Mortality burden from seasonal influenza in Chongqing, China, 2012–2018

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ABSTRACT

Purpose: To estimate influenza-associated excess mortality rates (EMRs) in Chongqing from 2012 to 2018.

Methods: We obtained weekly mortality data for all-cause and four underlying causes of death (circulatory and respiratory disease (CRD), pneumonia and influenza (P&I), chronic obstructive pulmonary disease (COPD) and ischemic heart disease (IDH)), and influenza surveillance data, from 2012 to 2018. A negative-binomial regression model was used to estimate influenza-associated EMRs in two age groups (<65 years and ≥65 years).

Results: It was estimated that an annual average of 10025 influenza-associated deaths occurred in Chongqing, corresponding to 5.2% of all deaths. The average EMR for all-cause death associated with influenza was 33.5 (95% confidence interval (CI): 31.5–35.6) per 100 000 persons, and in separate cause-specific models we attributed 24.7 (95% CI: 23.3–26.0), 0.8 (95% CI: 0.7–0.8), 8.5 (95% CI: 8.1–9.0) and 5.0 (95% CI: 4.7–5.3) per 100 000 persons EMRs to CRD, P&I, COPD and IDH, respectively. The estimated EMR for influenza B virus was 20.6 (95% CI: 20.3–21.0), which was significantly higher than the rates of 5.3 (95% CI: 4.5–6.1) and 7.5 (95% CI: 6.7–8.3) for A(H3N2) and A(H1N1) pdm09 virus, respectively. The estimated EMR was 152.3 (95% CI: 136.1–168.4) for people aged ≥65 years, which was significantly higher than the rate for those aged <65 years (6.8, 95% CI: 6.3–7.2).

Conclusions: Influenza was associated with substantial EMRs in Chongqing, especially among elderly people. Influenza B virus caused relatively higher excess mortality impact compared with A(H1N1) pdm09 and A(H3N2). It is advisable to optimize future seasonal influenza vaccine reimbursement policy in Chongqing to curb disease burden.

Introduction

Globally, seasonal influenza has been associated with substantial morbidity and mortality every year. At the global level, influenza has been estimated to cause approximately 290 000–650 000 respiratory deaths annually, which was higher than previous estimates-roughly 250 000–500 000 respiratory and circulatory deaths each year.1

Estimation of influenza-associated mortality burden is important for understanding the epidemiology of influenza, guiding vaccination programs, evaluating the use of diagnostic tests and antiviral drugs, and planning for seasonal epidemics and future pandemics. However, estimating the mortality burden associated with influenza remains challenging due to the following challenges: first, influenza diagnosis is usually based on symptoms and laboratory confirmation is not routinely conducted in hospitals; second, many deaths that may be caused by influenza occur after virus can be detected; third, influenza is rarely recorded as the cause of death in the death registration system. Therefore, directly counting influenza deaths usually grossly underestimate the mortality burden of influenza. To overcome underestimation of influenza-related deaths, various statistical models have been employed to estimate the mortality burden associated with influenza,1,3,4 among which negative-binomial regression model has been widely used.5,6 The rationale for the modeling approach was to estimate influenza-associated excess mortality rate (EMR), which was defined as the difference between observed and expected mortality based on the regression model in the absence of influenza.

Considering the diverse seasonality patterns, income levels, and healthcare access, influenza mortality burden varies across geographical locations.1,4,7 With the latitude of 29.6°N and a subtropical climate with four distinct seasons, Chongqing is the largest municipality with over 30 million registered inhabitants.
which is located in Southwestern China (Figure 1). Previous study demonstrated that influenza virus circulated throughout the year and showed two possible peaks. However, little is known about the impact of influenza on death in this area.

To address this gap, we applied a negative-binomial model to the weekly counts of deaths and influenza viral data to estimate the mortality burden of influenza in Chongqing by death category, age group, and influenza type/subtypes during the period of 2012–2018.

Materials and methods

Mortality data and population denominators

According to China Center for Disease Control and Prevention (CDC), every individual death certificate in China is required to be registered in the death registration system. The causes of mortality are coded according to the International Classification of Diseases, the 10th version (ICD-10). Coding practices are based on a standardized protocol, and quality control is conducted routinely by staff from the local CDC. We obtained separate data for five underlying causes of death in Chongqing from 2012 to 2018: circulatory and respiratory disease (CRD, ICD-10: J00–J99 or I00–I99), pneumonia and influenza (P&I, ICD-10: J10-J18), chronic obstructive pulmonary disease (COPD, ICD-10: J40-J47), ischemic heart disease (IHD, ICD-10: I20-I25), as well as total deaths.

The annual population data were obtained from the Household Registration Department of Chongqing Municipal Statistic Bureau. EMR was stratified by death category, influenza type/subtypes and two age-groups (0–64, and ≥65 years).

Influenza virological surveillance

Influenza surveillance was conducted in seven sentinel hospitals throughout the year in Chongqing from 2012 to 2018. The seven sentinel hospitals were selected based on high accessibility among patients, high qualification of medical staff, adequate specimen storage capacity, and the desire of the physicians and nurses to participate voluntarily in the surveillance program. Surveillance is conducted in sentinel hospital emergency rooms and internal medicine and pediatric outpatient departments. The influenza surveillance protocol in Chongqing is in accord with the national influenza surveillance protocol and has been stated in a previous study. We obtained influenza virological surveillance data from seven sentinel hospitals in Chongqing, including weekly numbers of specimens tested positive for influenza A (H1N1)pdm09, influenza A(H3N2), influenza B, and calculated weekly positive rate using weekly number of specimens as the denominator. An influenza type or subtype was considered dominant when it accounted for at least 50% of all influenza-positive specimens.

Estimating of influenza-associated EMRs

Given over-dispersion in mortality data, we applied negative-binomial regression models to estimate EMRs, using weekly mortality counts as the outcome and weekly proportions of specimens testing positive for influenza A(H1N1)pdm09, A(H3N2) and B as the explanatory variables.

The negative-binomial model was applied to each of the five disease categories (CRD, P&I, COPD, IHD and all-cause) and two age groups (age <65 years and ≥65 years) using a log link function. The model used was as follows:
Annual deaths by underlying diagnosis

In the study period 2012–2018, an annual mean of 193 757 deaths were recorded in Chongqing, including 117 503 coded as CRD, 3163 coded as P&I, 33 326 coded as COPD and 23 903 coded as IHD, representing 60.6%, 1.6%, 17.2% and 12.3% of all deaths, respectively (Table 1). Adults aged ≥65 years accounted for 73.9% of all-cause deaths. The proportion of deaths coded as CRD, P&I, COPD, and IHD as well as all causes were 83.9%, 82.0%, 89.4%, 81.9%, and 85.3% for people age ≥65 years, respectively.

Annual influenza virological surveillance

Table 2 showed the influenza surveillance data in Chongqing during 2012–2018. Overall, 27 036 specimens from ILI cases were collected for virus detection. Among tested specimens, 10.9% (2947/27036) were positive for influenza virus by reverse transcription-polymerase chain reaction. Influenza A (H1N1)pdm09, A (H3N2), and B virus comprised 23.1%, 36.6% and 40.3% of the positive influenza isolated, respectively.

Influenza A(H3N2) was the predominant virus in 2012 and 2014, while A(H1N1)pdm09 predominated in 2013 and 2018, influenza B predominant in 2015 and 2016, and influenza A (H1N1)pdm09, A(H3N2) and B co-circulated in 2017 (Table 2).

### Table 1. Annual number of deaths in Chongqing, China, 2012–2018.

| Age group | All-cause | CRD | P&I | COPD | IHD |
|-----------|-----------|-----|-----|------|-----|
| All age   |           |     |     |      |     |
| 2012      | 176537    | 605 | 109480 | 375 | 2874 | 10 |
| 2013      | 183419    | 623 | 110296 | 375 | 2881 | 10 |
| 2014      | 195482    | 658 | 118670 | 400 | 3179 | 11 |
| 2015      | 198729    | 664 | 120015 | 401 | 3106 | 10 |
| 2016      | 205696    | 682 | 124078 | 411 | 3515 | 12 |
| 2017      | 186662    | 612 | 112194 | 368 | 3117 | 10 |
| 2018      | 209777    | 682 | 127789 | 416 | 3467 | 11 |
| Total     | 1356302   | 4527 | 822522 | 2745 | 22139 | 74 |

| Age ≥65   |           |     |     |      |     |
| 2012      | 126174    | 2450 | 89449 | 1737 | 2210 | 43 |
| 2013      | 130521    | 3725 | 90506 | 2564 | 2327 | 66 |
| 2014      | 142613    | 3937 | 89819 | 2731 | 2561 | 71 |
| 2015      | 146034    | 4004 | 100392 | 2758 | 2541 | 70 |
| 2016      | 153177    | 3705 | 104918 | 2538 | 2969 | 72 |
| 2017      | 141506    | 3814 | 95758 | 2581 | 2613 | 70 |
| 2018      | 162912    | 4007 | 109701 | 2701 | 2934 | 72 |
| Total     | 1002937   | 25642 | 689993 | 17630 | 18155 | 464 |

| Age <65   |           |     |     |      |     |
| 2012      | 50363     | 209 | 20031 | 83  | 664  | 3  |
| 2013      | 52898     | 204 | 19730 | 76  | 554  | 2  |
| 2014      | 52869     | 203 | 19751 | 76  | 618  | 2  |
| 2015      | 52695     | 201 | 19423 | 74  | 565  | 2  |
| 2016      | 52519     | 202 | 19160 | 74  | 546  | 2  |
| 2017      | 45156     | 169 | 16436 | 61  | 504  | 2  |
| 2018      | 46865     | 176 | 17998 | 67  | 533  | 2  |
| Total     | 353365    | 1363 | 132529 | 511 | 3984 | 15 |

Denotes number.
Denotes circulatory and respiratory disease.
Denotes pneumonia and influenza.
Denotes chronic obstructive pulmonary disease.
Denotes ischemic heart disease.
Weekly number of influenza-associated death per five causes and the proportion of influenza-positive in all age groups (Figure 2) showed that each of the five health outcomes has a similar pattern to that seen with influenza activity.

**Influenza-associated EMRs**

Influenza was significantly associated with all health outcomes for all age groups. For people aged ≥65 years, the annual average influenza-associated EMR was 152.3 (95% CI: 136.1–168.4) per 100 000 persons, which was significantly higher than the rate among those aged <65 years (6.8, 95% CI: 6.3–7.2). Age-stratified analysis revealed that influenza-associated EMRs for CRD, P&I, COPD, and IDH were more than 20-fold higher among people aged ≥65 years than among those aged <65 years (Table 3).

Compared with influenza A virus, influenza B virus showed a significantly higher mortality burden. Table 3 showed that for all age group influenza B virus accounted for the highest EMR of all-cause mortality (20.6, 95% CI: 20.3–21.0), followed by A(H1N1)pdm09 (7.5, 95% CI: 6.7–8.3) and A(H3N2) (5.3, 95% CI: 4.5–6.1) per 100 000 persons. A similar pattern was also observed for CRD, P&I, COPD and IDH among both those aged ≥65 years and those aged <65 years.

**Discussion**

This study estimated the mortality burden of seasonal influenza in Chongqing based on robust vital statistics and mortality data during 2012–2018. We estimated an average of 10,025 influenza-associated all-cause deaths per year, accounting for 5.2% of all-cause death, 7.8 (95% CI: 1.8–50.4) per 100,000 persons for all-cause death, 7.8 (95% CI: 1.8–50.4) per 100,000 persons for CRD, 0.5 (95% CI: 0.1–2.3) per 100,000 persons for P&I, 1.0 (95% CI: 0.1–7.0) per 100,000 persons for IDH and 3.0 (95% CI: 0.7–12.0) per 100,000 persons for COPD excess mortality associated with influenza annually in five south cities (Shanghai, Wuhan, Yichang, Ningbo, and Guangzhou) from 2003 to 2008. The possible explanations for the differences might be associated with the regional variation in socioeconomic and demographic factors, different models used and different study periods. Furthermore, differences in successful implementation of seasonal influenza vaccination might also have played an important role. The influenza vaccination subsidy policy was quite different in different regions. Many high-income countries conducted influenza vaccination program in older adults with the goal of reducing the influenza-associated mortality in this high-risk group. China in general has low vaccination coverage in the population, and only in a few regions such as Beijing where the local government fully subsidizes the vaccination in older adults. At present, the cost of influenza vaccination is borne using the surplus fund of basic social medical insurance for urban residents individual accounts in Chongqing and many people have to pay for the seasonal influenza vaccine out of pocket, which might lead to very low influenza vaccination coverage in this area.

Overall, the impact of influenza on mortality in Chongqing disproportional affected people aged ≥65 years, which is consistent with the findings of previous studies. According to the 2010 census results in China, the proportion of people ≥65 years old in Chongqing was the highest in China, which has reached the average level of developed countries. Given the high excess mortality among elderly people and the serious aging problem in Chongqing, great efforts should be made to increase seasonal influenza vaccination coverage in this population.

It is not surprising that CRD was the major contributor to total influenza-associated deaths, as CRD was the primary cause in Chongqing. Our data also suggested a significant association between influenza and COPD death. This finding was not unexpected given multiple reports relating the association between COPD death and seasonal influenza. The relation may be explained by the dysfunction of innate immune defenses and destruction of the lung parenchyma or airway remodeling by acute virus infections. In China, COPD was the third leading cause of death and accounted for more 965,9 thousand deaths in 2017. There was accumulating evidence suggesting that influenza vaccination was associated with a reduced risk of mortality in COPD patients and
seasonal influenza vaccination was recommended by international and national health organizations; nonetheless coverage remains sub-optimal compared to recommended targets.

Notably, our study observed that influenza B caused the highest burden compared with A(H1N1)pdm09 and A(H3N2). This mortality pattern is consistent with those described in studies conducted by China CDC, Beijing CDC and Guangzhou CDC, but differs from studies conducted in other regions and countries such as Yancheng, Hefei, Hong Kong, Singapore, South Korea, United States, and New Zealand, where the highest EMR was associated with influenza A(H3N2). The inconsistent severity profile of influenza type/subtypes warrants further investigation in more locations in future studies.

Despite providing insightful estimates of influenza-associated disease burden in Chongqing, this study has several limitations. Firstly, this was an ecological study with...
aggregated data, so ecologic fallacy was inevitable. Secondly, it was not possible to adjust for other co-circulating respiratory viruses such as respiratory syncytial virus, adenovirus, and parainfluenza virus, which may have confounded the results. In future, the establishment of such surveillance system may improve the accuracy of influenza-associated mortality burden. Thirdly, our results were dependent on the coding and registration of deaths, errors including possible underreporting and misclassification of deaths could lead to the underestimation of influenza-associated excess mortality, especially for disease-specific mortality indicators. Finally, we only examined the impact of influenza epidemics on excess mortality. In future, a more comprehensive assessment including hospitalization, year-of-life lost and economic burden of influenza would help to fully assess the disease burden of influenza in Chongqing.

Conclusions

Our study demonstrated a substantial influenza-related mortality burden in the largest municipality in China from 2012 to 2018, primarily associated with CRD and COPD deaths in the elderly. Influenza B virus caused a relatively higher excess mortality impact compared with A (H1N1)pdm09 and A (H3N2). This study supported the recent recommendation by the National Immunization Advisory Committee on “Technical guidelines for seasonal influenza vaccination in China (2018–2019)” for elderly people and individuals with chronic underlying conditions, such as COPD, CVD or diabetes, be treated as priority groups for seasonal influenza vaccination.28 It is advisable to optimize future seasonal influenza vaccine reimbursement policy in Chongqing to curb disease burden.

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Disclosures

No potential conflicts of interest were disclosed.

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