MAJOR ARTICLE

Excess Mortality Associated With Influenza A and B Virus in Hong Kong, 1998–2009

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Background. Although deaths associated with laboratory-confirmed influenza virus infections are rare, the excess mortality burden of influenza estimated from statistical models may more reliably quantify the impact of influenza in a population.

Methods. We applied age-specific multiple linear regression models to all-cause and cause-specific mortality rates in Hong Kong from 1998 through 2009. The differences between estimated mortality rates in the presence or absence of recorded influenza activity were used to estimate influenza-associated excess mortality.

Results. The annual influenza-associated all-cause excess mortality rate was 11.1 (95% confidence interval [CI], 7.2–14.6) per 100 000 person-years. We estimated an average of 751 (95% CI, 488–990) excess deaths associated with influenza annually from 1998 through 2009, with 95% of the excess deaths occurring in persons aged ≥65 years. Most of the influenza-associated excess deaths were from respiratory (53%) and cardiovascular (18%) causes. Influenza A(H3N2) epidemics were associated with more excess deaths than influenza A(H1N1) or B during the study period.

Conclusions. Influenza was associated with a substantial number of excess deaths each year, mainly among the elderly, in Hong Kong in the past decade. The influenza-associated excess mortality rates were generally similar in Hong Kong and the United States.

Human influenza virus causes substantial morbidity and mortality worldwide [1–4]. Although the majority of infections are mild, some influenza virus infections can lead to fatal complications such as viral pneumonia or secondary bacterial pneumonia, although influenza virus infections might not be confirmed with laboratory testing for various reasons [5]. Influenza has also been associated with deaths from concurrent diseases or complications of preexisting medical conditions, such as cardiovascular diseases [6], and in those cases influenza would typically not be listed as the primary cause of death [7]. For these reasons, statistical estimates of excess mortality rather than rates of laboratory-confirmed influenza deaths are typically used to quantify the burden of influenza in a population [1–4].

A variety of statistical models have been applied to estimate influenza-attributable excess mortality. In temperate countries with sinusoidal patterns in mortality and influenza epidemics every winter, Serfling-type cyclic regression models have sometimes been used [8, 9]. This method, which was originally developed to identify peaks in influenza activity [10], does not differentiate between excess deaths associated with influenza or other winter causes, and tends to overestimate excess mortality associated with influenza compared with other commonly used methods [11]. This approach is not well suited to use in tropical or subtropical settings with prolonged periods of influenza activity and less clearly defined seasonality. Another commonly used approach to estimate excess deaths associated with influenza is regression modeling [12].

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These models can account for varying seasonal patterns if present. They can also directly incorporate covariates reflecting the activity of influenza as well as other cocirculating viruses possibly related to mortality such as respiratory syncytial virus (RSV), typically based on virologic surveillance data [7, 13]. Linear regression might be preferred to Poisson regression, since the latter assumes a multiplicative increase in the mortality rate associated with additive changes in influenza activity, whereas if the case fatality risk were constant through time we would expect excess deaths to increase additively with influenza activity [14, 15]. In addition, because of seasonal changes in the number of specimens sent for diagnostic testing throughout the year, the number of specimens positive for influenza and the proportion of specimens positive for influenza may not accurately reflect influenza activity [14, 16].

In this study, we estimated the excess mortality associated with influenza types and subtypes in Hong Kong, a subtropical city with a population of around 7 million. Hong Kong typically experiences 2 peaks of influenza activity every year, the first in January–March and the second in June–August [17]. We examined cause-specific mortality as well as all-cause mortality to fully capture the potential effects on deaths from influenza and to investigate any potential patterns in the association between influenza and mortality from specific causes.

METHODS

Sources of Data

Age-specific weekly deaths from 1998 to 2009 were obtained from the Census and Statistics Department of the Hong Kong Government. We selected 7 of the leading major causes of death in Hong Kong that might potentially be related to influenza. These causes of death, which were coded according to the *International Classification of Diseases, Ninth Revision* (*ICD-9*) and *Tenth Revision* (*ICD-10*), included cardiovascular disease, respiratory disease, malignant neoplasm, diabetes mellitus, kidney disease, chronic liver disease, and degenerative disease of the nervous system [14]. Within cardiovascular diseases, 2 subcategories were extracted including heart disease and cerebrovascular disease. Within respiratory diseases, pneumonia and influenza and chronic lower respiratory disease were extracted. We also extracted deaths coded as femoral fracture as controls. The *ICD-9* and *ICD-10* codes for each of these specific underlying causes are provided in Supplementary Table 1. After extracting all-cause deaths and deaths from the 7 major causes listed above, we created one new time series for deaths from "other causes" as those deaths in Hong Kong that did not fall under these 7 major causes. The age-specific midyear population sizes for each year from 1998 through 2009 were obtained from official statistics published by the Census and Statistics Department and used as the denominators for estimation of mortality rates.

The Hong Kong Centre for Health Protection conducts routine outpatient and laboratory surveillance for influenza [17]. A network of about 50 sentinel private outpatient clinics reports the weekly proportion of consultations due to influenza-like illness, defined as fever plus cough or sore throat. The public health laboratory receives specimens for diagnostic and surveillance purposes from sentinel outpatient clinics and local hospitals, and reports the weekly proportions of specimens that tested positive for influenza (by type and subtype) and RSV. Meteorological parameters including daily temperature and relative humidity were reported by the Hong Kong Observatory. Data on influenza activity and meteorological measurements were available from 1998 through 2009.

Statistical Analysis

We applied linear regression models to investigate the underlying association between weekly all-cause and disease-specific mortality rates and influenza activity. We used linear regression, assuming an additive relation between influenza activity and mortality rates [14]. Linear models were chosen to reflect the assumption that increases in influenza activity would lead to corresponding additive increases in mortality, rather than multiplicative increases as in a Poisson regression model with a log link. Influenza activity was estimated by the weekly proportion of consultations for influenza-like illness at sentinel clinics multiplied by the weekly type/subtype-specific influenza detection rate in the local public health laboratory, to give separate estimates of influenza activity for seasonal influenza A(H1N1), A(H3N2), B, and 2009 pandemic influenza A(H1N1). This proxy measure may be more closely related to influenza incidence than the separate proportions of patients with influenza-like illness or the proportions of laboratory tests positive for influenza [14, 16]. Temperature and absolute humidity can affect influenza activity [18] and mortality [19, 20] and the weekly averages of these environmental factors were included as covariates in the regression models. RSV activity, estimated by the weekly proportion of consultations for influenza-like illness at sentinel clinics multiplied by the weekly RSV detection rate in the local public health laboratory, was also included in the regression models as a potential confounder, because it could be associated with influenza activity through virus interference, and could be associated with mortality rates. Another covariate was included into the model to account for the impact of the transition of coding system (ie, from *ICD-9* to *ICD-10*), in Hong Kong since 2001.

Given the likely delay between onset of influenza illness and death, we specified a lag of 1 week between influenza activity and mortality rates. In sensitivity analyses we explored the effect on excess mortality estimates of no lag, or a 2-week lag. The influenza-associated excess mortality rates were estimated by subtracting the predicted mortality rate estimated from the fitted regression model setting influenza activity for a specific

type or subtype to zero from the predicted mortality rate from the model based on the reported weekly influenza activity. The 95% confidence intervals (CIs) for excess mortality rates were estimated with a bootstrap approach. To permit comparison with other countries, mortality rates were directly standardized to the World Standard Population [21]. Our overall estimates of influenza-associated excess mortality in each year were based on the full calendar year. To examine the impact of influenza-associated excess mortality in certain periods of peak influenza activity ("influenza seasons") where certain types or subtypes were predominant, we determined influenza seasons by the time period with at least 2 consecutive weeks in which the influenza activity metric exceeded 0.005. If an interval between 2 such time periods was no more than 3 weeks, the 2 time periods were combined into one season. This threshold was chosen to permit discrimination between different seasons with different predominant types/subtypes in the same year. Further technical details of the statistical methods are provided in the Supplementary Appendix. All statistical analyses were conducted in R, version 2.9.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Between 1998 and 2009, we estimated that influenza was associated with an annual excess mortality rate of 11.1 (95% CI, 7.2–14.6) per 100 000 person-years from all causes in 1998–2009. The age-standardized mortality rate was 8.5 (95% CI, 5.6–11.4) per 100 000 person-years. The annual influenza-associated all-cause mortality rates ranged between 7.4 and 14.4 per 100 000 person-years through the period, accounting for approximately 500–1000 excess deaths each year (Supplementary Table 2), which was around 2% of all deaths in Hong Kong.

Of the 12 years covered, 2 influenza seasons were identified in 7 of the years and only 1 season was observed in the other years. Most of the years with a single season, including 2001, 2004, 2005, and 2007, had prolonged influenza activity for >5–6 months (Figure 1). The only year in which we did not identify substantial influenza activity during the summer was 2003. In 2009 the first wave of pandemic influenza A(H1N1) peaked in September–October, having been preceded by a winter season where seasonal influenza A(H1N1) predominated and a summer season where influenza A(H3N2) predominated. In the years with 2 influenza seasons, the influenza-associated mortality risk in the winter seasons was generally higher than in the summer seasons regardless of the type/subtype of the predominant strain(s) (Table 1). During the influenza seasons defined in the study, the average influenza-associated mortality risk in A(H3N2) predominant seasons, including the years that A(H3N2) cocirculated with other viruses, was approximately double that in the seasons during which influenza A(H1N1) was predominant, and only slightly higher (10% more) than the influenza B predominant seasons (Table 1).

Two or more influenza subtypes cocirculated in 9 of the 19 seasons, and influenza A(H3N2) predominated in 14 of the 19 seasons (Figure 1). From 1998 through 2009, the annual excess all-cause mortality rates associated with seasonal influenza A(H3N2), A(H1N1), and B averaged 6.9, 1.6, and 2.5 per 100 000 person-years, respectively (Table 2).

There was no statistically significant excess mortality associated with influenza in children, whereas influenza was associated with an average of 1.3, 3.3, and 89.7 deaths per 100 000 person-years in younger adults, older adults, and the elderly, respectively (Table 3). Approximately 95% of the influenza-associated excess mortality occurred in the elderly, accounting for 2.6% of all-cause deaths in that age group. Influenza A(H3N2) accounted for approximately 62.1% of all of the excess deaths associated with influenza during the study period, and the estimated age-specific mortality rate in the elderly associated with this subtype was higher, at 58.8 per 100 000 person-years, than for A(H1N1) and B. Excess mortality rates associated with pandemic and seasonal influenza A(H1N1) and influenza B were similar to each other.

Influenza was associated with an average of 2.0 and 5.8 deaths per 100 000 person-years from cardiovascular and respiratory diseases, respectively (Table 3). When added to the estimated influenza-associated deaths from malignant neoplasms, diabetes mellitus, renal disease, chronic liver disease, and degenerative disease of the nervous system, the influenza-associated excess deaths from these 7 major causes together accounted for 88% (9.71/11.08) of the estimated influenza-associated excess deaths from all causes, with good consistency between the estimates for specific groups and subgroups of causes (Figure 2, Table 3). The influenza-associated excess mortality rates for pneumonia and influenza were similar to those for chronic lower respiratory diseases. Almost all (82%; 1.68/2.04) of the estimated influenza-associated excess cardiovascular deaths were from heart diseases rather than cerebrovascular causes (Figure 2, Table 3). The negative control used in the model, deaths caused by femoral fracture, was not associated with influenza virus infection (Table 3).

In sensitivity analyses, we examined the influenza-associated excess mortality rates based on the models without any time lag and with a 2-week lag between the time when influenza and RSV activity were measured and the death rates were reported, respectively (data not shown). According to the adjusted R^2 statistics, the best-fitting regression models were those that included a 1-week lag between influenza activity and excess mortality (data not shown).

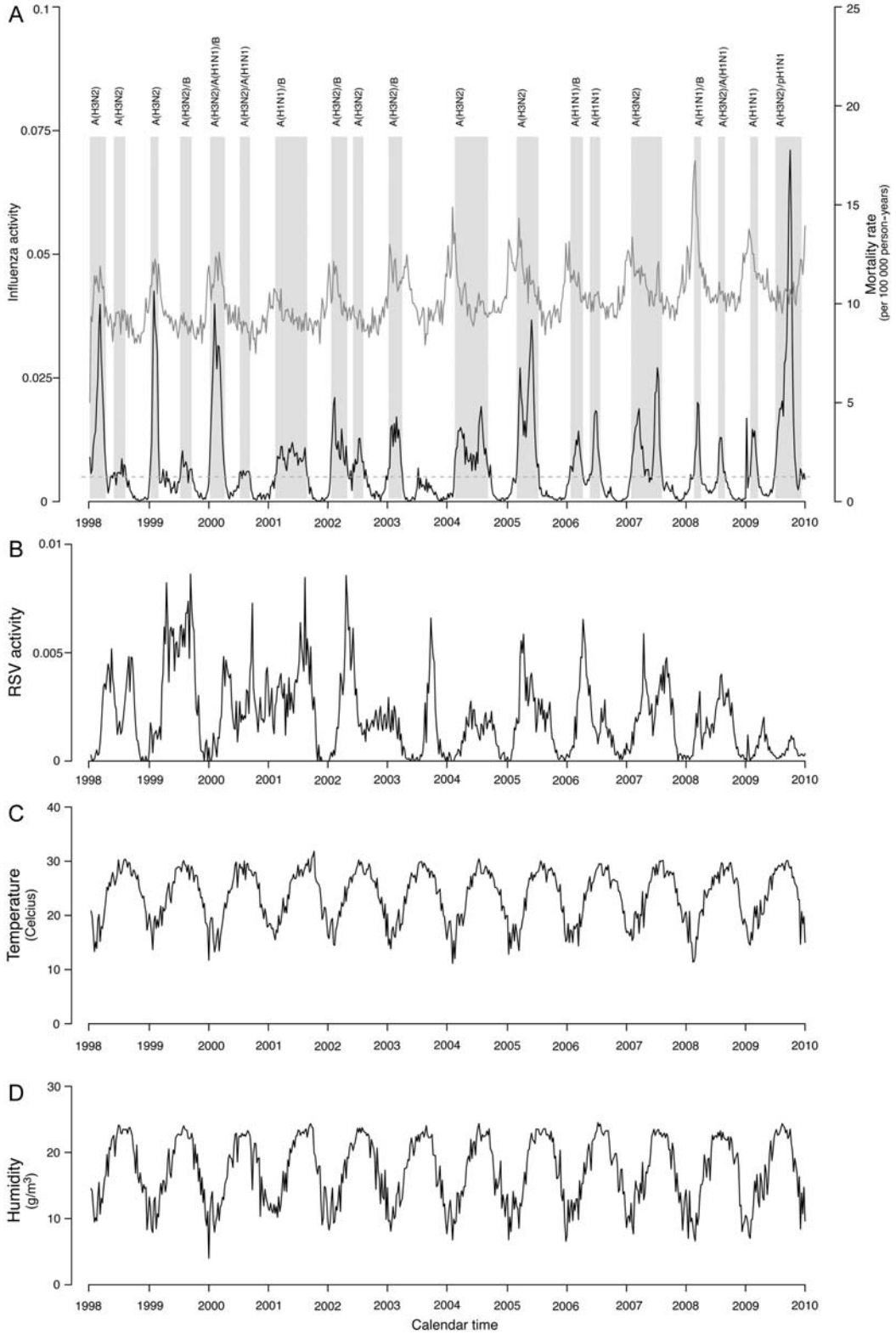

Figure 1. (*A*) Weekly influenza activity (*black line*), weekly all-cause mortality (*gray line*), and 19 influenza seasons (*gray areas*); (*B*) weekly respiratory syncytial virus (RSV) activity; (*C*) averaged weekly mean temperature; and (*D*) averaged weekly mean absolute humidity, in Hong Kong, 1998–2009. Influenza activity was estimated by the weekly proportion of consultations for influenza-like illness at sentinel clinics multiplied by the weekly influenza detection rate in the local public health laboratory. Influenza seasons were defined as periods of at least 2 consecutive weeks with influenza activity exceeding 0.005 (*gray dashed line*). RSV activity was estimated by the weekly proportion of consultations for influenza-like illness at sentinel clinics multiplied by the weekly RSV detection rate in the local public health laboratory.

Table 1. Type and Subtype-Specific Excess Mortality Risk in Each Influenza Season in Hong Kong, 1998–2009

			Excess Mortality Risk (per 100 000 Population)									
Year	Season[a]	Predominant Strain(s)[a]	A(sH1N1)	(95% CI)	A(sH3N2)	(95% CI)	A(pH1N1)	(95% CI)	B	(95% CI)	All Influenza	(95% CI)
1998	Winter	A(sH3N2)	0.11	(−.02, .24)	9.01	(5.57, 12.27)	…	…	0.10	(−.02, .22)	9.22	(5.82, 12.48)
	Summer	A(sH3N2)	0.00	(.00, .00)	1.86	(1.15, 2.53)	…	…	0.47	(−.10, 1.03)	2.33	(1.41, 3.14)
1999	Winter	A(sH3N2)	0.00	(.00, .01)	6.75	(4.17, 9.19)	…	…	0.22	(−.05, .49)	6.98	(4.47, 9.35)
	Summer	A(sH3N2), B	…[b]	…	2.12	(1.31, 2.88)	…	…	0.57	(−.12, 1.25)	2.69	(1.58, 3.63)
2000	Winter	A(sH3N2), A(sH1N1), B	2.55	(−.55, 5.62)	4.27	(2.64, 5.81)	…	…	3.50	(−.73, 7.62)	10.33	(5.53, 14.54)
	Summer	A(sH3N2), A(sH1N1)	0.29	(−.06, .64)	1.50	(.92, 2.04)	…	…	0.09	(−.02, .21)	1.88	(1.27, 2.48)
2001	One season	A(sH1N1), B	3.85	(−.83, 8.48)	0.58	(.36, .78)	…	…	3.39	(−.71, 7.38)	7.82	(2.16, 12.81)
2002	Winter	A(sH3N2), B	0.30	(−.07, .67)	4.15	(2.57, 5.65)	…	…	1.73	(−.36, 3.76)	6.18	(3.62, 8.46)
	Summer	A(sH3N2)	…[b]	…	3.05	(1.89, 4.16)	…	…	0.03	(−.01, 0.07)	3.09	(1.92, 4.18)
2003	One season	A(sH3N2), B	0.02	(.00, .04)	3.07	(1.90, 4.17)	…	…	2.41	(−.50, 5.24)	5.49	(2.37, 8.32)
2004	One season	A(sH3N2)	0.04	(−.01, .10)	10.86	(6.71, 14.78)	…	…	0.57	(−.12, 1.25)	11.47	(7.47, 15.39)
2005	One season	A(sH3N2)	0.62	(−.13, 1.36)	9.99	(6.18, 13.60)	…	…	2.22	(−.47, 4.84)	12.83	(8.35, 16.96)
2006	Winter	A(sH1N1), B	1.51	(−.33, 3.32)	0.11	(.07, .15)	…	…	1.82	(−.38, 3.95)	3.43	(.89, 5.77)
	Summer	A(sH1N1)	2.70	(−.59, 5.95)	0.03	(.02, .04)	…	…	0.14	(−.03, .30)	2.87	(−.37, 6.13)
2007	One season	A(sH3N2)	0.12	(−.03, .26)	9.00	(5.56, 12.25)	…	…	2.32	(−.49, 5.05)	11.43	(6.96, 15.35)
2008	Winter	A(sH1N1), B	0.70	(−.15, 1.54)	0.42	(.26, .57)	…	…	1.61	(−.34, 3.51)	2.73	(.83, 4.56)
	Summer	A(sH3N2), A(sH1N1)	0.76	(−.16, 1.68)	1.00	(.62, 1.36)	…	…	0.19	(−.04, .41)	1.94	(.98, 2.80)
2009	Winter	A(sH1N1)	1.64	(−.35, 3.60)	0.44	(.27, .59)	…	…	0.13	(−.03, .27)	2.20	(.24, 4.14)
	Summer	A(sH3N2), A(pH1N1)	0.38	(−.08, .85)	2.72	(1.68, 3.70)	2.07	(−4.66, 8.45)	0.20	(−.04, .44)	5.37	(−1.14, 11.51)

Abbreviations: A(sH1N1), seasonal influenza A(H1N1); A(sH3N2), seasonal influenza A(H3N2); A(pH1N1), 2009 pandemic influenza A(H1N1); CI, confidence interval.

[a] Influenza seasons were determined via a proxy measure of weekly influenza activity, estimated by the weekly proportion of consultations for influenza-like illness at sentinel clinics multiplied by the weekly influenza detection rate in the local public health laboratory. Strains that constituted 30% or more of all influenza virus detections in a particular season were considered to be predominant in that season.

[b] In these seasons, influenza A(H1N1) was not detected by local public health laboratory and therefore no deaths were attributed to this subtype.

Table 2. Average Type and Subtype-Specific Annual Excess All-Cause Mortality Rates in Different Age Groups in Hong Kong, 1998–2009

Virus	Average Excess Mortality Rate (per 100 000 Population per Year)										
	0–4 y	(95% CI)	5–14 y	(95% CI)	15–44 y	(95% CI)	45–64 y	(95% CI)	≥65 y	(95% CI)	All Ages	(95% CI)
All influenza	−0.68	(−3.73, 2.37)	−0.24	(−.96, .48)	1.26	(.31, 2.42)	3.31	(.05, 6.12)	89.68	(61.77, 113.68)	11.08	(7.18, 14.63)
A(sH1N1)	0.91	(−.32, 2.38)	0.11	(−.21, .48)	0.77	(.14, 1.26)	0.23	(−1.52, 1.78)	8.42	(−6.04, 21.70)	1.56	(−.34, 3.34)
A(sH3N2)	0.18	(−1.74, 2.24)	−0.06	(−.51, .41)	0.55	(−.02, 1.41)	1.88	(−.12, 3.89)	58.79	(40.49, 75.97)	6.88	(4.26, 9.37)
A(pH1N1)	−3.04	(−7.64, 2.50)	−0.69	(−1.89, .73)	−0.79	(−2.64, 1.00)	−0.78	(−6.36, 5.30)	23.42	(−23.71, 75.87)	2.15	(−4.84, 8.79)
B	−1.54	(−4.02, .82)	−0.25	(−.82, .30)	0.00	(−.79, .93)	1.27	(−1.27, 3.63)	20.28	(.13, 41.54)	2.45	(−.51, 5.33)

Abbreviations: A(sH1N1), seasonal influenza A(H1N1); A(sH3N2), seasonal influenza A(H3N2); A(pH1N1), 2009 pandemic influenza A(H1N1).

DISCUSSION

The influenza-associated all-cause excess mortality rates estimated from this study suggested an annual average of 740 excess deaths associated with influenza in Hong Kong from 1998 through 2009, similar to earlier estimates for 1996–1999 [4] and 2004–2006 [22]. The majority of influenza-associated excess deaths occurred in elderly persons, comparable to the findings from other developed countries [1].

We estimated that influenza was associated with annual mortality rates of approximately 11 per 100 000 person-years, and in separate cause-specific models we attributed 53% of the influenza-associated excess deaths to respiratory causes, 18% to cardiovascular diseases, and the remaining 29% to other underlying causes (Table 3, Figure 2). Our approach was given face validity by the consistency between the sum of influenza-associated mortality rates for 7 major causes and the overall all-cause mortality rates (Figure 2). Respiratory and cardiovascular diseases are often identified as the 2 most common causes of death associated with influenza virus infections [4, 12, 14]. The contribution of cardiovascular diseases to influenza-associated mortality may be due to the possible relationship between infection and atherosclerosis [23, 24]. A lower fraction of influenza impact through cardiovascular diseases here than that estimated from studies conducted in other developed countries such as the United States [12, 14] might be partially explained by the relatively lower age-standardized mortality rate from heart diseases locally compared with the United States [25, 26], or differences in coding causes of death.

In previous studies, influenza A(H3N2) has typically been associated with higher infection rates and more severe clinical symptoms than other subtypes [27, 28]. In our study, there was higher influenza-associated mortality in seasons when influenza A(H3N2) predominated compared with seasons dominated by other subtypes (Table 1). Higher mortality associated with A(H3N2) was not likely attributed to the longer duration of the seasons predominated by A(H3N2), because the average weekly influenza-associated mortality in A(H3N2)-dominant seasons was still about 2 times that in seasons when A(H1N1) predominated. Possible reasons for the greater impact of seasonal A(H3N2) include greater virulence [29, 30], a higher infection attack rates mediated by faster antigenic drift escaping population immunity from past epidemics [31], or antigenic sin providing greater protection against A(H1N1) viruses to individuals born before 1957 (ie, older adults and the elderly) [32].

Influenza seasonality in Hong Kong is unusual, with peaks in activity in the winter and in the summer [17]. The absence of a summer peak in 2003 was probably a result of the stringent community control measures implemented during the severe acute respiratory syndrome outbreak in 2003 [33], while the 2009 pandemic disrupted the seasonal patterns of

Table 3. Average Influenza-Associated Cause-Specific Excess Mortality Rates in Different Age Groups, 1998–2009

	Average Mortality Rate (per 100 000 Population per Year)											
	0–4 y	(95% CI)	5–14 y	(95% CI)	15–44 y	(95% CI)	45–64 y	(95% CI)	≥65 y	(95% CI)	All Ages	(95% CI)
Cardiovascular disease	0.28	(−.65, 1.27)	0.03	(−.19, .28)	0.09	(−.17, .40)	0.85	(−.56, 2.35)	18.96	(9.61, 31.18)	2.04	(.63, 3.58)
Heart disease	0.54	(−.15, 1.33)	0.11	(.06, .30)	0.07	(−.11, .30)	0.51	(−.53, 1.52)	14.05	(7.50, 22.08)	1.68	(.64, 2.62)
Cerebrovascular disease	−0.22	(−.59, .26)	−0.06	(−.16, .03)	−0.01	(−.12, .16)	0.29	(−.46, 1.14)	3.21	(−1.79, 8.47)	0.31	(−.31, .96)
Respiratory disease	−0.06	(−.91, .78)	0.11	(−.13, .33)	−0.20	(−.48, .14)	1.77	(.90, 2.65)	49.64	(37.06, 61.03)	5.83	(4.09, 7.29)
Pneumonia & influenza	0.22	(−.36, .82)	0.11	(−.06, .31)	0.01	(−.16, .20)	0.62	(−.03, 1.40)	25.25	(17.12, 33.74)	2.99	(1.81, 4.16)
Chronic lower respiratory disease	−0.17	(−.39, .04)	−0.04	(−.39, .04)	−0.12	(−.33, .12)	0.87	(.45, 1.28)	23.01	(17.05, 29.26)	2.62	(1.98, 3.29)
Malignant neoplasm	−0.45	(−1.09, .23)	−0.11	(−.50, .24)	0.12	(−.37, .60)	−1.59	(−3.69, .29)	9.90	(3.90, 16.15)	0.79	(−.12, 1.68)
Diabetes mellitus	−0.07	(−.14, .05)	−0.01	(−.03, .01)	0.03	(−.02, .08)	0.14	(−.18, .50)	3.22	(1.21, 5.07)	0.36	(.12, .60)
Renal disease	0.21	(−.08, .56)	−0.07	(−.17, −.03)	0.02	(−.09, .11)	−0.04	(−.48, .43)	3.59	(1.12, 6.44)	0.34	(.02, .66)
Chronic liver disease	0.25	(.08, .46)	0.00	(−.02, .04)	−0.02	(−.11, .04)	−0.25	(−.61, .21)	−0.45	(−1.48, 1.01)	−0.10	(−.28, .11)
Degenerative disease of nervous system	0.05	(−.09, .23)	−0.03	(−.08, .06)	−0.01	(−.02, .01)	0.03	(−.02, .10)	0.05	(−.22, .36)	0.01	(−.02, .05)
7 major causes	0.21	(−1.25, 1.60)	−0.13	(−.66, .36)	0.00	(−.63, .75)	1.03	(−1.87, 3.96)	84.63	(60.74, 106.10)	9.71	(6.27, 12.43)
Other causes[a]	−0.91	(−3.46, 1.60)	−0.19	(−.63, .32)	1.11	(.40, 1.91)	1.60	(.34, 3.17)	6.04	(−.71, 12.73)	1.53	(.52, 2.61)
Control												
Femoral fracture	…	…	0.01	(−.01, .04)	−0.01	(−.01, .01)	0.02	(−.02, .06)	0.28	(−.26, .76)	0.04	(−.03, .09)
All causes	−0.68	(−3.74, 2.37)	−0.24	(−.96, .48)	1.26	(.41, 2.34)	3.31	(.13, 6.08)	89.68	(61.91, 114.69)	11.08	(7.18, 14.63)

Abbreviation: CI, confidence interval.

[a] Other causes refer to the causes of death other than the 7 major causes shown in Table 3. The time series of deaths from other causes was derived by subtracting deaths from the 7 major causes from the all-cause deaths.

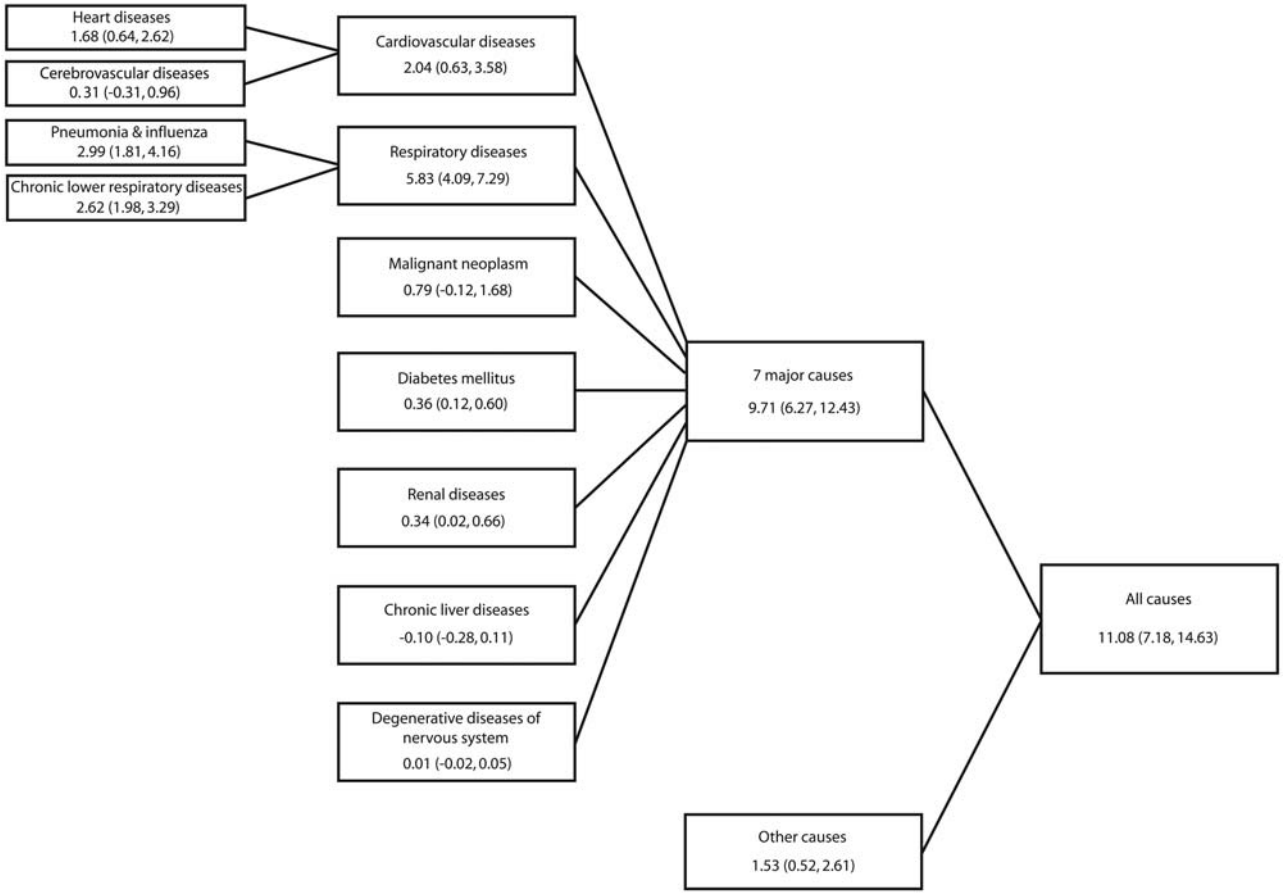

Figure 2. Breakdown of the estimated annual influenza-associated excess mortality rates (95% confidence intervals) from 7 major causes and all causes in Hong Kong from 1998 through 2009. Separate regression models were fitted for 4 subcategories of major causes, 7 major causes, the sum of the 7 major causes, other causes, and for all-cause mortality, with good consistency between the estimates. "Other causes" refers to the causes of death other than the 7 major causes shown in the Figure. The time series of deaths from other causes was derived by subtracting deaths from the 7 major causes from the all-cause deaths.

influenza and other viruses in the following years [34]. In years when there were 2 distinct seasons, the winter epidemic tended to have a greater impact on excess mortality than the summer epidemic (Table 1). One potential explanation for the reduced impact of the summer peak is a reduced overall infection attack rate. Another explanation could be a reduced severity profile of infections due to changes in host immunity [35], or for other reasons.

During the 2009 pandemic influenza A(H1N1), greatest incidence of infection was in children and young adults, while a substantial number of deaths were reported in young adults with confirmed infection [36]. However, we estimated that most of the pandemic influenza A(H1N1) associated excess deaths occurred among individuals ≥65 years. Other studies in Spain, Austria, and the Netherlands have also estimated excess deaths in the elderly despite the absence of laboratory-confirmed deaths in this age group [37–39] and low incidence of infection due to preexisting immunity [40]. This is consistent with increasing severity of influenza with age [40]. Similar observations have been made for seasonal influenza [6].

We did not have information on patterns in influenza vaccination coverage through our study period in Hong Kong, although vaccination has been subsidized in recent years. In addition to increasing vaccination coverage among the elderly, alternative strategies may need to be explored to reduce the annual burden of influenza [41]. The immunogenicity of inactivated vaccines is often suboptimal in elderly persons [42, 43]. Previous studies suggested that *Streptococcus pneumoniae* might be associated with many secondary bacterial pneumonias in influenza-infected patients, specifically, more severe cases [44], and a synergistic effect exists between influenza and pneumococcal infection [45]. Considering that pneumococcal vaccine is currently available in Hong Kong, increasing pneumococcal vaccination coverage among the elderly could be an effective way to further reduce influenza-associated

hospitalizations and deaths, although it might be considered unlikely that such a strategy could reduce all-cause deaths in the elderly by as much as 35% [46], since we estimated that only 2.6% of all deaths in the elderly were associated with influenza.

There are some limitations to our study. First, the current model only explained 83% of the variation in the all-cause deaths, and other unobserved factors such as changes in chronic diseases, epidemics of infectious diseases, or other environmental factors such as air pollution could also affect mortality rates in Hong Kong, although it is unclear if they would confound the estimates of influenza-associated excess mortality presented here. Second, our proxy measure of influenza activity, combining clinical and laboratory surveillance data, may not have accurately measured influenza incidence throughout the study period because of changes in sentinel reporting practices, laboratory testing procedures, changes in healthcare seeking behavior, or other reasons. However, our proxy measure was more closely correlated to estimated incidence of 2009 pandemic influenza A(H1N1) infection than clinical or laboratory surveillance data alone [40]. We did not have age-specific surveillance data on influenza-like illnesses or laboratory confirmations of influenza, and the use of aggregate surveillance data as the proxy of influenza activity in our study could have led to biases in the estimates of the impact of influenza in some age groups. Third, we did not have laboratory information on other respiratory viruses which might also affect influenza activity through virus interference [47–49], and could be associated with mortality rates [50]. However influenza and RSV are thought to have the most impact among all respiratory viruses. Fourth, the unavailability of data did not allow us to further investigate the impact of transition in coding system on the estimate of excess mortality, although a covariate has been included into the model to account for the changes in the trend of recorded mortality. Finally, the majority of influenza-associated excess deaths occurred in the elderly, and therefore the cause-specific analyses for all ages are mainly representative of deaths in this age group. Further investigation could clarify the age-specific patterns in cause-specific deaths associated with influenza.

In conclusion, our study confirmed the substantial annual burden of influenza virus in Hong Kong, primarily associated with respiratory and cardiovascular deaths in the elderly. The higher influenza-associated excess mortality in the elderly indicates that further improvements in influenza control measures are needed to reduce the impact of this infectious disease in Hong Kong.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/jid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Centers for Disease Control and Prevention. Estimates of deaths associated with seasonal influenza—United States, 1976–2007. MMWR Morb Mortal Wkly Rep **2010**; 59:1057–62.
2. Cohen C, Simonsen L, Kang J-W, et al. Elevated influenza-related excess mortality in South African elderly individuals, 1998–2005. Clin Infect Dis **2010**; 51:1362–9.
3. Viboud C, Alonso WJ, Simonsen L. Influenza in tropical regions. PLoS Med **2006**; 3:e89.
4. Wong CM, Chan KP, Hedley AJ, Peiris JS. Influenza-associated mortality in Hong Kong. Clin Infect Dis **2004**; 39:1611–7.
5. Simonsen L, Clarke MJ, Williamson GD, Stroup DF, Arden NH, Schonberger LB. The impact of influenza epidemics on mortality: introducing a severity index. Am J Public Health **1997**; 87:1944–50.
6. Finelli L, Chaves SS. Influenza and acute myocardial infarction. J Infect Dis **2011**; 203:1701–4.
7. Thompson WW, Comanor L, Shay DK. Epidemiology of seasonal influenza: use of surveillance data and statistical models to estimate the burden of disease. J Infect Dis **2006**; 194(Suppl 2):S82–91.
8. Simonsen L, Fukuda K, Schonberger LB, Cox NJ. The impact of influenza epidemics on hospitalizations. J Infect Dis **2000**; 181:831–7.
9. Dushoff J, Plotkin JB, Viboud C, Earn DJ, Simonsen L. Mortality due to influenza in the United States—an annualized regression approach using multiple-cause mortality data. Am J Epidemiol **2006**; 163:181–7.
10. Serfling R. Methods for current statistical analysis of excess pneumonia-influenza deaths. Public Health Rep **1963**; 78:494–506.
11. Thompson WW, Weintraub E, Dhankhar P, et al. Estimates of US influenza-associated deaths made using four different methods. Influenza Other Respi Viruses **2009**; 3:37–49.
12. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA **2003**; 289:179–86.
13. Thompson WW, Moore MR, Weintraub E, et al. Estimating influenza-associated deaths in the United States. Am J Public Health **2009**; 99(Suppl 2):S225–30.
14. Goldstein E, Viboud C, Charu V, Lipsitch M. Improving the estimation of influenza-related mortality over a seasonal baseline. Epidemiology **2012**; 23:829–38.

15. Gay NJ, Andrews NJ, Trotter CL, Edmunds WJ. Estimating deaths due to influenza and respiratory syncytial virus. JAMA **2003**; 289:2499.
16. Goldstein E, Cobey S, Takahashi S, Miller JC, Lipsitch M. Predicting the epidemic sizes of influenza A/H1N1, A/H3N2, and B: a statistical method. PLoS Med **2011**; 8:e1001051.
17. Cowling BJ, Wong IOL, Ho L-M, Riley S, Leung GM. Methods for monitoring influenza surveillance data. Int J Epidemiol **2006**; 35: 1314–21.
18. Shaman J, Kohn M. Absolute humidity modulates influenza survival, transmission, and seasonality. Proc Natl Acad Sci U S A **2009**; 106: 3243–8.
19. Dilaveris P, Synetos A, Giannopoulos G, Gialafos E, Pantazis A, Stefanadis C. Climate impacts on myocardial infarction deaths in the Athens territory: the CLIMATE study. Heart **2006**; 92:1747–51.
20. Keatinge WR, Donaldson GC, Cordioli E, et al. Heat related mortality in warm and cold regions of Europe: observational study. BMJ **2000**; 321:670–3.
21. Ahmad OB, Boschi-Pinto C, Lopez AD, Murray CJL, Lozano R, Inoue M. Age standardization of rates: a new WHO standard. GPE discussion paper No. 31. Geneva: World Health Organization, **2001**.
22. Yang L, Ma S, Chen PY, et al. Influenza associated mortality in the subtropics and tropics: results from three Asian cities. Vaccine **2011**; 29:8909–14.
23. Gurevich VS. Influenza, autoimmunity and atherogenesis. Autoimmun Rev **2005**; 4:101–5.
24. Epstein SE, Zhou YF, Zhu J. Infection and atherosclerosis: emerging mechanistic paradigms. Circulation **1999**; 100:e20–8.
25. Lee ET, Keen H, Bennett PH, Fuller JH, Lu M. Follow-up of the WHO multinational study of vascular disease in diabetes: general description and morbidity. Diabetologia **2001**; 44(Suppl 2):S3–13.
26. Xu J, Kochanek KD, Murphy SL, Tejada-Vera B. Deaths: Final data for 2007, National Vital Statistics Reports. **2010**.
27. Frank AL, Taber LH, Wells JM. Comparison of infection rates and severity of illness for influenza A subtypes H1N1 and H3N2. J Infect Dis **1985**; 151:73–80.
28. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. JAMA **2004**; 292:1333–40.
29. Memoli MJ, Jagger BW, Dugan VG, Qi L, Jackson JP, Taubenberger JK. Recent human influenza A/H3N2 virus evolution driven by novel selection factors in addition to antigenic drift. J Infect Dis **2009**; 200:1232–41.
30. Wright PF, Thompson J, Karzon DT. Differing virulence of H1N1 and H3N2 influenza strains. Am J Epidemiol **1980**; 112:814–9.
31. Rambaut A, Pybus OG, Nelson MI, Viboud C, Taubenberger JK, Holmes EC. The genomic and epidemiological dynamics of human influenza A virus. Nature **2008**; 453:615–9.
32. Morens DM, Burke DS, Halstead SB. The wages of original antigenic sin. Emerg Infect Dis **2010**; 16:1023–4.
33. Lo JY, Tsang TH, Leung YH, Yeung EY, Wu T, Lim WW. Respiratory infections during SARS outbreak, Hong Kong, 2003. Emerg Infect Dis **2005**; 11:1738–41.
34. Mak GC, Wong AH, Ho WY, Lim W. The impact of pandemic influenza A(H1N1) 2009 on the circulation of respiratory viruses 2009–2011. Influenza Other Respi Viruses **2012** [Epub ahead of print].
35. Yang L, Wong C, Chan K, et al. Seasonal effects of influenza on mortality in a subtropical city. BMC Infect Dis **2009**; 9:133.
36. Van Kerkhove MD, Vandemaele KAH, Shinde V, et al. Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis. PLoS Med **2011**; 8:e1001053.
37. Castilla J, Etxeberria J, Ardanaz E, Floristan Y, Lopez Escudero R, Guevara M. Estimating the impact of the 2009 influenza A(H1N1) pandemic on mortality in the elderly in Navarre, Spain. Euro Surveill **2010**; 15:pii/19481.
38. Redlberger-Fritz M, Aberle J, Popow-Kraupp T, Kundi M. Attributable deaths due to influenza: a comparative study of seasonal and pandemic influenza. Eur J Epidemiol **2012**; 27:567–75.
39. van den Wijngaard CC, van Asten L, Koopmans MPG, et al. Comparing pandemic to seasonal influenza mortality: moderate impact overall but high mortality in young children. PLoS One **2012**; 7:e31197.
40. Wong JYT, Wu P, Nishiura H, et al. The infection fatality risk of pandemic influenza A(H1N1) in Hong Kong in 2009. Am J Epidemiol. In press.
41. Simonsen L, Taylor RJ, Viboud C, Miller MA, Jackson LA. Mortality benefits of influenza vaccination in elderly people: an ongoing controversy. Lancet Infect Dis **2007**; 7:658–66.
42. Kumar R, Burns EA. Age-related decline in immunity: implications for vaccine responsiveness. Expert Rev Vaccines **2008**; 7:467–79.
43. Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: a quantitative review. Vaccine **2006**; 24:1159–69.
44. Grijalva CG, Griffin MR. Unveiling the burden of influenza-associated pneumococcal pneumonia. J Infect Dis **2012**; 205:355–7.
45. McCullers JA, McAuley JL, Browall S, Iverson AR, Boyd KL, Henriques Normark B. Influenza enhances susceptibility to natural acquisition of and disease due to *Streptococcus pneumoniae* in ferrets. J Infect Dis **2010**; 202:1287–95.
46. Hung IFN, Leung AYM, Chu DWS, et al. Prevention of acute myocardial infarction and stroke among elderly persons by dual pneumococcal and influenza vaccination: a prospective cohort study. Clin Infect Dis **2010**; 51:1007–16.
47. Anestad G. Interference between outbreaks of respiratory syncytial virus and influenza virus infection. Lancet **1982**; 1:502.
48. Glezen WP, Paredes A, Taber LH. Influenza in children. Relationship to other respiratory agents. JAMA **1980**; 243:1345–9.
49. Cowling BJ, Fang VJ, Nishiura H, et al.. Increased risk of noninfluenza respiratory virus infections associated with receipt of inactivated influenza vaccine. Clin Infect Dis **2012**; 54:1778–83.
50. Ruuskanen O, Lahti E, Jennings LC, Murdoch DR. Viral pneumonia. Lancet **2011**; 377:1264–75.