Influenza-associated mortality in temperate and subtropical Chinese cities, 2003–2008

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Objective To estimate influenza-associated mortality in urban China.
Methods Influenza-associated excess mortality for the period 2003–2008 was estimated in three cities in temperate northern China and five cities in the subtropical south of the country. The estimates were derived from models based on negative binomial regressions, vital statistics and the results of weekly influenza virus surveillance.
Findings Annual influenza-associated excess mortality, for all causes, was 18.0 (range: 10.9–32.7) deaths per 100 000 population in the northern cities and 11.3 (range: 7.3–17.8) deaths per 100 000 in the southern cities. Excess mortality for respiratory and circulatory disease was 12.4 (range: 7.4–22.2) and 8.8 (range: 5.5–13.6) deaths per 100 000 people in the northern and southern cities, respectively. Most (86%) deaths occurred among people aged ≥ 65 years. Influenza-associated excess mortality was higher in B-virus-dominant seasons than in seasons when A(H3N2) or A(H1N1) predominated, and more than half of all influenza-associated mortality was associated with influenza B virus.
Conclusion Between 2003 and 2008, seasonal influenza, particularly that caused by the influenza B virus, was associated with substantial mortality in three cities in the temperate north of China and five cities in the subtropical south of the country.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

Influenza is one of the most prevalent vaccine-preventable diseases. Every year it causes an estimated 3 million cases of illness and from 250 000 to 500 000 deaths throughout the world.[1] Influenza poses a particular risk of severe or fatal outcomes in the elderly, the very young and those with underlying chronic medical conditions.[2] In temperate regions in both the northern[3–13] and southern hemispheres,[14–16] epidemics of seasonal influenza in winter often lead to dramatic increases in hospitalizations and mortality. Although little information is available on the burden posed by influenza in tropical and subtropical regions,[17,18] the disease is thought to be responsible for substantial morbidity and mortality in the subtropical Hong Kong Special Administrative Region (SAR), and in tropical Singapore and Thailand.[19–24] Only a few estimates of the burden posed by influenza-associated mortality in low- and middle-income countries have been published.[14,16]

As few cases of influenza undergo laboratory confirmation, deaths caused by influenza may go unrecognized and be attributed to co-morbidities or to secondary complications of the infection.[25,26] For several decades, the mortality attributable to influenza has therefore been estimated using statistical models and the elevations in mortality (i.e. the "excess" mortalities) recorded during seasonal epidemics of influenza.[3–15,18–23] Such estimates can be useful in identifying high-risk groups and in guiding vaccination policy.

China is a lower middle-income country whose population of 1.3 billion people is the largest in the world. The general perception that seasonal influenza does not cause substantial mortality in China may contribute to the underutilization of influenza vaccines in the country.[27] In this study, we used the results of the city-wide registration of vital statistics and weekly viral surveillance to estimate the influenza-associated mortality that occurred in eight Chinese cities between 2003 and 2008.

Methods

Mortality data and population denominators

As China has no national system for the registration of vital statistics, we focused on eight cities (Appendix A, available at: http://www.chinacdc.cn/xiazai/Feng-BullWorldHealthOrgan-2012-AppendixA.pdf) with high-quality, population-based systems for mortality registration and low rates of underreporting and misclassification in the study period (2003–2008). Three of the cities (Dalian, Qingdao and Zhaoyuan) lie in the temperate north of China and have a combined population

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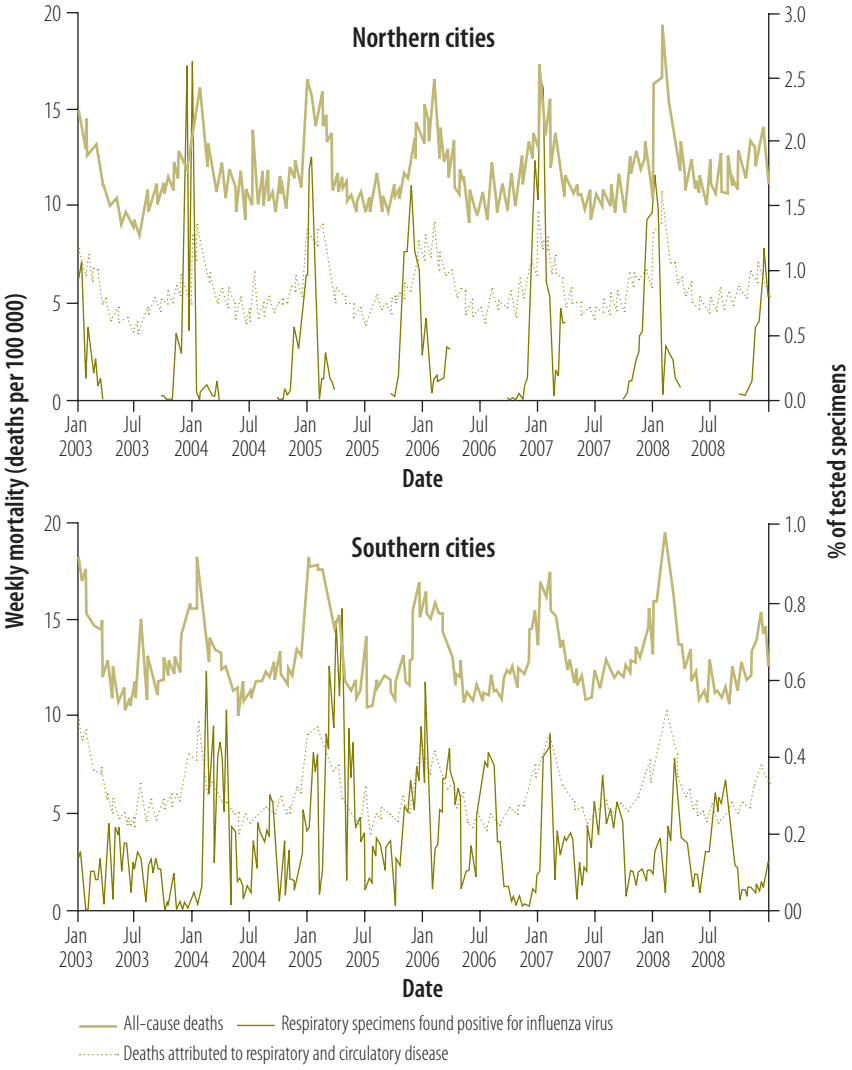
of about 10 million. The other five cities (Shanghai, Wuhan, Yichang, Ningbo and Guangzhou) are in the subtropical south and have a combined population of about 21 million. Underlying cause-of-death data were manually coded and verified by locally trained coders using the 10th revision of the International Classification of Diseases (ICD-10).[28] Coding practices were based on a standardized protocol, and quality control and assurance were conducted routinely by staff from the Centre for Disease Control (CDC) in each location. As the data were not adjusted for underreporting, the estimated mortality rates that are reported below represent minimum values.[29] As in previous studies,[4,19–22] we obtained separate data for deaths from all causes and for deaths attributed to pneumonia and influenza (ICD-10 codes J10–J18), respiratory and circulatory disease (codes J00–J99 or I00– I99), ischaemic heart disease (codes I20–I25) and chronic obstructive pulmonary disease (codes J40–J47). Mortality was stratified by year, week of death occurrence and two age groups (0–64 years and ≥ 65 years).

Influenza virological surveillance

National surveillance of influenza-like illness (ILI) was launched in China in 2000. During the period investigated in the present study, sentinel hospitals reported the numbers of total outpatient visits and the numbers of visits by outpatients with ILI, either weekly throughout the year (in the 99 sentinel hospitals in the 15 subtropical southern provinces) or once a week in the cooler months of October to March (in the 94 sentinel hospitals in the 15 temperate northern provinces). These numbers were recorded on a centralized online system maintained by the Chinese Centre for Disease Control and Prevention in Beijing. In each sentinel hospital, on each day of the weeks in which surveillance data were recorded, respiratory specimens were collected from the first one or two ILI cases. This produced 10–15 such specimens per hospital per surveillance week. The specimens were sent to one of the 62 province- or prefecture-level CDCs and there they were tested for influenza virus using the protocols and kits released by the Chinese National Influenza Centre (a World Health Organization Collaborating Centre for Reference and Research on Influenza). As only sparse virological surveillance data were available for the cities we were investigating, the surveillance data for the temperate northern provinces and subtropical southern provinces (Appendix A) were aggregated to represent the influenza circulation patterns in the northern and southern study cities, respectively. An influenza type or subtype (A/H3N2, A/H1N1 or B) was considered dominant during an influenza season when it accounted for at least 50% of the respiratory specimens that were typed.

Fig. 1. **Deaths attributed to respiratory and circulatory disease, all-cause deaths and specimen positivity to influenza viruses, China, 2003–2008**



Note: The upper and lower panels show the results for the three northern cities and five southern cities, respectively.

Influenza-associated excess mortality

Our main estimates are based on negative binomial regression models applied to the mortality and virological surveillance data for the eight study cities.[22] As a sensitivity analysis, we also applied Serfling regression models to the mortality data for the three northern cities, each of which showed an obvious peak in influenza activity during each winter in the study period (Fig. 1). A brief description of the methodological approach is presented below but more details can be found in Appendix A.

We applied negative binomial regression models, separately for each disease outcome, the two age groups and the northern and southern cities, using weekly mortality counts as the outcome and the weekly proportions of respiratory specimens testing positive for influenza A(H1N1), A(H3N2) or B as the explanatory variables. The models included terms for seasonality, time trends and weekly population-size offsets, and they used an identity link.

Compared with the over-dispersion of Poisson regression models, negative binomial models provided a better goodness of fit.[30] Viral surveillance data were lagged by 0 to 3 weeks; the optimum lag (3 weeks for all death outcomes) was identified by computing Pearson coefficients (r) for the correlations with mortality outcomes (without any filtering).[19,20] Influenza-associated excess deaths were estimated separately for influenza A(H1N1), A(H3N2) and B viruses (Fig. 1).

Since no surveillance for respiratory syncytial virus was conducted, no term for this pathogen was included in the model. As influenza circulated year-round in the subtropical southern provinces (Fig. 1), we used a spectral-analysis approach to decide whether the use of one or two periods in the model for the southern cities was preferable.[31] Based on the results, we used 26- and 52-week periods for that model. The number of deaths attributable to influenza was calculated as the difference between the predictions from the full model and the predictions from the model with the covariates for every influenza subtype set to zero (Appendix A).

A Serfling regression model was used to provide an alternative estimate of influenza-associated mortality in the northern cities.[9,10] In this approach, the baseline mortality in the absence of influenza virus circulation was established by fitting a seasonal linear regression model, after excluding periods with high influenza activity (i.e. weeks 44–52 and 1–8; Fig. 1).

Epidemic weeks were defined as those weeks during each influenza season (weeks 40–52 and 1–13) when the observed number of deaths exceeded the epidemic threshold (defined as the upper 95% confidence limit on the baseline) for two or more consecutive weeks. Rates of weekly excess mortality were calculated as the observed mortality minus the baseline for all epidemic weeks (Appendix A). Seasonal excess mortality was then estimated as the sum of the weekly excess mortalities. Although all model terms representing linear and nonlinear time trends yielded statistical significance ($P < 0.05$), the terms representing seasonal fluctuations did not ($P > 0.05$). Overall, the Serfling regression models for the three northern cities fitted the mortality data for people aged ≥ 65 years moderately well when the deaths analysed were those coded as respiratory and circulatory disease ($R^2 = 0.57$; fit excluding winter weeks), ischaemic heart disease ($R^2 = 0.61$), chronic obstructive pulmonary disease ($r = 0.36$) or any cause ($R^2 = 0.51$), but they only gave a poor fit with deaths attributed to pneumonia and influenza ($R^2 = 0.04$). For people aged < 65 years, the R^2 values for each death category were generally lower, having ranged from 0.16 to 0.27, and the fit with the data on deaths coded as pneumonia and influenza was too poor to yield statistical significance.

Wilcoxon signed-rank tests were used to compare the annual mean death rates for the three northern cities that were estimated using the negative binomial model with: (i) the corresponding estimates from the Serfling model, and (ii) the rates in the five southern cities that were also estimated using the negative binomial model.

Version 9.1 of the SAS software package (SAS Institute, Cary, USA) was used for all the statistical analyses. A P-value of < 0.05 was considered indicative of a statistically significant difference.

Results

Mortality

Between 2003 and 2008, the mean annual mortality rates, in deaths per 100 000 population, were 618 (range: 581–659) in the three northern cities and 692 (range: 673–708) in the five southern cities. Most of the deaths (69.6% in the northern cities and 77.8% in the southern) occurred among individuals aged ≥ 65 years. The coded cause of almost half of all deaths (49.0% in the northern cities and 46.2% in the southern cities) was respiratory and circulatory disease (Table 1, available at: http://www.who.int/bulletin/volumes/90/4/11-096958). Death rates for the other disease outcomes varied between the southern and northern cities, with the northern cities recording relatively high numbers of deaths attributed to ischaemic heart disease or pneumonia and influenza and relatively low numbers of deaths attributed to chronic obstructive pulmonary disease. In all the study cities, the underlying cause of death was rarely coded as influenza.

During the 6-year study period, all categories of death peaked in the winter months in each city that was investigated. A second peak in mortality was observed in the southern cities in June and July (Fig. 1 and Appendix A). In general, annual death rates were relatively constant throughout the study period. However, the annual mortality attributed to ischaemic heart disease in the northern cities increased over the study period (the linear regression of death rate against week gave a P-value of < 0.01), while that attributed to chronic obstructive pulmonary disease in southern cities showed a significant decrease ($P < 0.01$). Influenza virus activity in the three temperate northern cities showed marked seasonality matching mortality patterns, whereas influenza apparently circulated year-round in the five subtropical southern cities, with no clear seasonality (Fig. 1).

Influenza-associated excess deaths

Negative binomial models

The negative binomial models indicated that, for the period 2003–2008, the mean annual numbers of influenza-associated all-cause excess deaths in the northern cities and southern study cities were 1825 (range: 1103–3397) and 2446 (range: 1551–3844), respectively. The corresponding annual mortality in the northern cities was higher than that in the southern cities (18.0 versus 11.3 influenza-associated excess deaths per 100 000 persons), but the difference did not quite reach statistical significance in a Wilcoxon signed-rank test ($P = 0.063$; Table 2). Most influenza-associated excess deaths (93.7% and 86.3% of those in the northern and southern cities, respectively) occurred among people aged ≥ 65 years, and the rates of influenza-associated excess mortality in this age group were much higher than among younger individuals, in both the northern study cities (150.8 versus 1.3 deaths per 100 000) and the southern cities (75.4 versus 1.8 per 100 000).

The rates of influenza-associated mortality attributed to respiratory and circulatory disease were higher in northern than in southern cities (12.4 versus 8.8 deaths per 100 000) but, again, the difference did not reach statistical significance in a Wilcoxon signed-rank test ($P = 0.091$). Almost all of the influenza-associated deaths attributed to respiratory and circulatory disease occurred among people aged ≥ 65 years in both the northern (95.7%) and southern (94.0%) cities, and the corresponding mortality rates were higher in people aged ≥ 65 years than in younger individ-

Table 2. **Influenza-associated excess deaths in eight cities, by age and coded[a] cause of death, China, 2003–2008**

Season	No. of epidemic weeks	Three northern cities[b] (Serfling model)				Three northern cities[b] (negative binomial model)				Five southern cities[c] (negative binomial model)			
		Total[d]		Age ≥ 65 years		Total[d]		Age ≥ 65 years		Total[d]		Age ≥ 65 years	
		No. (CI)	Rate[e] (CI)	No. (CI)	% of total	No. (CI)	Rate[e] (CI)	No. (CI)	% of total	No. (CI)	Rate[e] (CI)	No. (CI)	% of total
R&C													
2002–03[f]	7	1154 (432–1960)	23.6 (8.8–40.1)	1030 (430–1630)	89.2	480 (156–2098)	9.8 (3.2–42.9)	461 (156–1723)	96.0	562 (0–3539)	5.3 (0–33.2)	534 (0–3219)	95.0
2003–04	7	1249 (539–2056)	12.7 (5.5–20.9)	1136 (536–1736)	90.9	945 (515–4360)	9.6 (5.2–44.2)	918 (515–3574)	97.1	1186 (206–6844)	5.5 (1.0–32.0)	1146 (206–6135)	96.6
2004–05	9	1664 (807–2688)	16.6 (8.1–26.9)	1588 (807–2368)	95.4	1493 (732–4606)	14.9 (7.3–46.0)	1432 (732–3868)	95.9	3018 (790–8887)	14.0 (3.7–41.3)	2847 (767–7984)	94.3
2005–06	4	736 (256–1223)	7.2 (2.5–12.1)	529 (162–896)	71.9	751 (90–4138)	7.4 (0.9–40.8)	704 (90–3270)	93.7	2020 (588–7441)	9.3 (2.7–34.3)	1873 (565–6556)	92.7
2006–07	6	1031 (430–1762)	10.0 (4.2–17.2)	993 (430–1557)	96.3	1450 (490–4806)	14.1 (4.8–46.8)	1384 (490–4010)	95.4	1379 (67–6747)	6.3 (0.3–30.9)	1305 (67–6021)	94.6
2007–08	9	2296 (1 278–3439)	22.1 (12.3–33.1)	2079 (1 211–2946)	90.5	2309 (1 198–6164)	22.2 (11.5–59.4)	2210 (1 198–5238)	95.7	3018 (760–9093)	13.6 (3.4–41.1)	2803 (738–8176)	92.9
2008–09[f]	0	0 (0–0)	0 (0–0)	0 (0–0)	0	111 (0–2157)	2.1 (0–41.4)	104 (0–1728)	93.7	310 (0–3165)	2.8 (0–28.3)	292 (0–2845)	94.2
Mean	7	1355 (624–2188)	13.4 (6.2–21.6)	1226 (596–1855)	90.5	1257 (530–4722)	12.4 (5.2–46.6)	1202 (530–3902)	95.7	1916 (402–7619)	8.8 (1.8–35.1)	1800 (391–6823)	94.0
All-cause													
2002–03[f]	7	1823 (659–3164)	37.3 (13.5–64.7)	1527 (633–2421)	83.7	748 (248–3496)	15.3 (5.1–71.5)	695 (248–2645)	92.9	700 (15–4503)	6.6 (0.1–42.3)	598 (15–3630)	85.4
2003–04	6	1562 (538–2707)	15.8 (5.5–27.5)	1297 (530–2063)	83.0	1346 (642–6941)	13.7 (6.5–70.4)	1219 (642–5191)	90.6	1551 (64–10 248)	7.3 (0.3–47.9)	1285 (64–8226)	82.8
2004–05	9	2322 (1 012–3955)	23.2 (10.1–39.5)	2177 (1 012–3341)	93.7	2154 (1 026–7146)	21.5 (10.2–71.4)	2011 (1 026–5587)	93.4	3829 (568–13 077)	17.8 (2.6–60.8)	3291 (564–10 611)	85.9
2005–06	2	417 (43–821)	4.1 (0.4–8.1)	308 (34–582)	73.9	1103 (194–6297)	10.9 (1.9–62.1)	1075 (194–4795)	97.5	2604 (551–10 968)	12.0 (2.5–50.6)	2280 (544–8660)	87.6
2006–07	2	515 (179–925)	5.0 (1.7–9.0)	458 (179–738)	89.0	2026 (618–7241)	19.7 (6.0–70.5)	1888 (618–5655)	93.2	1753 (14–9864)	8.0 (0.1–45.2)	1511 (14–7843)	86.2
2007–08	10	3721 (1 857–5802)	35.8 (17.9–55.9)	3170 (1 733–4606)	85.2	3397 (1 778–9563)	32.7 (17.1–92.1)	3198 (1 778–7614)	94.1	3844 (646–13 101)	17.4 (2.9–59.2)	3355 (641–10 746)	87.3

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Season	No. of epidemic weeks	Three northern cities[b] (Serfling model)				Three northern cities[b] (negative binomial model)				Five southern cities[f] (negative binomial model)			
		Total[d]		Age ≥ 65 years		Total[d]		Age ≥ 65 years		Total[d]		Age ≥ 65 years	
		No. (CI)	Rate[e] (CI)	No. (CI)	% of total	No. (CI)	Rate[e] (CI)	No. (CI)	% of total	No. (CI)	Rate[e] (CI)	No. (CI)	% of total
Mean	6	1727 (715–2896)	17.0 (7.1–28.6)	1489 (687–2292)	86.3	1825 (751–7383)	18.0 (7.4–72.9)	1711 (751–5701)	93.7	2446 (310–10 940)	11.3 (1.4–50.4)	2111 (307–8781)	86.3

CI: 95% confidence interval; R&C: respiratory and circulatory disease.

[a] *International statistical classification of diseases and related health problems*; tenth revision.[28]

[b] Dalian, Qingdao and Zhaoyuan.

[c] Guangzhou, Ningbo, Shanghai, Wuhan and Yichang.

[d] The sum of the estimates of excess influenza-associated deaths for the people aged < 65 years and the people ≥ 65 years.

[e] In deaths per 100 000.

[f] Because the study was based on data collected between the start of 2003 and the end of 2008, only the results for the last half of the 2002–03 season (i.e. January 2003 to June 2003) and the first half of the 2008–09 season (i.e. July 2008 to December 2008) are included.

uals. In general, the influenza-associated mortality attributed to other causes linked to influenza (i.e. ischaemic heart disease, chronic obstructive pulmonary disease and pneumonia and influenza) showed similar age- and region-specific patterns, although the mortality attributed to chronic obstructive pulmonary disease was higher in the southern cities than in the northern ones (Appendix A).

The influenza-associated excess all-cause mortality and the corresponding excess mortality attributed to respiratory and circulatory disease showed season-to-season variability. Most influenza-associated excess deaths were associated with the B or A(H3N2) viruses; only 11% of such deaths in the northern cities investigated and no such deaths in the southern cities were associated with A(H1N1) (Table 3). Of the influenza-associated excess deaths, a greater proportion was associated with the B virus than with A(H3N2), both in the northern cities (49.6% versus 39.7% for respiratory and circulatory disease; 50.9% versus 38.2% for all-cause) and in the southern ones (66.1% versus 33.9% for respiratory and circulatory disease; 64.8% versus 35.2% for all-cause). However, the corresponding *P*-values from Wilcoxon signed-rank tests (0.735, 0.735, 0.128 and 0.176, respectively) were all too high to indicate statistical significance.

The rate of influenza B-associated excess mortality in the B-predominant season (2007–2008) was about double that of the A(H3N2)-associated mortality in the A(H3N2)-predominant seasons (i.e. the 2003–2004 and 2006–2007 seasons in the northern cities and the 2003–2004 and 2004–2005 seasons in the southern cities) and much higher than the A(H1N1)-associated mortality in the A(H1N1)-predominant season (2005–2006; Table 3). This pattern was observed in both age groups that we considered and in both the northern and southern cities (Appendix A). In both the northern and the southern cities, the excess rates of all-cause mortality and of mortality attributed to respiratory and circulatory disease were positively correlated with the percentages of specimens testing positive for influenza B (Fig. 2).

Serfling models

The age-specific rates of influenza-associated excess mortality that were estimated using Serfling models were similar to those derived using negative binomial models (Wilcoxon signed-rank tests, $P > 0.05$; Table 2 and Appendix A). Most of the excess deaths estimated using Serfling models (86.3% of the all-cause deaths and 90.5% of those attributed to respiratory and circulatory disease) occurred among people aged ≥ 65 years.

Discussion

Our findings demonstrate that influenza activity is associated with excess deaths in China – a lower middle-income country with the world's largest population and diverse climate patterns. Our estimates of the annual rates for total influenza-associated all-cause mortality and for influenza-associated mortality attributed to respiratory and circulatory disease in eight Chinese cities are similar to estimates from other countries.[3–5,10–12,15,16,19,21,22] The impact of seasonal influenza on mortality in China disproportionately affects people aged ≥ 65 years (e.g. between 2003 and 2008, > 85% of the influenza-associated deaths in the study cities occurred in this age group). This finding is consistent with observations made in Hong Kong SAR,[19] Singapore[22] and the United States of America,[4] where about 90% of influenza-associated deaths have been found to occur among the elderly.

In the temperate study areas of northern China, where influenza circulation is strongly seasonal, we used both Serfling and negative binominal models to estimate the excess mortality associated with influenza. The fact that these two approaches produced similar estimates for all-cause mortality and for mortality associated with respiratory and circulatory disease demonstrates the robustness of our results. The coding of very few deaths as having been caused by pneumonia and influenza in China may explain why the fit of the Serfling models to the data on such deaths was particularly poor.

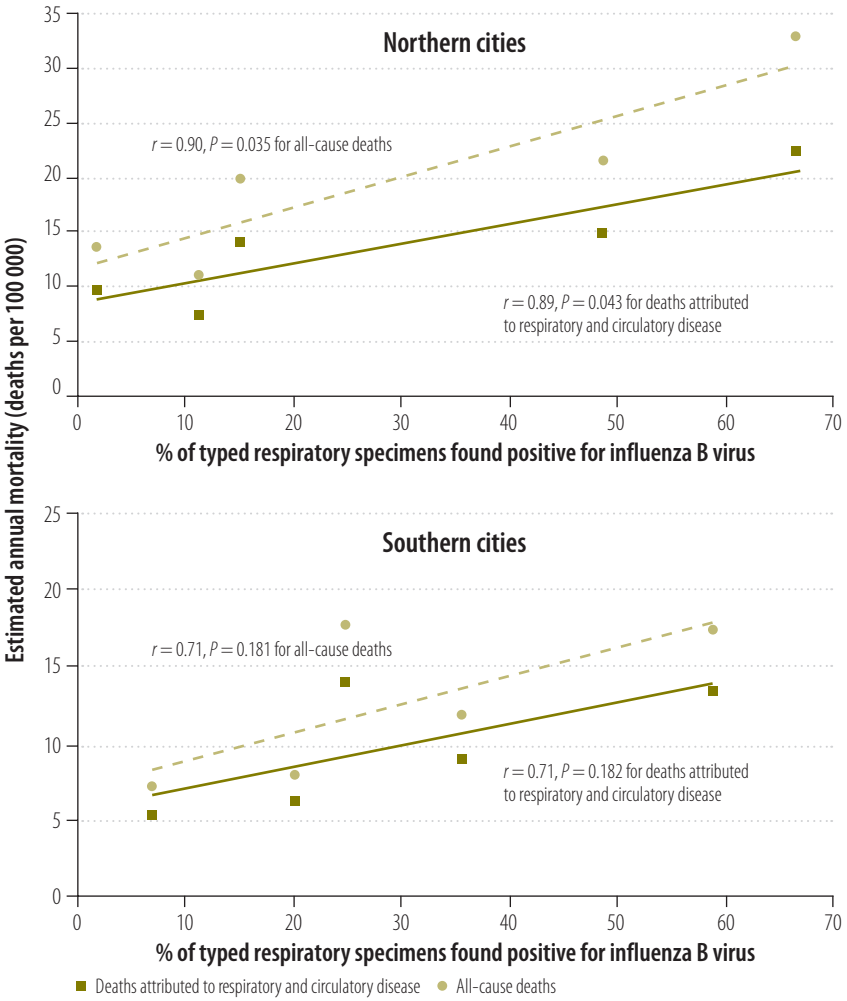
The rate of influenza-associated mortality in the temperate study areas was higher than that in the subtropical study areas farther south, particularly among the elderly. Among the possible explanations for this difference are regional variation in socioeconomic and demographic factors; the reporting of vital statistics, and influenza seasonality. The estimates of excess influenza-associated mortality made in the present study are similar to the corresponding estimates published for temperate Australia,[15] Italy,[11,12] Mexico[16] and the United

Table 3. **Influenza-associated excess mortality in eight cities, by influenza virus type and subtype, China, 2003–2008**

Season	Positive respiratory specimens (%)			No. (%) of excess deaths per 100 000 people with death coded as:							
				Respiratory and circulatory disease				All-cause			
	A(H1N1)	A(H3N2)	B	All	A(H1N1)	A(H3N2)	B	All	A(H1N1)	A(H3N2)	B
Three northern cities[a]											
2002–03[b]	4.3	54.3	41.4	9.8	0.1 (1.3)	3.8 (39.2)	5.8 (59.6)	15.3	0.2 (1.2)	5.8 (38.0)	9.3 (60.8)
2003–04	3.4	94.7	1.8	9.6	0.2 (1.6)	9.1 (95.3)	0.3 (3.1)	13.7	0.2 (1.6)	13.0 (94.9)	0.5 (3.4)
2004–05	2.2	49.1	48.7	14.9	0.1 (0.7)	5.2 (35.1)	9.6 (64.2)	21.5	0.2 (0.8)	7.2 (33.6)	14.1 (65.6)
2005–06	81.3	7.7	11.1	7.4	4.3 (58.1)	0.8 (11.3)	2.3 (30.6)	10.9	6.2 (57.5)	1.2 (11.2)	3.4 (31.4)
2006–07	31.7	53.2	15.0	14.1	2.2 (15.9)	7.8 (55.5)	4.0 (28.6)	19.7	3.2 (16.2)	10.6 (53.9)	5.9 (29.9)
2007–08	1.2	32.3	66.5	22.2	0.0 (0.2)	4.7 (21.1)	17.5 (78.7)	32.7	0.1 (0.3)	6.6 (20.0)	26.1 (79.7)
2008–09[b]	97.2	2.3	0.5	2.1	2.0 (93.7)	0.1 (3.6)	0.1 (2.7)	3.4	3.2 (95.5)	0.1 (2.8)	0.1 (1.7)
Mean	38.5	33.9	27.6	12.4	1.3 (10.7)	4.9 (39.7)	6.2 (49.6)	18.0	2.0 (10.9)	6.9 (38.2)	9.2 (50.9)
Five southern cities[c]											
2002–03[b]	4.0	74.0	22.0	5.3	0 (0)	2.3 (44.0)	3.0 (56.0)	6.6	0 (0)	3.1 (46.7)	3.5 (53.3)
2003–04	0.0	93.2	6.8	5.5	0 (0)	4.5 (82.0)	1.0 (18.0)	7.3	0 (0)	6.0 (82.3)	1.3 (17.7)
2004–05	8.7	66.3	24.9	14.0	0 (0)	5.8 (41.7)	8.2 (58.3)	17.8	0 (0)	7.8 (43.7)	10.0 (56.3)
2005–06	53.2	11.1	35.7	9.3	0 (0)	1.0 (10.6)	8.3 (89.4)	12.0	0 (0)	1.4 (12.1)	10.6 (87.9)
2006–07	35.0	44.7	20.3	6.3	0 (0)	2.9 (45.3)	3.5 (54.7)	8.0	0 (0)	3.6 (44.8)	4.4 (55.2)
2007–08	5.7	35.2	59.1	13.6	0 (0)	2.3 (16.9)	11.3 (83.1)	17.4	0 (0)	3.1 (17.8)	14.3 (82.2)
2008–09[b]	71.3	12.9	15.8	2.8	0 (0)	0.6 (23.2)	2.1 (76.8)	3.5	0 (0)	0.9 (25.7)	2.6 (74.3)
Mean	29.7	38.9	31.4	8.8	0 (0)	3.0 (33.9)	5.8 (66.1)	11.3	0 (0)	4.0 (35.2)	7.3 (64.8)

[a] Dalian, Qingdao and Zhaoyuan.
[b] Because the study was based on data collected between the start of 2003 and the end of 2008, only the results for the last half of the 2002–03 season (i.e. January 2003 to June 2003) and the first half of the 2008–09 season (i.e. July 2008 to December 2008) are included.
[c] Guangzhou, Ningbo, Shanghai, Wuhan and Yichang.

Fig. 2. **Estimates of influenza-associated mortality plotted against specimen positivity for influenza B virus, China, 2003–2008**



Note: The upper and lower panels show the results for the three northern cities (Dalian, Qingdao and Zhaoyuan) and the five southern cities (Guangzhou, Ningbo, Shanghai, Wuhan and Yichang), respectively.

States,[3–5,10] the subtropical city of Guangzhou in China,[21] subtropical Hong Kong SAR[19] and tropical Singapore[22] (Table 4, available at: http://www.who.int/bulletin/volumes/90/4/11-096958). However, at least three issues must be considered when comparing our results with those of other studies: the presence or absence of other variables, such as indicators of respiratory syncytial virus activity, in the model used[4,22]; differences in the study periods, each with distinct influenza activities and dominant strains; and potential differences in the quality of the viral surveillance and mortality data used.

Our most interesting findings were that influenza-associated death rates were highest during periods when influenza B virus was circulating, rather than during periods when A(H3N2) was dominant, and that very few or no deaths were associated with the A(H1N1) virus. These results differ substantially from the mortality patterns seen in Hong Kong SAR and the United States,[4,9,10,19] where the highest death rates were associated with A(H3N2) activity. However, our results should be treated with caution since they are based on data collected over only five influenza seasons. The prevalence of influenza B during the study period may have been unusually high, and the patterns of influenza seasonality and circulation in China appear to be complex. Additional studies exploring the association between influenza B and mortality are warranted in China and other parts of the world. Limited information is available on the clinical severity of influenza B infections in China, and, unfortunately, too few young children were included in our study to give a reasonable estimate of influenza B-associated mortality in this age group. Further studies in subtropical southern China would be very interesting in this respect, as influenza viruses there circulate year-round, with peaks in both summer and winter months and a complex cycling of subtypes. Additionally, surveillance data for other respiratory viral and bacterial infections, including respiratory syncytial virus, are crucial if the patterns of influenza-related mortality in China are to be fully elucidated.

Our study has several potential limitations. Even in the large urban cities that we investigated, some deaths during the study period were probably not registered and the recorded underlying causes of some of the registered deaths were probably not specific enough to be coded accurately.[29,32,33] Such underreporting and misclassification of deaths could lead to the underestimation of influenza-associated excess mortality in China. Our estimates of the influenza-associated excess mortalities attributed to pneumonia and influenza are much lower than those reported from more developed countries, probably owing to between-country differences in coding practices for diseases of the lower respiratory tract.[4,5,10,12,19,22] In addition, as influenza virus surveillance in China gradually expanded between 2000 and 2005, year-to-year variations in surveillance coverage and/or laboratory methods may have influenced our estimates, despite our attempts to adjust for the annual number of specimens tested for influenza. Finally, given the substantial regional differences in climate, access to medical care and socioeconomic determinants of health, as well as the disparities between urban and rural areas, our estimates based on mortality data from eight relatively wealthy cities in eastern China may not be generalizable to the rest of the country.

This study highlights the substantial mortality associated with influenza in both temperate and subtropical areas of China. The findings have important implications for China's strategies to prevent and control influenza. First, our results contrast with the general perception that influenza is not an important contributor to mortality in China. Second, they support the recommendation issued by the Chinese Centre for Disease Control and Prevention to practice annual influenza vaccination of the elderly (as the target population at the greatest

risk of developing severe complications from influenza infections).[34] Third, the finding that seasons in which influenza B virus dominates are associated with relatively high mortality deserves special attention and scrutiny, and it suggests the need to improve seasonal surveillance and characterization of influenza B virus variants. Our strategy of using the mortality data available for a period of about 5 years from large cities to model influenza-associated deaths may be applicable in other countries that lack national mortality registration.

The present estimates of seasonal influenza-associated deaths in selected urban cities represent only the first step in quantifying the burden posed by influenza in China. The next steps include describing the impact on mortality of infection with A(H1N1)pdm09 and a more comprehensive assessment of seasonal influenza-associated mortality using a nationally-representative system of death registration. In addition, further studies are needed to evaluate the impact of underlying host susceptibility, access to medical care, socioeconomic status and co-circulating bacterial and viral pathogens on the influenza burden in different areas of China. Such studies can help strengthen evidence-based decision-making and guide the introduction of national programmes of influenza immunization to mitigate the global impact of inter-pandemic influenza. ■

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ملخص

الوفيات المرتبطة بالأنفلونزا في المدن الصينية المعتدلة وشبه الاستوائية، 2003 – 2008

الغرض تقدير الوفيات المرتبطة بالأنفلونزا في المناطق الحضرية في الصين.

الطريقة تم تقدير المعدل المفرط للوفيات المرتبطة بالأنفلونزا في الفترة ما بين 2003 – 2008 في ثلاث مدن في المنطقة الشمالية المعتدلة في الصين وخمس مدن في المنطقة الجنوبية شبه الاستوائية من البلد. وتم استقاء هذه التقديرات من نماذج معتمدة على الارتدادات السلبية ثنائية الحدود والإحصاءات الحيوية ونتائج المراقبة الأسبوعية لفيروس الأنفلونزا.

النتائج بلغ المعدل السنوي المفرط للوفيات المرتبطة بالأنفلونزا، لجميع الأسباب، 18.0 حالة وفاة (النطاق: 10.9–32.7) لكل 100000 نسمة في المدن الشمالية و11.3 حالة وفاة (النطاق: 7.3–17.8) لكل 100000 نسمة في المدن الجنوبية. يُعزى معظم المعدل المفرط للوفيات – 12.4 (النطاق: 7.4–22.2) و8.8 حالة وفاة (النطاق: 5.5–13.6) لكل 100000 نسمة في المدن الشمالية والجنوبية، على التوالي – إلى الإصابة بأمراض الجهاز التنفسي و/أو الجهاز الدوري. وحدثت معظم حالات الوفاة (86 ٪) بين الأشخاص ≥ 65 عامًا. وكان المعدل المفرط للوفيات المرتبطة بالأنفلونزا أعلى في الفصول التي يكون ينتشر فيها الفيروس B عن في الفصول التي ينتشر فيها الفيروس(H3N2) A أو A(H1N1) وارتبط أكثر من نصف معدل الوفيات المرتبطة بالأنفلونزا بفيروس الأنفلونزا B.

الاستنتاج فيما بين عامي 2003 و2008، ارتبطت الأنفلونزا الموسمية، وبالأخص التي يسببها فيروس الأنفلونزا B بعدد كبير من الوفيات في ثلاث مدن في المنطقة الشمالية المعتدلة في الصين وخمس مدن في المنطقة الجنوبية شبه الاستوائية من ذات البلد.

摘要

2003 年至 2008 年在中国温带及亚热带城市中流感引起的死亡率

目的 估算中国城市流感引起的死亡率

方法 根据负二项回归模式、人口动态统计及每周流感病毒监控结果, 对 2003 年至 2008 年间中国北方三个温带城市及南方五个亚热带城市流感引起的非自然性死亡率进行估算。

结果 每年因各种原因由流感引起的非自然性死亡率在北方城市为每 10 万人口中 18（范围：10.9 - 32.7）例死亡患者，在南方城市为每 10万个人口中 11.3（范围：7.3 - 17.8）例死亡患者。由流感引起呼吸系统及循环系统疾病而导致的非自然性死亡率在北方城市为每10万人口中12.4 (范围: 7.4 – 22.2) 例死亡患者，在南方城市为每10万人口中8.8 (范围: 5.5 – 13.6) 例死亡患者。大多数（86%）死亡患者的年龄大于等于 6 5岁。在 B 类病毒高发期季节里引起的非自然性死亡率高于在A(H3N2) 或 A(H1N1) 病毒高发期的季节引起的非自然性死亡率。超过一半的流感引起的死亡病例均缘于 B 类流感病毒。

结论 2003 年至 2008 年间，在被调查的中国北方三个温带城市及南方五个亚热带城市，大多数死亡病例缘于季节性流感（特别是 B 型病毒引起的流感）。

Résumé

Mortalité associée à la grippe dans les villes des zones tempérées et subtropicales de Chine, 2003–2008

Objectif Estimer la mortalité associée à la grippe en Chine urbaine.

Méthodes La mortalité excessive associée à la grippe pour la période 2003–2008 a été évaluée dans trois villes de la zone tempérée du nord de la Chine et dans cinq villes de la zone subtropicale du pays. Les estimations ont été établies sur des modèles basés sur des régressions binomiales négatives, des statistiques vitales et les résultats de la surveillance hebdomadaire de la grippe.

Résultats La mortalité annuelle excessive associée à la grippe, dans tous les cas, a été de 18 (plage: 10,9–32,7) décès pour une population de 100 000 personnes dans les villes du nord et de 11,3 (plage: 7,3–17,8) décès pour une population de 100 000 personnes dans les villes du sud. La plus grande partie de cette mortalité excessive – respectivement 12,4 (plage: 7,4–22,2) et 8,8 (plage: 5,5–13,6) décès pour une population de 100 000 personnes dans les villes du nord et du sud – a été attribuée à des maladies respiratoires et/ou circulatoires. La plupart des décès (86%) sont survenus chez des personnes de ≥65 ans. La mortalité excessive associée à la grippe a été plus élevée lors des saisons où prédominait le virus B plutôt que lors de celles où prédominaient les virus A(H3N2) ou A(H1N1) et plus de la moitié de l'ensemble de la mortalité associée à la grippe a été associée au virus B de la grippe.

Conclusion De 2003 à 2008, la grippe saisonnière, surtout celle provoquée par le virus B, a été associée à une mortalité substantielle dans trois villes du nord tempéré de Chine et dans cinq villes du sud subtropical du pays.

Резюме

Влияние эпидемий гриппа на смертность в в городах умеренного и субтропического пояса Китая в 2003–2008 годах

Цель Произвести оценку влияния эпидемий гриппа на смертность среди городского населения Китая.

Методы В 2003-2008 гг. среди жителей трех городов северного Китая с умеренным климатом и пяти городов субтропического юга страны была произведена оценка роста смертности, связанного с заболеванием гриппом. Оценивание осуществлялось с помощью моделей, основанных на отрицательной биномиальной регрессии, а также на основании демографической статистики и результатов еженедельных наблюдений за распространением вируса гриппа.

Результаты Годовой рост смертности, связанный с заболеванием гриппом, независимо от причины смерти составил 18,0 (диапазон: 10,9 – 32,7) смертей на 100 000 жителей в северных городах и 11,3 (диапазон: 7,3–17,8) смертей на 100 000 жителей в южных городах. Большая часть данного роста – 12,4 (диапазон: 7,4 – 22,2) и 8,8 (диапазон: 5,5 – 13,6) количества смертей на 100 000 жителей в северных и южных городах, соответственно, вызвана респираторными заболеваниям и/или заболеваниями, протекающими с расстройством кровообращения. Большая часть (86%) смертей произошла в возрастной группе ≥ 65 лет. Рост смертности, связанной с заболеванием гриппом, был выше в периоды доминирования вируса B по сравнению с периодами, когда преобладали вирусы A(H3N2) либо A(H1N1); более половины всех связанных с заболеванием гриппом случаев смерти относится к вирусу гриппа B.

Вывод В период между 2003 и 2008 гг. существенное повышение уровня смертности в трех городах севера Китая с умеренным климатом и пяти городах субтропического юга страны было связано с сезонной заболеваемостью гриппом, вызванной, главным образом, вирусом гриппа B.

Resumen

La mortalidad asociada a la gripe en ciudades chinas con clima templado y subtropical, 2003–2008

Objetivo Calcular la mortalidad asociada a la gripe en la China urbana.

Métodos Se calculó el exceso de mortalidad asociado a la gripe durante el periodo comprendido entre 2003 y 2008 en tres ciudades del norte de China con clima templado y en cinco ciudades del sur del país con clima subtropical. Los cálculos se obtuvieron de modelos basados en regresiones binomiales negativas, estadísticas vitales y de los resultados de la vigilancia semanal del virus de la gripe.

Resultados El exceso de mortalidad anual asociado a la gripe, por todas las causas, fue de 18,0 (rango: 10,9–32,7) muertes por cada 100 000 habitantes en las ciudades del norte y de 11,3 (rango: 7,3–17,8) muertes por cada 100 000 habitantes en las ciudades del sur. La mayor parte de este exceso de mortalidad – 12,4 (rango: 7,4–22,2) y 8,8 (rango: 5,5–13,6) muertes por cada 100 000 habitantes en las ciudades del norte y del sur, respectivamente – se atribuyeron a una enfermedad respiratoria y/o circulatoria. La mayoría de las muertes (el 86%) ocurrió en personas con una edad ≥ 65 años. El exceso de mortalidad asociado a la gripe fue superior en épocas con un virus B dominante que en épocas en las que predominaron los virus A(H3N2) o A(H1N1). Más de la mitad de la mortalidad total asociada a la gripe se asoció al virus B de la gripe.

Conclusión Entre 2003 y 2008, la gripe estacional, particularmente la causada por el virus B de la gripe, estuvo asociada a la mortalidad sustancial en tres ciudades de China con clima templado y en cinco ciudades del sur del país con clima subtropical.

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Table 1. **All-cause (AC) deaths and coded[a] causes of death in eight cities, China, 2003–2008**

City and year	Population (millions)	Deaths per 100 000 people (% of AC)					
		AC	R&C	IHD	COPD	P&I	In
Three northern cities[b]							
2003	9.8	580.5	272.7 (47.0)	64.2 (11.1)	23.1 (4.0)	9.2 (1.6)	0.4 (0.1)
2004	9.9	613.1	294.0 (48.0)	72.0 (11.8)	25.4 (4.1)	8.9 (1.5)	0.3 (0.1)
2005	10.1	614.2	306.7 (49.9)	80.2 (13.1)	23.6 (3.8)	8.3 (1.4)	0.2 (0.0)
2006	10.2	612.9	308.3 (50.3)	87.8 (14.3)	26.6 (4.3)	8.3 (1.4)	0.3 (0.0)
2007	10.3	623.6	312.7 (50.1)	89.8 (14.4)	30.4 (4.9)	8.5 (1.4)	0.1 (0.0)
2008	10.4	659.1	319.0 (48.4)	94.7 (14.4)	28.9 (4.4)	8.2 (1.2)	0.1 (0.0)
Mean	10.1	617.7	302.5 (49.0)	81.7 (13.2)	26.4 (4.3)	8.6 (1.4)	0.2 (0.0)
Five southern cities[c]							
2003	21.3	690.4	322.4 (46.7)	56.6 (8.2)	93.8 (13.6)	6.1 (0.9)	0.2 (0.0)
2004	21.4	673.3	306.1 (45.5)	56.4 (8.4)	77.4 (11.5)	6.5 (1.0)	0.1 (0.0)
2005	21.6	707.6	330.0 (46.6)	62.8 (8.9)	81.6 (11.5)	6.9 (1.0)	0.2 (0.0)
2006	21.7	668.4	300.7 (45.0)	61.6 (9.2)	69.4 (10.4)	6.1 (0.9)	0.1 (0.0)
2007	21.9	708.0	325.6 (46.0)	68.3 (9.6)	74.9 (10.6)	6.5 (0.9)	0.1 (0.0)
2008	22.4	702.1	330.8 (47.1)	71.4 (10.2)	75.2 (10.7)	8.5 (1.2)	0.1 (0.0)
Mean	21.7	691.7	319.3 (46.2)	62.9 (9.1)	78.7 (11.4)	6.8 (1.0)	0.1 (0.0)

R&C, respiratory and circulatory disease; IHD, ischaemic heart disease; COPD, chronic obstructive pulmonary disease; P&I, pneumonia and influenza; In, influenza.

[a] *International statistical classification of diseases and related health problems*, tenth revision.[28]

[b] Dalian, Qingdao and Zhaoyuan.

[c] Guangzhou, Ningbo, Shanghai, Wuhan and Yichang.

Table 4. **Comparison of estimates of annual influenza-associated excess mortality in China and other selected locations, by age and cause of death as coded[a] or recorded**

Study area	Model	Study period	Proportion of influenza seasons by:		Excess deaths (per 100 000 people)					
			A(H3N2)	B	All ages			Age ≥ 65 years		
					P&I	R&C	AC	P&I	R&C	AC
Australia[15]	Poisson	1997–2004	NA	NA	NA	NA	NA	15.2	80.4	101.2
China (Guangzhou)[21]	Poisson	2004–2006	2/3	0/3	1.0	9.9	10.6	NA	104.1	111.3
China (northern cities)[b]	Negative binomial	2003–2008	2.5/6	1/6	0.4	12.4	18.0	3.1	106.0	150.8
China (northern cities)[b]	Serfling	2003–2008	2.5/6	1/6	0.4	13.4	17.0	2.6	108.1	131.3
China (southern cities)[b]	Negative binomial	2003–2008	2.5/6	1/6	0.5	8.8	11.3	3.6	64.3	75.4
China (Hong Kong SAR)[19]	Poisson	1996–1999	4/4	0/4	4.1	12.4	16.4	39.3	102.0	136.1
Italy[11,12]	Serfling	1970–2001	21/31	5/31	1.9–2.2	NA	11.6–18.6	12.7–14.2	NA	71.2–115.7
Mexico[16]	Serfling	2000–2008	6/9	1/9	1.5	12.7	15.7	10.4[c]	115.6[c]	147.4[c]
Singapore[22]	Negative binomial	1996–2003	8/8	0/8	2.9	11.9	14.8	46.9	155.4	167.8
United States[4]	Poisson	1990–1999	6/9	2/9	3.1	13.8	19.6	22.1	98.3	132.5
United States[3]	Poisson	1976–2002	14/27	9/27	NA	9.9	NA	NA	72.4	NA
United States[5]	Poisson	1976–2007	17/31	9/31	2.4	9.0	NA	17.0	66.1	NA
United States[10]	Serfling	1980–2001	12/21	6/21	2.9	NA	15.0	22.0	NA	100.0

AC, all-cause; NA, not available; P&I, pneumonia and influenza; R&C, respiratory and circulatory disease; SAR, Special Administrative Region.

[a] *International statistical classification of diseases and related health problems*, tenth revision.[28]

[b] Data from present study.

[c] Data for age ≥ 60 years.