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Influenza-associated morbidity in subtropical Taiwan

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Summary

Objectives: The purpose of this study was to assess the characteristics of influenza-associated morbidity in subtropical Taiwan, corresponding to the seasonal patterns, weather, and cocirculation of influenza (sub)types, and other respiratory viruses, where the burden of influenza is poorly quantified. *Methods:* This study applied the virus variation-guided Poisson seasonal regression models to

Methods: This study applied the virus variation-guided Poisson seasonal regression models to evaluate the impact of epidemic influenza on morbidity in Taiwan for 1999–2006. The models allow for the adjusting of influenza-associated morbidity for factors such as annual trend, seasonality, temperature, relative humidity, influenza A (H1N1), A (H3N2), B, and respiratory syncytial virus. *Results:* Influenza-associated morbidity was associated more strongly with temperature than relative humidity. Influenza A (H3N2) was more coordinated with other virus (sub)types than A (H1N1). Type B dominated simultaneously with A (H3N2) at times, whereas A (H3N2) and A (H1N1) rarely dominated simultaneously with each other. Epidemiologically, A (H3N2) appeared to be the dominant subtype (51%), followed by type B (39%) and then A (H1N1) (10%) for influenza-associated morbidity.

Conclusions: This study suggests that seasonality and influenza (sub)types contribute significantly to influenza morbidity in subtropical Taiwan. This is important for influenza control managers who are involved actively in using epidemic and climate information to achieve influenza-reduction targets in subtropical regions.

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Introduction

KEYWORDS

Influenza;

Morbidity;

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Models

Seasonality;

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Influenza epidemics pose a threat for morbidity and mortality on a global scale, with nearly 3-5 million cases of severe illness and a quarter to half a million deaths annually

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worldwide (World Health Organization, 2003; http://www. who.int/mediacentre/factsheets/fs211/en/). A number of influenza-related incidences showing evidence of seasonality, in both the elderly and children, in tropical and subtropical regions, have been identified.^{1–9}

Recently, the US National Centers for Disease Control and Prevention (USCDC) developed a method based on a proportional relation between virus activity and the number of hospital admissions or deaths attributable to influenza, to assess the impact of a particular influenza epidemic.^{10,11} This

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virus variation-guided modeling approach employs an agespecific Poisson regression model to fit national mortality and viral surveillance data (from 1976 to 1998) to estimate annual influenza- and respiratory syncytial virus (RSV)-associated deaths in the USA by influenza types (A and B) and subtypes (A (H1N1) and A (H3N2)).¹⁰

This USCDC-developed approach not only enhances the traditional method usually used in temperate countries with clear and well-established non-epidemic periods,^{12–15} but is also particularly suitable for use in tropical and subtropical regions where there are no clearly predictable and well-defined non-epidemic periods.^{6–8,16} Chow et al.⁶ and Wong et al.⁷ appropriately applied the recently developed modeling approach of the USCDC to fit data of weekly mortality or weekly hospital admissions for each disease category and RSV as the dependent variables, and weekly average of temperature and relative humidity, as well as trend and seasonality as independent variables, to assess the impact of influenza-associated deaths and hospital admissions in tropical Singapore and subtropical Hong Kong, respectively.

Lowen et al.¹⁷ provided experimental evidence to support the role of weather conditions in the dynamics of influenza epidemics, indicating that cold temperature and low relative humidity are favorable to the spread of influenza virus. They argued that the extended exposure of a small proportion of the population to outdoor winter conditions would comprise a sufficient force to create seasonal epidemics, and implied that weather conditions of relative humidity and temperature would provide valuable insight into the seasonality of influenza. Therefore, surveillance data may be used to verify the importance of temperature and relative humidity in the epidemiology and infection of influenza. To this end, surveillance data based on a regional scale and concurrent meteorological data are needed.

Taken together, recent advances in assessing the impact of influenza-associated morbidity and mortality in temperate, tropical, and subtropical regions have highlighted the development of appropriate statistical techniques to estimate the burden of influenza. These statistical models allow for the adjusting of the burden of influenza for such factors as annual trend, seasonality, temperature, relative humidity, and disease category as well as RSV. Furthermore, recent integrated modeling studies on the burden of influenza in tropical and subtropical countries have shed light on the significant impact of influenza on the proportion of mortality.^{5,6,9,16} However, many of these studies have focused on tropical Singapore and the subtropical region of Hong Kong where influenza has a major impact on hospital admissions and deaths.

In Taiwan, a subtropical country ($22^{\circ}-25^{\circ}N$ and $120^{\circ}-122^{\circ}E$), the annual pneumonia- and influenza-associated deaths have been estimated at 16.78–25.14 per 100 000 population for the period 2001–2005 (Taiwan Centers of Disease Control (Taiwan CDC), https://teb.cdc.gov.tw/main/news_list.aspx?id=1978). Typically, in subtropical Taiwan, the average (\pm standard deviation) temperatures during spring (March to May), summer (June to August), fall (September to November), and winter (December to February) from 1999 to 2006 were 22.27 ± 2.97 , 29.07 ± 1.00 , 24.55 ± 2.96 , and $17.37 \pm 1.17^{\circ}C$, respectively, with a relative humidity ranging from 75% to 78% and a maximum rainfall occurring in June (7800 mm) and August (8527 mm) (Central

Weather Bureau, Taiwan). Typically, most tropical and subtropical countries experience these weather conditions.

Tsai et al.² indicated that Taiwan exhibited a moderate seasonality of influenza A high activity in January–February, July–August, and November–December; influenza B was also observed in the spring and early summer of 1997 and 1999. In northern Taiwan, RSV showed a significant positive correlation with mean weekly temperature, with a peak between July and October in the period 1995–1999, yet no significant correlation with mean relative humidity or rainfall.³ Tsai et al.,² however, showed no seasonal pattern of RSV infection in Taiwan during 1997–1999. Shih et al.¹⁸ also indicated that influenza seasonality in Taiwan was not clear during the four seasons from October 2000 to March 2004.

Little is known about the impact of influenza on morbidity in subtropical Taiwan, taking into account seasonal patterns and weather for influenza associated with the co-circulation of other respiratory viruses. However, there is low confidence in predictions of future risk of influenza incidence because of uncertainty over future seasonal patterns and weather conditions. Recent changes in the distributions and patterns of a number of infections can be ascribed with confidence to regional seasonal influenza variability. There are strong interactions between the effects of seasonality and the effects of weather, because seasonality might influence the season of emergence of a pandemic strain of influenza, making both sensitive to additional stresses such as climate change.

The purposes of this study were: (1) to quantify the burden of influenza and the seasonality of virus circulation, and predicting the impact of influenza-associated morbidity in Taiwan by using a general framework that is similar to that recently published by the USCDC, and (2) to provide a best-fit Poisson seasonal regression model for influenza-associated morbidity in subtropical Taiwan by quantifying the seasonal and course of influenza morbidity, where the potential weather effects attributable to temperature and relative humidity are also adjusted.

Methods

Weekly numbers of influenza cases were obtained from the Taiwan CDC for the period 1999–2006. The Taiwan CDC implemented influenza monitoring activity in 1999; 14 collaborating laboratories were contracted by the Taiwan CDC for the surveillance of influenza activity based on laboratory isolation of influenza viruses. This study focused on Taipei City (northern region), Taichung City (central region), and Kaohsiung City (southern region). The weekly number of cases was divided by the year-end population to obtain the morbidity expressed as the morbidity per 100 000 population.

The burden of morbidity was classified into high, moderate, and low non-epidemic baselines. The high non-epidemic baseline was obtained by averaging out the 8-year morbidity data excluding yearly data for weeks 1–5 and 43–52. The moderate non-epidemic baseline was obtained from the morbidity data where the highest peaks occurred in week 27 in 1999 to week 26 in 2000. The low non-epidemic baseline was obtained by estimating the highest peak morbidity in the winter season from 2005 to 2006. The average weekly

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Table 1Annual influenza virus and respiratory syncytial virus surveillance data (mean \pm SD) in subtropical Taiwan for 1999–2006.

Year	Influenza virus	Influenza virus				All specimens ^c
	Influenza type	Influenza type		Influenza A subtype		
	Influenza A Positive rate (%)	Influenza B Positive rate (%) ^a	A (H1N1) Positive rate (%) ^a	A (H3N2) Positive rate (%) ^a		
1999–2000	NA	NA	NA	NA	NA	NA
2000-2001	NA	NA	NA	NA	NA	NA
2001-2002	1.18 (0.78) ^b	NA	NA	NA	NA	NA
2002-2003	2.81 (2.48) ^b	1.76 (2.09)	1.27 (3.19)	1.26 (1.25)	NA	NA
2003-2004	5.06 (5.87) ^b	0.96 (1.39)	0.03 (0.16)	2.19 (3.22)	NA	NA
2004–2005	6.44 (5.42) ^c	1.19 (1.10)	0.03 (0.09)	5.62 (4.50)	0.15 (0.24) ^c	297.14 (52.74)
2005-2006	3.40 (2.73) ^c	4.68 (6.87)	0.40 (0.57)	2.94 (2.67)	0.17 (0.22) ^c	357.23 (133.96)
2006-2007	5.97 (6.27) ^c	3.27 (7.17)	4.16 (5.54)	1.77 (1.58)	0.37 (0.47) ^c	293.57 (85.55)

RSV, respiratory syncytial virus; NA, not available.

^aAdopted from Taiwan CDC.¹⁹

^bAdopted from Shih et al.¹⁸

^cAdopted from Taiwan CDC.²⁰

temperature and monthly relative humidity data for 1999–2006 were obtained from the Taiwan Central Weather Bureau.

The weekly numbers of total respiratory specimens tested for influenza and positive-influenza isolates by virus (sub)types from October 2000 to March 2004 were obtained from Shih et al.¹⁸ (Table 1). The surveillance data of the type B and subtypes A (H1N1) and A (H3N2) from 2002 to 2006 were provided by the Taiwan CDC¹⁹ (Table 1). Weekly influenza A and RSV data were obtained from the Taiwan CDC for the period 2004–2006²⁰ (Table 1). The weekly percentages of specimens that tested positive for both influenza and RSV were used to estimate the association of virus circulation with weekly morbidity in Taiwan (Table 1).

A full model with all variables was built, and then one by one, those variables that did not significantly contribute to the model were removed to derive a final model containing only significant variables. To explore the weather factors associated with the influenza-associated morbidity, the correlations between temperature and morbidity as well as relative humidity and morbidity were examined. A Poisson seasonal regression model was used to estimate the morbidity attributable to influenza and weather conditions:^{10,11}

$$Y(t) = \exp\left\{a_0 + a_1 t + a_2 t^2 + a_3 \sin\left(\frac{2\pi t}{52}\right) + a_4 \cos\left(\frac{2\pi t}{52}\right) + a_5 tem p_t + a_6 RH_t\right\},$$
 (1)

where t denotes the week, Y(t) is the estimated weekly morbidity number, a_0 , a_1 , and a_2 stand for the intercept in the model, linear time, and squared time trends, respectively, $\sin(2\pi t/52)$ and $\cos(2\pi t/52)$ represent the season, $temp_t$ is the weekly average temperature, and RH_t is the monthly average relative humidity.

To examine further the relationships between proportion of morbidity and the respiratory viruses, i.e., influenza A (H1N1) virus, influenza A (H3N2) virus, influenza B virus, and RSV, equation 1 was extended to estimate influenza-associated morbidity attributable to disease category associated with seasonality and weather factors:

$$Y(t) = \exp\left\{a_{0} + a_{1}t + a_{2}t^{2} + a_{3}\sin\left(\frac{2\pi t}{52}\right) + a_{4}\cos\left(\frac{2\pi t}{52}\right) + a_{5}tem p_{t} + a_{6}RH_{t} + a_{7}[A(H1N1)_{t}] + a_{8}[A(H3N2)_{t}] + a_{9}[B_{t}] + a_{10}[RSV_{t}]\right\},$$
(2)

where a_7 through a_9 represent coefficients associated with the weekly proportion of specimens testing positive.

Estimates of excess weekly morbidity were calculated as the difference between observed and predicted baseline morbidities during epidemic periods.¹⁴ The significant level of the epidemic threshold was defined by setting the upper limit of the 95% confidence interval (CI) (i.e., 1.96 standard deviations with sample size greater than 30) above the expected non-epidemic baseline. Estimates of excess seasonal epidemic morbidity were calculated as the difference between observed and expected morbidities.

The Poisson seasonal regression model in equation 1 was fitted to influenza morbidity data available for 1999–2006. Then the influenza and RSV model in equation 2 was fitted to laboratory-based surveillance data integrated from the Taiwan CDC and the available literature for 2001–2006, when both weekly influenza and RSV data were available. A Monte Carlo (MC) technique with 10 000 iterations was performed to generate 2.5- and 97.5-percentiles as the 95% CI for all fitted models. Crystal Ball[®] software (version 2000.2, Decisioneering, Inc., Denver, Colorado, USA) was employed to implement the MC simulation. All analyses were performed using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA), TableCurve 2D (version 5, AISN Software Inc., Mapleton, OR, USA), and SPSS (version 13.0 for Windows, SPSS Inc., Chicago, IL, USA) software.

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Table 2 Summary of Poisson seasonal regression models used in this study.

Poisson seasonal regression model

$\overline{Y(t)} = \exp\{a_0 + a_1t + a_2t^2 + a_3 \cdot \sin(2\pi t/52) + a_4 \cdot \cos(2\pi t/52)\}$	(T1)
$Y(t) = \exp\{a_0 + a_1t + a_2t^2 + a_3 \cdot \sin(2\pi t/52) + a_4 \cdot \cos(2\pi t/52) + a_5 \cdot temp_t\}$	(T2)
$Y(t) = \exp\{a_0 + a_1t + a_2t^2 + a_3 \cdot \sin(2\pi t/52) + a_4 \cdot \cos(2\pi t/52) + a_5 \cdot temp_t + a_6[A_t] + a_7[B_t] + a_8[RSV_t]\}$	(T3)
$Y(t) = \exp\{a_0 + a_1t + a_2t^2 + a_3 \cdot \sin(2\pi t/52) + a_4 \cdot \cos(2\pi t/52) + a_5 \cdot temp_t + a_6[H1N1_t] + a_7[H3N2_t] + a_8[B_t]\}$	(T4)

Y(t) represents influenza morbidity; a_0 represents intercept; a_1 represents linear time trend; a_2 represents non-linear time trends; a_3 and a_4 represent seasonal changes in morbidity; a_5 represents the effect on temperature; a_6 through a_8 represent coefficients associated with the specimens testing positive for a given week.

Results

Table 2 summarizes all the morbidity-based Poisson seasonal regression models used; equation T1 gives the basic Poisson seasonal regression model. Figure 1 shows the weekly reported influenza-associated morbidities along with the

average weekly temperature and monthly relative humidity in the three major cities of Taipei, Taichung, and Kaohsiung for 1999–2006. Generally, influenza-associated morbidities occurred primarily in the winter months (Figure 1). The results indicate that temperature had a higher negative correlation (r^2 ranging from 0.23 to 0.51 with an exponential



Figure 1 Time series of weekly influenza-associated morbidity associated with weekly average temperature and monthly relative humidity in (A) Taipei, (B) Taichung, and (C) Kaohsiung for 1999–2006.



Figure 2 Relationship between weekly influenza-associated morbidity and monthly average temperature as well as relative humidity in (A, B) Taipei, (C, D) Taichung, and (E, F) Kaohsiung for 1999–2006.

slope around -0.07) with morbidity than relative humidity in the three major cities ($r^2 < 0.07$) (Figure 2). Figure 2 also reveals that there was a statistically significant interaction between temperature and city, indicating that the effect of temperature on morbidity was not the same for the three cities. A relatively higher significant correlation was found in the northern Taiwan region (in Taipei ($25^{\circ}03N$), $r^2 = 0.51$ and in Taichung ($24^{\circ}09N$), $r^2 = 0.29$) than in the southern region (in Kaohsiung ($22^{\circ}42N$), $r^2 = 0.23$) (Figure 2). There was no difference in the effect of relative humidity on morbidity in the three cities.

However, by removing the independent variable of relative humidity from equation 1 to obtain equation T2 (Table 2), equation T2 was then fitted to the morbidity data shown in Figure 1, showing peaks in weekly morbidity corresponding very well with troughs in weekly temperature (Figure 3). There was no statistically significant effect of temperature on morbidity in this particular Poisson seasonal regression model shown in equation T2 (p > 0.05). The basic Poisson seasonal regression model (equation T1) is used to

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obtain high, moderate, and low non-epidemic baselines (Figure 4A). This study indicates that seasonality had significant (p < 0.05) effect on influenza-associated morbidity in 1999–2006.

The time courses of moderate influenza morbidity baseline shown in Figure 4A, C, and E were used to estimate excess morbidities for Taipei, Taichung, and Kaohsiung. Table 3 shows the overall influenza-associated morbidity and excess morbidity estimates for 1999-2006. The highest excess morbidities per 100 000 population occurred in Taipei in 1999–2000 with mean range values of 33–44, in Taichung in 1999-2003 with mean range values of 14-29, and in Kaohsiung in 1999-2002 with mean range values of 17-20 (Table 3). Generally, the excess morbidities in the three regions varied weekly. The probabilistic density function was then applied to characterize the excess morbidities for 1999–2006. A lognormal distribution (LN(geometric mean, geometric standard deviation)) was optimally fitted to the averaged excess morbidity estimates per 100 000 population based on the high, moderate, and low non-epidemic



Figure 3 Relationship between trends in weekly influenza-associated morbidity and weekly average temperature and that of an expected morbidity estimated by Poisson seasonal regression model for (A) Taipei, (B) Taichung, and (C) Kaohsiung for 1999–2006.

baselines, resulting in LN(9.58, 2.76) for Taipei, LN(10.47, 2.76) for Taichung, and LN(10.31, 2.48) for Kaohsiung (Figure 4B, D, and F).

This study examined first the relationship between morbidity and each respiratory virus (influenza A, influenza B, and RSV) from 2004 to 2006, where the data were available (Figure 5A, B), by using the Poisson seasonal regression approach (equation T3, Table 2). The result indicates that influenza A and B had significant (p < 0.05) effects on weekly morbidity in the Taiwan region, with an r^2 of 0.6, reflecting a relatively good correlation with the observed data (Figure 5C). Temperature and RSV, however, had no significant effects on morbidity from 2004 to 2006 (p > 0.05).

The variable 'influenza A' was then replaced with influenza A subtypes (A (H1N1) and A (H3N2)) in the Poisson seasonal regression model (equation T4, Table 2), where the data were available for 2002 to 2006 (Figure 6A), to investigate the relationship between weekly morbidity and each virus (sub)type. Seasonal A (H3N2) morbidity exhibiting highly defined peaks coincided with weakly defined peaks in

type B and in A (H1N1) morbidities based on the measures of the morbidity peakedness²¹ for A (H3N2) against type B (Wilcoxon signed-rank test, W = 37, Z = -4.48, n = 260, p < 0.001) and A (H1N1) (W = 14, Z = -7.63, n = 260, p < 0.001) having negatively correlated relationships (Figure 6A).

A (H1N1) dominated only in the winter season from 2001 to 2002 and dominated simultaneously with A (H3N2) only in the winter season from 2005 to 2006 (Figure 6A). Influenza A (H3N2) was coordinated more with other virus (sub)types than with A (H1N1). A (H1N1)-associated morbidities that dominated in the winter season from 2001 to 2002 reappeared in the winter season from 2005 to 2006, with A (H3N2)-dominant from 2002 to 2005 (Figure 6A). The major reason for this phenomenon or trend is unknown, and this should be considered in future studies.

The results show that only the seasonal influenza A (H3N2) virus had significant (all p < 0.05) effects on weekly morbidities from 2002 to 2006 in the Taiwan region, with a high correlation between the observed and fitted model



Figure 4 Dynamics of epidemic classification based on high, moderate, and low non-epidemic baselines in (A) Taipei, (C) Taichung, and (E) Kaohsiung. Lognormal distribution for the three different baselines of burden of influenza on average excess morbidity estimation in (B) Taipei, (D) Taichung, and (F) Kaohsiung, respectively.

 $(r^2 = 0.70)$ (Figure 6B). This study indicates that A (H3N2) contributes nearly 50.69%, type B 38.69%, and influenza subtype A (H1N1) 10.62%, to the influenza-associated morbidity (Figure 6C). Therefore, influenza-associated excess morbidities from 2002 to 2006 were dominated epidemiologically by influenza A (H3N2) viruses (Figure 6D), focusing notably on 2003–2005 with average range values of 3.06–6.01 per 100 000 population (Table 4).

Discussion

Estimates derived from the weekly number of cases of influenza from the Taiwan CDC likely underestimated the true

impact due to the difficulty in attaining the number of cases based on the regional scales. The proportion of sentinel physician surveillances was planned in order to obtain a 1.5% coverage rate for the total Taiwan population, with an aim of approximately one sentinel physician per 750 people. However, the largest numbers of sentinel physician surveillance sites are located in areas of high population density such as Taipei City and Taipei County.²² Chang et al.²³ also indicated that sentinel physician surveillance had a 75% coverage rate in Taiwan, and the number of cases of influenza-like illness were reported by 500 sentinel physicians in the influenza season of 2005 to 2006. Hence, this study indicates that the highest morbidity per 100 000 population occurred in influenza season 1999–2000 with mean

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Year	Morbidity (1/100 000 po	pulation)		Excess morbidity (1/100	000 population)	
	Taipei	Taichung	Kaohsiung	Taipei	Taichung	Kaohsiung
1999-2000) 59.36 (6.15–162.26)	36.93 (13.48–80.43)	24.56 (17.50–33.17)	44.14 (7.65–140.54)	13.98 (1.05-61.94)	19.25 (0.93–94.29)
2000-2001	47.70 (7.80–163.62)	68.13 (25.66–149.92)	24.53 (17.20–33.59)	32.65 (1.88–152.21)	29.02 (4.79–97.55)	17.06 (1.23–77.32)
2001-2002	42.92 (21.39–76.90)	53.56 (23.45–106.18)	24.16 (16.37–34.42)	9.61 (1.26–36.54)	15.20 (2.51–52.80)	20.24 (9.36–38.71)
2002-2003	43.05 (19.57–82.46)	50.53 (28.57-82.59)	25.03 (18.17–33.52)	8.46 (0.65–39.57)	14.51 (4.18–36.75)	18.91 (8.60–36.19)
2003-2004	1 37.75 (14.05–82.63)	30.17 (6.46–89.44)	23.74 (11.88–42.16)	16.54 (2.70–56.48)	17.31 (2.63–58.57)	12.52 (4.03-30.81)
2004-2005	33.99 (22.79–49.10)	24.71(11.69—46.19)	25.12 (17.88–34.23)	2.40 (0.50–7.39)	3.79 (0.73–11.75)	7.16 (1.65–20.43)
2005-2006	40.68 (21.17–71.28)	34.65 (14.56–70.76)	24.78 (16.47–35.74)	9.11 (1.41–30.57)	10.00 (1.21–37.18)	10.33 (2.75–27.63)
2006-2007	7 37.17 (19.81–63.51)	25.63 (8.63–58.59)	24.73 (17.50–34.00)	5.60 (0.35–25.62)	8.66 (0.61–39.57)	8.38 (0.94–32.68)

range values of 59.36 (6.15–162.26) for Taipei, influenza season 2000–2001 with mean range values of 68.13 (25.66–149.92) for Taichung, and influenza season 2004 to 2005 with mean range values of 25.12 (17.88–34.23) for Kaohsiung.

Modeling the epidemiological investigations according to season is based primarily on the assumptions of many aspects of influenza transmission and exposure.²⁴ From a modeling perspective, mathematical approaches are available for incorporating periodic forcing into epidemiological data.²⁵ The Poisson seasonal regression model has been applied to describe influenza-related hospital admissions and deaths worldwide.^{7,8,10,11,13,26,27} This study used a Poisson seasonal regression model to estimate the morbidity attributable to influenza and weather conditions. The best fitted Poisson seasonal regression model is equation T4 (Table 2), which captures the effects of annual trend, season, weekly average temperature, and influenza subtype A (H1N1), subtype A (H3N2), and type B on influenza-associated morbidity. A relatively higher correlation was found for equation T4 $(r^2 = 0.70)$ than for equations T3 $(r^2 = 0.6)$ and T2 $(r^2 = 0.36 - 0.50).$

However, Simonsen et al.¹³ reported some of the limitations (including vaccination coverage) of the Poisson seasonal regression model simulation so that systematic bias could be avoided in future studies. At the same time, assessing the impact of influenza on morbidity in Taiwan cannot neglect the self-intrinsic errors of missing variables for the selected Poisson seasonal regression model. This study suggests that more detailed surveillance data (including influenza virus (sub)types) could well explain the peak values rather than missing information (Figures 3, 5, and 6). Therefore, seeking novel mechanisms and providing both biological plausibility and epidemiological evidence for existing theories are still needed in future studies.²²

This study reveals several findings. First, influenza-associated morbidity was associated more strongly with temperature than relative humidity, but there was no statistically significant effect of temperature on morbidity in this particular Poisson seasonal regression model (equation T2) in subtropical Taiwan. This implies that the patterns of seasonality dominated influenza-associated morbidity rather than temperature only.^{1,5,6,9} On the other hand, Lowen et al.¹⁷ provided direct and experimental evidence to support the role of environmental factors (e.g., weather conditions) in the dynamics of influenza. Lowen et al.²⁸ also suggested that high temperatures could block the aerosol transmission of influenza virus, implying that the morbidity trends in subtropical Taiwan do not correlate significantly with temperature. In fact, the results also show similar trends in the three regions. This study indicates that influenza-associated morbidity of the higher latitude region (Taipei) exhibited a better correlation with temperature than that of the lower one (Kaohsiung) (Figure 2). Hsieh et al.²⁹ also indicated that influenza activity usually started in northern Taiwan in November, then spread to central and southern Taiwan.

Second, type B at times dominated simultaneously with influenza A (H3N2), whereas influenza A (H3N2) and influenza A (H1N1) rarely dominated simultaneously with each other in subtropical Taiwan, implying an evolutionary interaction between influenza virus subtypes.³⁰ This suggests that influenza A (H1N1)-associated morbidities are suppressed by





Figure 5 The association of virus circulation with weekly morbidity in Taiwan for 2004–2006. The horizontal shaded blocks represent the winter seasons. (A) Positive rate (%) of influenza A and B isolation in Taiwan. (B) Positive rate (%) of respiratory syncytial virus isolation in Taiwan. (C) Comparison of weekly influenza-associated morbidity and expected morbidity based on Poisson seasonal regression model.

cross-immunity when influenza A (H3N2) is dominant.^{21,30} Thus infections with one subtype can usually protect against re-infection with the other in sequential epidemics. Moreover, the positive rate of influenza type and subtype confirmed the patterns of influenza-associated morbidity occurring primarily during the winter months. This study reveals that influenza A (H3N2) appeared to be the dominant subtype followed by influenza type B and then influenza A (H1N1) in subtropical Taiwan (Figure 6A). The results suggest that: (1) influenza type B was not regulated by the seasonal

Table 4 Estimated influenza A (H1N1), A (H3N2), and type B-associated excess morbidity (mean with 95% confidence interval) in Taiwan for 2002–2007.

	Excess morbidity (1/100 000	Excess morbidity (1/100 000 population)			
Year	A (H1N1)	A (H3N2)	В		
2002–2003	13.11 (3.02-37.43)	1.99 (0.36-6.51)	1.63 (0.31-4.96)		
2003-2004	0 (0)	6.01 (1.39–17.79)	2.62 (0.72-6.78)		
2004–2005	0.04 (0)	3.06 (0.50-10.76)	0.69 (0.14-2.10)		
2005-2006	0.30 (0.02-1.35)	3.69 (0.42-13.87)	6.90 (1.25-22.85)		
2006-2007	0.83 (0.09-3.34)	0.98 (0.26-2.67)	0.70 (0.12-2.29)		

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Time (year)

Figure 6 Time series dynamics of influenza type and subtype for 2002–2006. The horizontal shaded blocks represent the winter seasons. (A) Positive rate of influenza A (H1N1), A (H3N2), and B isolation in Taiwan. (B) Comparison of weekly influenza-associated morbidity and expected morbidity based on Poisson seasonal regression model. (C) Contributions of influenza A (H1N1), A (H3N2), and B to the influenza-associated morbidity. (D) Estimated influenza-associated excess morbidity for influenza A (H1N1), A (H3N2), and B.

stimulus in the same manner as type A. Although the mechanisms underlying this seasonal stimulus are still largely unresolved, prevailing hypotheses suggest that most of the factors are associated with winter such as indoor crowding, lower temperatures, decreased humidity, and reduced levels of direct sunlight.^{8,17,24,31} (2) These findings are also consistent with the well-established pattern occurring in the most temperate regions.^{32,33} In subtropical/tropical Hong Kong and Singapore, influenza is an important cause of hospital admission, with rates exceeding those reported for temperate regions.^{4,6,7} Overall influenza-associated mortality in a region such as subtropical Hong Kong is comparable with that documented in the temperate regions.^{7,10,11,16}

Third, Taiwan and other subtropical countries (e.g., Hong Kong and Singapore) have no well-defined non-epidemic periods for influenza-associated morbidity. This study indicates that different non-epidemic periods indeed affect the results obtained from the Poisson seasonal regression models (equation T1) and the estimates of excess morbidity. However, this study could not implicate explicitly the relationships of the well-defined non-epidemic periods among the different characteristics of weather, population density, medical resources, and the dominant influenza subtypes. This study could not provide a comparative analysis with other research on annual influenza-associated deaths in Singapore,⁶ Hong Kong,⁷ and the USA.¹⁰ However, the welldefined non-epidemic periods for a specific area or country may decide the government policy even to establish the management of an early warning system. More information on acceptable well-defined periods in the subtropics area is needed.

In conclusion, this study suggests that seasonality and influenza virus (sub)types contributed significantly to influenza-associated morbidity in subtropical Taiwan.

Influenza-associated morbidity in subtropical Taiwan

Characteristics of influenza virus (sub)types in subtropical Taiwan have also been quantified. It is necessary to obtain more samples of influenza virus at the type and subtype levels from long-term year-round viral surveillance and reliable morbidity to develop a virus variation-guided Poisson seasonal regression model.³³

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