of our main results. The statistical significance in this study was

defined as $p<0.05$. All the analyses were performed using the mgcv package of R

software (version 3.2.0.) (R Development Core Team 2015).

**Results**

Influenza was active year-round in subtropical cities of Shanghai and Hong Kong (Figure

1). Influenza usually occurred in winter and summer/autumn in Shanghai (Figure 1). The

seasonality of influenza in Hong Kong showed a semi-annual pattern during the study

period, with two peaks observed in winter and summer within one year (Figure 1).

Weekly numbers of influenza in British Columbia had a clear winter peak annually,

which was very different from those in Shanghai and Hong Kong (Figure 1). The first

wave of pandemic influenza was found in all three cities/regions during May-December

2009, but only Shanghai was attacked by the second wave in the winter of year 2010.

*Independent exposure-response model*

The exposure response curves for the independent effects of temperature, RH and VP are shown in Figure 2. In general, the patterns of temperature and VP on influenza seasonality were consistent among the three areas. Influenza activity increased as the temperature increased from the lowest to around 5°C, then decreased as the temperature continued increasing up to around 22°C, and finally increased again as the temperature increased to the highest (Figure 2). The exposure response curves of VP had a U-shape, with trough at around 20hPA for both Shanghai and Hong Kong (Figure 2). The maximum weekly mean VP was 18.47hPA in British Columbia, and influenza activity decreased steadily as the vapor pressure increased (Figure 2). The exposure response curves for RH showed heterogeneous patterns among the three cities. For Shanghai, influenza activity tended to increase when the relative humidity increased from the lowest to around 60%, then remain unchanged when RH ranged from 60% to 80%, finally increased again when RH exceeded 80% (Figure 2). For Hong Kong, influenza activity showed an upward trend as RH increased. For British Columbia, the pattern of RH on influenza seasonality was opposite to that of Shanghai with a downward trend, unchanged and again a downward trend when RH increased.

*Bivariate surface model*

Figure 3 shows the exposure response surface plots for the joint effects of temperature and RH, and VP and RH on influenza virus activity in Shanghai, Hong Kong and British Columbia. In Shanghai, there were apparent changes in curves of temperature across the levels of RH and the patterns were distinct from their independent exposure response

curves (Figure 3A). The temperature effect decreased steadily at low RH, but it first decreased and later turned upward at high RH in Shanghai (Figure 3A). The peaks of influenza infection risk were observed at low temperature or at high temperature with high RH (Figure 3A). The exposure response surface plot for Hong Kong showed an upward trend for influenza risk when temperature increased across different levels of RH (Figure 3C). The exposure response surface plot for British Columbia showed an exact opposite trend compared with Hong Kong (Figure 3E). However, it is of note that these two plots may not be directly comparable due to the different ranges of temperature and RH in Hong Kong and British Columbia. In general, the exposure response surface plots demonstrated a U shape relation between VP and influenza infection risk across RH levels, although the VP was too low in British Columbia to observe the upward turning point (Figures 3B, 3D & 3F).

*Stratification model*

The stratification analysis revealed that temperature and VP were significantly associated with influenza virus activity, with negative estimates consistently found across the RH levels for Shanghai and British Columbia, but positive estimates for Hong Kong (Table 2). The percentage change of notified influenza numbers associated with per unit increase in temperature or VP was highest at low relative humidity for Shanghai, and at middle relative humidity for Hong Kong and British Columbia (Table 2). All the percentage changes were much higher in temperate region of British Columbia than subtropical cities of Shanghai and Hong Kong (Table 2).

*Sensitivity analysis*

Similar results were found in the models with the effects of weather factors lagged up to three weeks (lag 1-3 weeks). The sensitivity analysis by excluding the pandemic period also showed similar results, which demonstrated the robustness of results in the main study.

**Discussion**

Although some attempts have been made to explore the linear relationship between weather factors and influenza seasonality (Loh et al. 2011; Tang et al. 2010), to our best knowledge, the study is the first comprehensive one to explore their linear and nonlinear relationship, together with the joint effects of these weather factors in both temperate and subtropical regions. We chose Shanghai, Hong Kong and British Columbia as our study sites, because all the three cities/regions had high quality influenza laboratory surveillance data facilitating the modeling of influenza seasonality. The three cities/regions distributed in different climate regions, which made feasible for the investigation of associations of influenza seasonality with weather factors. However, the three sites can only represent a small part of cities all over the world, and we will include more cities under different climates and social status in the future if data are available.

The independent exposure-response curves of temperature and VP, but not RH, showed a regional homogeneity among Shanghai, Hong Kong and British Columbia as long as we scaled the ranges. Maximal influenza activity was reached under the scenarios of low temperature or high temperature and high RH. Most previous hypotheses, if not all, for

13

the seasonality of influenza incidence were developed in the temperate regions and none of them could explain the influenza peaks during warm seasons in subtropical/tropical regions (Lipsitch and Viboud 2009). Our results suggested a possibility to find a universal model applicable to different climates. The future hypotheses for seasonal variation of influenza should take into account of interaction between different seasonal factors, and further population and experimental studies under different weather conditions are warranted to reveal the mystery of influenza seasonality.

Our exposure response curves of temperature and VP were partly consistent with some previous laboratory findings on virus transmission. Lowen and colleagues showed that transmission rates of influenza virus A/H3N2 between the hosts decreased when room temperature increased from 5°C to 30°C (Lowen et al. 2007). Tamerius et al. estimated a U-shaped relationship between the likelihood of an influenza peak and monthly specific humidity (Tamerius et al. 2013). Shaman and Kohn demonstrated a negative linear relationship between transmission rates of viruses and VP within the range of 5hPA to 20hPA, based on the same laboratory data (Shaman and Kohn 2009). Some studies also explored the survival and transmission rate of aerosolized viruses at different RH levels, but the results were inconsistent between different studies (Tellier 2009). The experiments in guinea pigs showed that transmission was most efficient at RH 20% and 35% at a fixed temperature of 20°C. However, these extremely dry conditions were seldom reached in all of three regions in our study. The same group also found that transmission was more efficient at an RH of 65% than those at 50% and 80% when ambient temperature was 20°C. Although these results seem contrast to our exposure

14

curves, the role of weather factors in regulating virus transmission could be complicated due to the uncertain transmission routes (Brankston et al. 2007). Influenza viruses are believed to spread by droplets, aerosols and direct contact, but it is unclear how the viruses switch between these routes. The experiments using guinea pigs showed that airborne transmission was completely blocked at 30°C and proposed that contact transmission was the major route under a high temperature (Lowen and Palese 2009; Lowen et al. 2008). However, it is of note that ups and downs of virus activity in the community are not only affected by its transmission and survival efficiency in the environment, but also by host susceptibility, though the latter is less likely directly linked to weather factors. In general, the patterns of VP from the surface plots are in line with their independent exposure response curves, with U-shaped for Shanghai and Hong Kong and steady downward trend for British Columbia. But significant VP-RH and temperature-RH interactions found in our study suggested that VP alone is unlikely the sole weather factor that contributes to seasonal variation of influenza virus activity.

The difference between influenza type A and B viruses has been widely reported. Influenza A viruses tended to have more frequent antigenic change and transmit more efficiently than influenza B viruses (Bouvier and Palese 2008), causing a heavier disease burden on mortality and morbidity (Reichert et al. 2004; Simonsen et al. 2000). However, the previous findings on association of weather factors and these two types of viruses were neither consistent nor conclusive. A German study found an inverse association of temperature with pediatric hospitalization of influenza A, but not with influenza B hospitalization (du Prel et al. 2009). Another Hong Kong study found the isolation

proportion of influenza B decreased as temperature increased, whereas influenza A was only associated with RH in a linear manner (Tang et al. 2010). But unfortunately, in the study influenza type/subtype data were unavailable, thus unable to elucidate the association between weather factors and influenza type/subtypes.

There are several limitations in this study. First, the quality of influenza surveillance data might be heterogeneous among the three regions because there is potential heterogeneity in influenza surveillance procedures and patient health seeking behavior. Second, this is an ecological study so that ecological fallacy may exist. Third, there are some other seasonal factors that could also play a role in regulation of influenza seasonality remained unadjusted for in our study. Several hypotheses have been proposed that except weather factors, influenza seasonality is driven by other factors including antigenicity change of virus strains, host susceptibility and behavior changes (Dowell et al. 2001; Lofgren et al. 2007; Murry et al. 2004). However, there are no data available to quantify the seasonal variation of antigenic change and behavior change of human hosts. The wide use of air conditioners in summer may decrease the indoor temperature that people are truly experiencing and in winter increase the temperature. On the other hand, indoor heating may also decrease RH levels in winter. Unfortunately, there is no data to show the prevalence of air conditioner usage in the regions under study; therefore it is unlikely for us to adjust for this factor in our model. Nevertheless, we used a smoothing function of time and seasonal trend as an adjustment for unmeasured confounders although it may not be adequate. In future, a model with more comprehensive data shall be considered to disentangle the mystery of influenza seasonality.

**Conclusions**

Although seasonal influenza transmission showed a great regional heterogeneity, our results demonstrated that the effects of temperature and VP were in general similar between the temperate and subtropical regions. These findings suggest the possibility to find a universal model to explain the seasonal outbreaks of influenza epidemics and develop an early warning system based on weather factors for influenza, in which the interaction of different weather factors might also be considered. More data from other regions with a variety of climate conditions are needed to confirm the results of this study.

Table 1. Descriptive statistics of weekly mean temperature, relative humidity, vapor pressure, total rainfall and weekly influenza virus activity from 2007–2011 in Shanghai, Hong Kong and British Columbia.

| Variables | Mean | SD | Percentile | | | | |
|---|---|---|---|---|---|---|---|
| | | | min | 25 | 50 | 75 | max |
| **Shanghai** | | | | | | | |
| Temperature(°C) | 17.50 | 8.80 | 0.60 | 9.50 | 18.20 | 25.40 | 32.30 |
| Relative humidity (%) | 69.20 | 8.20 | 40.90 | 64.10 | 69.60 | 75.50 | 87.90 |
| Vapor pressure (hPA) | 15.90 | 8.80 | 3.30 | 8.50 | 14.00 | 23.90 | 32.50 |
| Rainfall (mm) | 31.90 | 43.80 | 0.00 | 2.10 | 14.40 | 46.00 | 280.90 |
| Weekly influenza isolate numbers | 22.30 | 34.00 | 0.00 | 3.00 | 9.00 | 22.50 | 191.00 |
| | | | | | | | |
| **Hong Kong** | | | | | | | |
| Temperature(°C) | 23.35 | 4.97 | 11.39 | 19.59 | 24.34 | 27.95 | 30.29 |
| Relative humidity (%) | 77.36 | 8.34 | 51.00 | 73.14 | 78.50 | 83.32 | 93.57 |
| Vapor pressure (hPA) | 23.24 | 7.42 | 8.21 | 16.97 | 23.71 | 30.91 | 33.81 |
| Rainfall (mm) | 41.60 | 72.02 | 0.00 | 0.25 | 9.00 | 53.73 | 560.90 |
| Weekly influenza isolate numbers | 26.32 | 43.93 | 0.00 | 5.00 | 10.50 | 29.25 | 310.00 |
| | | | | | | | |
| **British Columbia** | | | | | | | |
| Temperature(°C) | 10.23 | 5.53 | -4.81 | 5.82 | 9.61 | 15.31 | 24.17 |
| Relative humidity (%) | 76.47 | 8.24 | 51.42 | 70.72 | 76.52 | 82.63 | 95.26 |
| Vapor pressure (hPA) | 9.90 | 3.05 | 2.46 | 7.56 | 9.27 | 12.39 | 18.47 |
| Rainfall (mm) | 20.83 | 20.82 | 0.00 | 3.95 | 16.70 | 30.05 | 130.00 |
| Weekly influenza isolate numbers | 41.08 | 144.04 | 0.00 | 0.00 | 3.00 | 34.25 | 1243.00 |

Table 2. Percentage change of influenza numbers associated with per unit increase of weather factors.

| Factors | Percentage change (%) | 95%CI | |
|---|---|---|---|
| **Shanghai** | | | |
| Temperature (Low RH) | -3.49 | -4.08 | -2.89 |
| Temperature (Mid RH) | -1.60 | -2.95 | -0.24 |
| Temperature (High RH) | -1.29 | -2.71 | 0.16 |
| VP (Low RH) | -4.92 | -5.79 | -4.04 |
| VP (Mid RH) | -1.26 | -3.16 | 0.69 |
| VP (High RH) | -0.47 | -2.42 | 1.51 |
| **Hong Kong** | | | |
| Temperature (Low RH) | 2.06 | 1.03 | 3.10 |
| Temperature (Mid RH) | 7.15 | 4.49 | 9.87 |
| Temperature (High RH) | 3.07 | 0.41 | 5.80 |
| VP (Low RH) | 3.79 | 2.92 | 4.67 |
| VP (Mid RH) | 5.30 | 3.25 | 7.39 |
| VP (High RH) | 2.26 | 0.12 | 4.43 |
| **British Columbia** | | | |
| Temperature (Low RH) | -25.08 | -25.86 | -24.29 |
| Temperature (Mid RH) | -32.06 | -33.50 | -30.59 |
| Temperature (High RH) | -13.06 | -15.41 | -10.65 |
| VP (Low RH) | -40.71 | -41.86 | -39.54 |
| VP (Mid RH) | -48.80 | -50.78 | -46.74 |
| VP (High RH) | -20.78 | -24.66 | -16.69 |

CI, confidence interval.

Figure 1. Time series plots of weekly numbers of influenza from 2007–2011 in Shanghai, Queen Mary Hospital in Hong Kong and British Columbia.
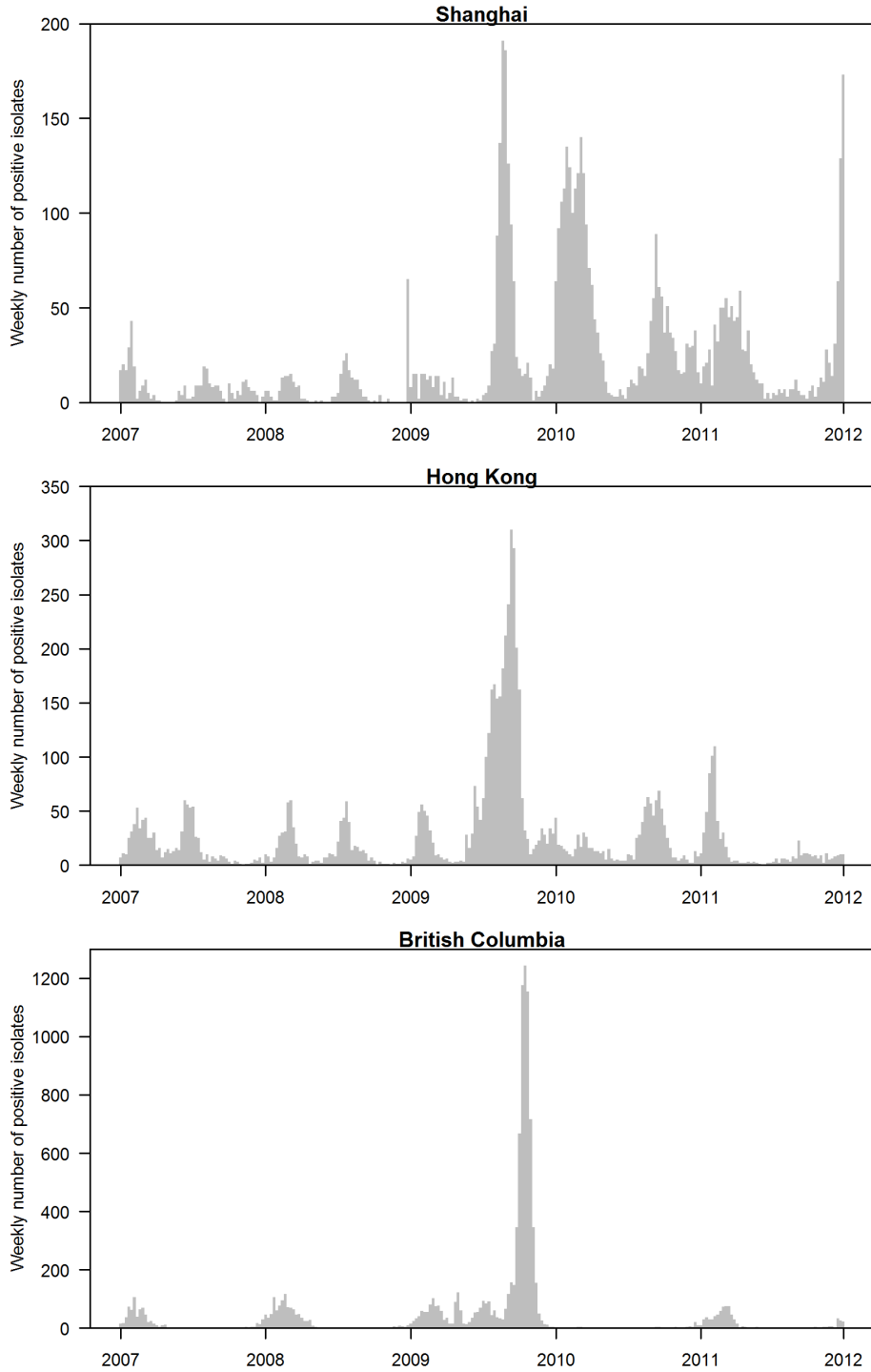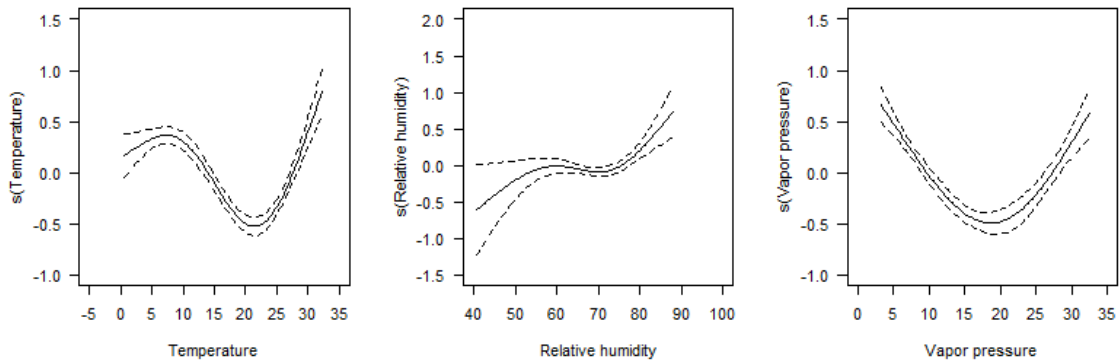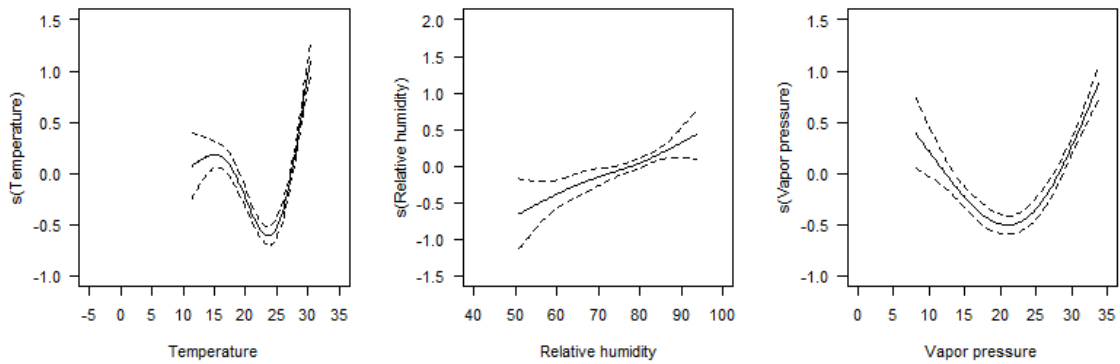
Figure 2. Exposure response curves for the independent effects of temperature, relative humidity and vapor pressure on influenza seasonality in Shanghai (A), Hong Kong (B) and British Columbia (C).
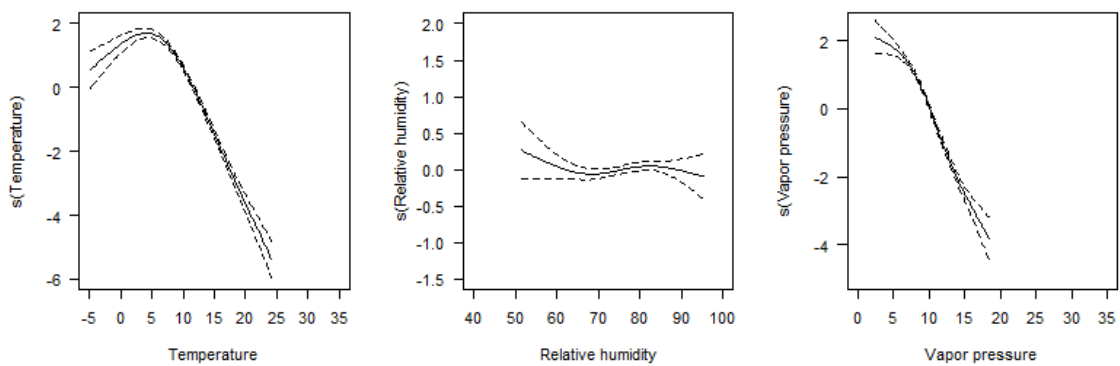
(A)

(B)

(C)

Figure 3. Exposure response surface plots of the joint effects of weather factors on influenza virus activity. (A) temperature and relative humidity in Shanghai, (B) vapor pressure and relative humidity in Shanghai; (C) temperature and relative humidity in Hong Kong, (D) vapor pressure and relative humidity in Hong Kong; (E) temperature and relative humidity in Columbia, (F) vapor pressure and relative humidity in British Columbia.
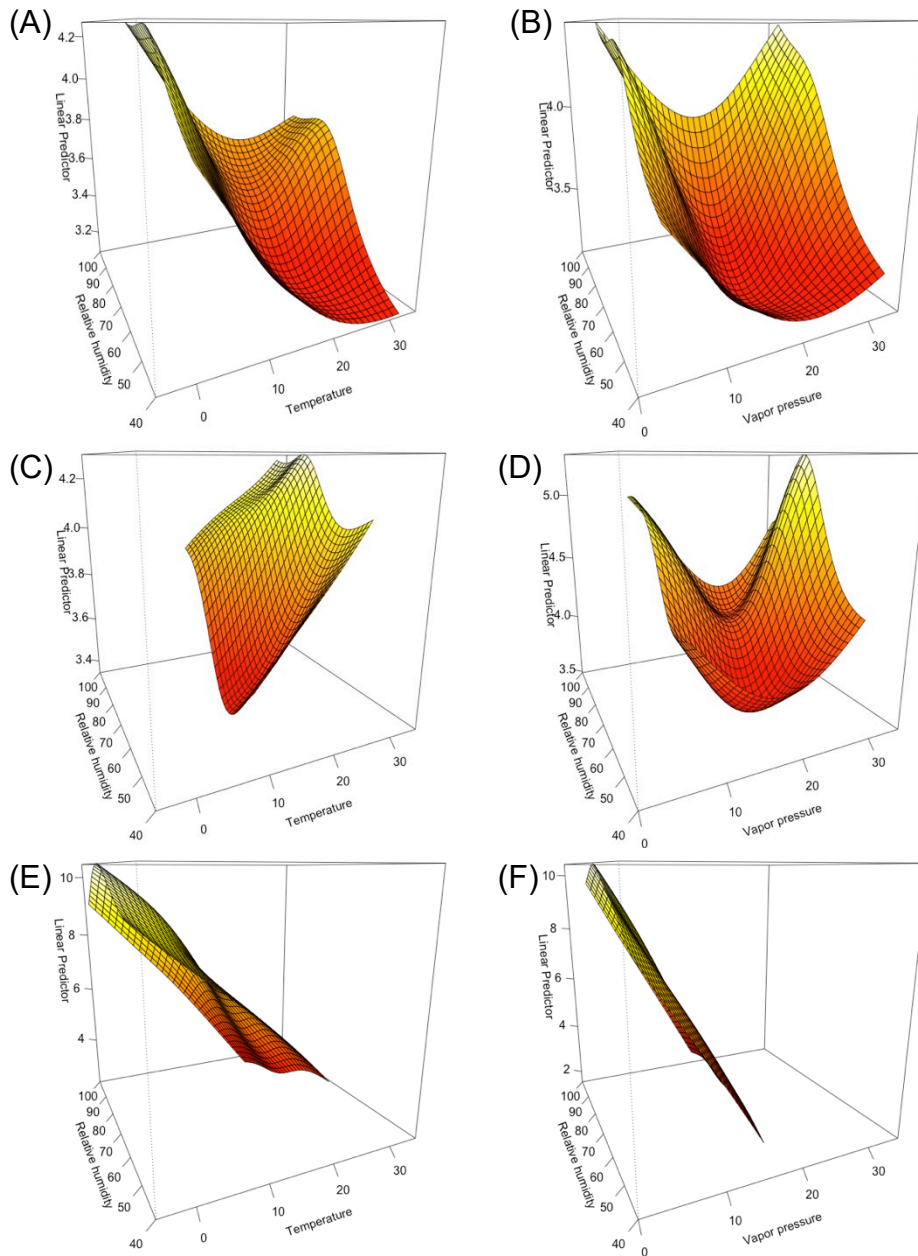
**References:**

Basu R, Feng WY, Ostro BD. 2008. Characterizing temperature and mortality in nine california counties. Epidemiology 19:138-145.

Bouvier NM, Palese P. 2008. The biology of influenza viruses. Vaccine 26 Suppl 4:D49-53.

Brankston G, Gitterman L, Hirji Z, Lemieux C, Gardam M. 2007. Transmission of influenza a in human beings. The Lancet infectious diseases 7:257-265.

Census and Statistics Department. 2012. 2011 ppopulation census summary results. Available: http://www.census2011.gov.hk/pdf/summary-results.pdf [accessed September 28 2015].

Chan KH, Maldeis N, Pope W, Yup A, Ozinskas A, Gill J, et al. 2002. Evaluation of the directigen flua+b test for rapid diagnosis of influenza virus type a and b infections. Journal of clinical microbiology 40:1675-1680.

Chow A, Ma S, Ling AE, Chew SK. 2006. Influenza-associated deaths in tropical singapore. Emerging infectious diseases 12:114-121.

Daniels MJ, Dominici F, Samet JM, Zeger SL. 2000. Estimating particulate matter-mortality dose-response curves and threshold levels: An analysis of daily time-series for the 20 largest us cities. American journal of epidemiology 152:397-406.

Dowell JA, Korth-Bradley J, Milisci M, Tantillo K, Amorusi P, Tse S. 2001. Evaluating possible pharmacokinetic interactions between tobramycin, piperacillin, and a combination of piperacillin and tazobactam in patients with various degrees of renal impairment. Journal of clinical pharmacology 41:979-986.

du Prel JB, Puppe W, Grondahl B, Knuf M, Weigl JA, Schaaff F, et al. 2009. Are meteorological parameters associated with acute respiratory tract infections? Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 49:861-868.

Greenland S. 1993. Basic problems in interaction assessment. Environmental health perspectives 101 Suppl 4:59-66.

Harper GJ. 1961. Airborne micro-organisms: Survival tests with four viruses. The Journal of hygiene 59:479-486.

Hastie T, Tibshirani R. 1990. Generalized additive models:Chapman & Hall.

Hemmes JH, Winkler KC, Kool SM. 1960. Virus survival as a seasonal factor in influenza and polimyelitis. Nature 188:430-431.

Lipsitch M, Viboud C. 2009. Influenza seasonality: Lifting the fog. Proceedings of the National Academy of Sciences of the United States of America 106:3645-3646.

Lofgren E, Fefferman NH, Naumov YN, Gorski J, Naumova EN. 2007. Influenza seasonality: Underlying causes and modeling theories. Journal of virology 81:5429-5436.

Loh TP, Lai FY, Tan ES, Thoon KC, Tee NW, Cutter J, et al. 2011. Correlations between clinical illness, respiratory virus infections and climate factors in a tropical paediatric population. Epidemiology and infection 139:1884-1894.

Lowen A, Palese P. 2009. Transmission of influenza virus in temperate zones is predominantly by aerosol, in the tropics by contact: A hypothesis. PLoS currents 1:RRN1002.

Lowen AC, Mubareka S, Steel J, Palese P. 2007. Influenza virus transmission is dependent on relative humidity and temperature. PLoS pathogens 3:1470-1476.

Lowen AC, Steel J, Mubareka S, Palese P. 2008. High temperature (30 degrees c) blocks aerosol but not contact transmission of influenza virus. Journal of virology 82:5650-5652.

Murry CE, Soonpaa MH, Reinecke H, Nakajima H, Nakajima HO, Rubart M, et al. 2004. Haematopoietic stem cells do not transdifferentiate into cardiac myocytes in myocardial infarcts. Nature 428:664-668.

Reichert TA, Simonsen L, Sharma A, Pardo SA, Fedson DS, Miller MA. 2004. Influenza and the winter increase in mortality in the united states, 1959-1999. American journal of epidemiology 160:492-502.

Schulman JL, Kilbourne ED. 1962. Airborne transmission of influenza virus infection in mice. Nature 195:1129-1130.

Shaman J, Kohn M. 2009. Absolute humidity modulates influenza survival, transmission, and seasonality. Proceedings of the National Academy of Sciences of the United States of America 106:3243-3248.

Shaman J, Pitzer VE, Viboud C, Grenfell BT, Lipsitch M. 2010. Absolute humidity and the seasonal onset of influenza in the continental united states. PLoS biology 8:e1000316.

Shamanna SG, Bosch JD. 2011. Injection laryngoplasty: A serious reaction to hyaluronic acid. Journal of otolaryngology - head & neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale 40:E39-42.

Shanghai Statistical Bureau. 2012. Shanghai statistical yearbook 2011. Available: http://www.stats-sh.gov.cn/data/toTjnj.xhtml?y=2011e [accessed September 28 2015].

Simonsen L, Fukuda K, Schonberger LB, Cox NJ. 2000. The impact of influenza epidemics on hospitalizations. The Journal of infectious diseases 181:831-837.

Statistics Canada. 2012. Focus on geography series, 2011 census. Available: http://www12.statcan.gc.ca/census-recensement/2011/as-sa/fogs-spg/Facts-pr-eng.cfm?Lang=Eng&GC=59 [accessed September 28 2015].

Tamerius JD, Shaman J, Alonso WJ, Bloom-Feshbach K, Uejio CK, Comrie A, et al. 2013. Environmental predictors of seasonal influenza epidemics across temperate and tropical climates. PLoS pathogens 9:e1003194.

Tang JW, Lai FY, Wong F, Hon KL. 2010. Incidence of common respiratory viral infections related to climate factors in hospitalized children in hong kong. Epidemiology and infection 138:226-235.

Tellier R. 2009. Aerosol transmission of influenza a virus: A review of new studies. Journal of the Royal Society, Interface / the Royal Society 6 Suppl 6:S783-790.

Viboud C, Alonso WJ, Simonsen L. 2006. Influenza in tropical regions. PLoS medicine 3:e89.

Wong CM, Chan KP, Hedley AJ, Peiris JS. 2004. Influenza-associated mortality in hong kong. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 39:1611-1617.

Wong CM, Yang L, Chan KP, Leung GM, Chan KH, Guan Y, et al. 2006. Influenza-associated hospitalization in a subtropical city. PLoS medicine 3:e121.

Yang L, Wong CM, Lau EH, Chan KP, Ou CQ, Peiris JS. 2008. Synchrony of clinical and laboratory surveillance for influenza in hong kong. PloS one 3:e1399.

Yang L, Wang XL, Chan KP, Cao PH, Lau HY, Peiris JS, et al. 2012. Hospitalisation associated with the 2009 h1n1 pandemic and seasonal influenza in hong kong, 2005 to

2010. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin 17:pii=20309.

Yu H, Alonso WJ, Feng L, Tan Y, Shu Y, Yang W, et al. 2013. Characterization of regional influenza seasonality patterns in china and implications for vaccination strategies: Spatio-temporal modeling of surveillance data. PLoS medicine 10:e1001552.