Influenza-associated excess respiratory mortality in China, 2010–15: a population-based study

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Summary

Background The estimation of influenza-associated excess mortality in countries can help to improve estimates of the global mortality burden attributable to influenza virus infections. We did a study to estimate the influenza-associated excess respiratory mortality in mainland China for the 2010–11 through 2014–15 seasons.

Methods We obtained provincial weekly influenza surveillance data and population mortality data for 161 disease surveillance points in 31 provinces in mainland China from the Chinese Center for Disease Control and Prevention for the years 2005–15. Disease surveillance points with an annual average mortality rate of less than 0·4% between 2005 and 2015 or an annual mortality rate of less than 0·3% in any given years were excluded. We extracted data for respiratory deaths based on codes J00-J99 under the tenth edition of the International Classification of Diseases. Data on respiratory mortality and population were stratified by age group (age <60 years and ≥60 years) and aggregated by province. The overall annual population data of each province and national annual respiratory mortality data were compiled from the China Statistical Yearbook. Influenza surveillance data on weekly proportion of samples testing positive for influenza virus by type or subtype for 31 provinces were extracted from the National Sentinel Hospital-based Influenza Surveillance Network. We estimated influenza-associated excess respiratory mortality rates between the 2010–11 and 2014–15 seasons for 22 provinces with valid data in the country using linear regression models. Extrapolation of excess respiratory mortality rates was done using random-effect meta-regression models for nine provinces without valid data for a direct estimation of the rates.

Findings We fitted the linear regression model with the data from 22 of 31 provinces in mainland China, representing 83·0% of the total population. We estimated that an annual mean of 88 100 (95% CI 84 200–92 000) influenza-associated excess respiratory deaths occurred in China in the 5 years studied, corresponding to 8·2% (95% CI 7·9–8·6) of respiratory deaths. The mean excess respiratory mortality rates per 100 000 person-seasons for influenza A(H1N1)pdm09, A(H3N2), and B viruses were 1·6 (95% CI 1·5–1·7), 2·6 (2·4–2·8), and 2·3 (2·1–2·5), respectively. Estimated excess respiratory mortality rates per 100 000 person-seasons were 1·5 (95% CI 1·1–1·9) for individuals younger than 60 years and 38·5 (36·8–40·2) for individuals aged 60 years or older. Approximately 71 000 (95% CI 67 800–74 100) influenza-associated excess respiratory deaths occurred in individuals aged 60 years or older, corresponding to 80% of such deaths.

Interpretation Influenza was associated with substantial excess respiratory mortality in China between 2010–11 and 2014–15 seasons, especially in older adults aged at least 60 years. Continuous and high-quality surveillance data across China are needed to improve the estimation of the disease burden attributable to influenza and the best public health interventions are needed to curb this burden.

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See **Comment** page e436

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Introduction

Influenza virus infections lead to substantial morbidity and mortality each year globally,[1,2] causing an estimated 290 000–650 000 respiratory deaths annually.[3] Many influenza virus infections are never laboratory confirmed because of delays in seeking health care and an absence of laboratory testing in many locations. Therefore, statistical analyses correlating temporal patterns in influenza circulation and mortality in populations are most often used to quantify the mortality burden associated with influenza.[1,3–5]

The mortality burden associated with influenza virus infections varies across populations and geographical locations.[1,3] Most of the available estimates of disease burden attributable to influenza are from high-income locations, whereas the burden in low-income and

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Research in context

Evidence before this study

Previous studies have shown that influenza virus causes substantial mortality burden globally in humans. Estimation of influenza-associated disease burden is the basis for implementation of interventions to control influenza. We searched PubMed for studies published between Jan 1, 1990, and April 13, 2019, using the key words "influenza OR flu", "Chinese OR China", "mortality OR death" and "burden OR impact" without language restrictions. Of the 111 articles identified, there were eight relevant published studies on estimation of influenza-associated mortality burden in China. We identified one national study before 2009–10 and there have been several studies estimating influenza burden in specific cities. There were no national estimates of influenza-associated mortality since the 2009 pandemic, while pre-pandemic estimates at the national level and post-pandemic estimates in selected cities were generally consistent with the recent global estimate on influenza effect of 4·0–8·8 influenza-associated excess respiratory deaths per 100 000 individuals per year, and the highest influenza-associated mortality rates occurring in older adults.

Added value of this study

To the best of our knowledge, we provided the first estimates of influenza-associated mortality for China at both the provincial level and overall. We estimated that a mean 88 100 (95% CI 84 200–92 000) influenza-associated excess respiratory deaths occurred in China every year during the 2010–11 through 2014–15 seasons, accounting for 8·2% (95% CI 7·9–8·6) of all reported respiratory deaths. Approximately 80% of the influenza-associated excess respiratory deaths occurred in individuals aged 60 years or older, leading to 38·5 (95% CI 36·8–40·2) excess respiratory deaths per 100 000 person-seasons, which was substantially higher than the estimate in individuals younger than 60 years.

Implications of all the available evidence

Influenza causes substantial mortality in China, associated with around 8% of all respiratory deaths. Greater investment in public health approaches that reduce the spread of influenza and mitigate its harms could appreciably reduce the excess respiratory mortality rate in China.

middle-income locations is less well understood.[6] In China, the expanded national immunisation pro-gramme does not include influenza vaccination, and over the past 15 years influenza vaccine coverage has only gradually increased to approximately 2% of the population.[7] Influenza virus activity varies substantially across provinces in China, with winter epidemics in northern provinces, and spring and summer epidemics in southern provinces.[8] Two previous studies estimated the national or regional excess mortality associated with seasonal influenza viruses and influenza A(H1N1)pdm09 in or before 2009–10 in mainland China by major cause of death: 9·4 per 100 000 population for the estimated influenza-associated excess respiratory and cardiovascular mortality during 2009–10[9] and 12·4 and 8·8 per 100 000 persons in northern and southern cities, respectively, for the estimated annual average influenza-associated excess respiratory and cardiovascular mortality rates during 2003–08.[10] Seven studies provided estimates of the influenza-associated mortality burden from several cities in China including Beijing,[11] Shanghai,[12] Yancheng,[13] Guangzhou,[14–16] and Hefei.[17] There have been no published national estimates of influenza-associated mortality since the 2009 pandemic. Here, we present findings from our study estimating the influenza-associated excess respiratory mortality for mainland China for the period 2010–11 through 2014–15.

See Online for appendix

Methods

Data sources

There are 31 provinces in mainland China (here we use provinces to indicate the major administrative divisions including provinces, autonomous regions, and muni-cipalities for simplicity). We obtained the weekly mortality and population data from 161 disease surveillance points across 31 provinces in China (following UN convention) for the years 2005–15 from the Chinese Centre for Disease Control and Prevention (China CDC).[9] For Shanghai, where organisation of the disease surveillance points was reconfigured partway through the study period, we used data from the local Shanghai CDC instead (appendix p 2). For the quality of the study, we excluded disease surveillance points with an annual mean mortality rate of less than 0·4% between 2005 and 2015 and those with an annual mortality rate of less than 0·3% in any of those years.[18] We reasoned that these low mortality values probably indicated under-reporting of mortality at these surveillance points. Data from 121 disease surveillance points in 30 provinces remained. Data from the Hainan province were excluded because the mortality rates of the disease surveillance points across this entire province met the exclusion criteria. Next, we identified and removed outliers from the weekly mortality data and imputed the deleted data points using statistical techniques (definition of outlier and the statistical techniques used for imputation in the appendix p 3). We extracted data for respiratory deaths based on codes J00-J99 in the tenth edition of the International Classification of Diseases (ICD). Data for respiratory mortality and population were stratified by age group (<60 years and ≥60 years) and aggregated by province. The overall annual population data from each province and national annual respiratory mortality data were compiled from the China Statistical Yearbook (figure 1).

Influenza surveillance data for the weekly proportion of samples testing positive for influenza virus by type or subtype (lab%) for 31 provinces were extracted from the National Sentinel Hospital-based Influenza Surveillance Network[9] (appendix p 4). Data from Tibet were excluded because there were few hospitals in the Influenza Surveillance Network and data were not sufficient for the analysis. Meteorological data for ambient temperature and relative humidity were obtained from the China Meteorological Data Sharing Service System.[19] We used meteorological data from all monitoring stations within the same province to estimate temperature and relative humidity for the province as a whole. Absolute humidity values were derived from temperature and relative humidity values.[5]

Data analysis

We used the lab% (by type or subtype) as the influenza virus activity proxy, intended to reflect patterns in incidence of infections with influenza A(H1N1)pdm09, A(H3N2), and B. An influenza season was defined in this study as the period between October in 1 year and September in the following year. The number of hospitals included in the Influenza Surveillance Network substantially expanded after the 2009 pandemic. To avoid the potential effect of changes in influenza surveillance coverage after 2009 on the estimation of the influenza-associated excess mortality in this study, we restricted our analyses to the post-pandemic period, and studied the five influenza seasons from 2010–11 through 2014–15. Additionally, to identify provinces where the monitoring data might be unreliable, we defined a data quality algorithm by calculating the ratios of the SDs of the detrended time-series of the respiratory death rates and lab% relative to the means of time-series. We excluded data from seven provinces (Hebei, Ningxia, Shanxi, Qinghai, Xinjiang, Yunnan, and Inner Mongolia) from the main analysis because the ratios were larger than thresholds (appendix pp 5–7), and deleted an abnormally increased datapoint in lab% in Jiangxi in late 2011 from the analysis (appendix p 8). We estimated influenza-associated excess respiratory mortality rates first at the provincial level, then at the national level (figure 1).

Single-province mortality estimates

We applied a linear model to derive single-province estimates of excess respiratory mortality rates between 2010–11 and 2014–15 for the 22 provinces with reliable data. Our model assumed an additive association between influenza incidence and mortality, which could be more biologically plausible than a multiplicative association.[1,4] A linear model was selected because respiratory mortality rates in all ages and in individuals aged at least 60 years approximately followed a normal distribution.[4,5] Respiratory mortality rates for all ages combined and in individuals aged at least 60 years as a specific subgroup were used as the dependent variables in the models, and regressed against the proxies for influenza A(H1N1)pdm09, A(H3N2), and B. A natural cubic spline of calendar week was used to allow for linear and non-linear changes in mortality rates over time. Natural cubic spline functions were also used to control for the effects of temperature and absolute humidity. We assumed that there was a lag of 1 week between the exposure variables, including influenza virus activity and climatic variables, and the model outcome respiratory mortality rate.[5]

The influenza-associated excess respiratory deaths for all ages and individuals aged 60 years or older were estimated by subtracting the predicted number of respiratory deaths assuming that the influenza virus activity proxy was 0 (E[Y|X=0]) from the predicted number of respiratory deaths using the observed influenza virus activity proxy (E[Y|X=x_obs]).[5] Y indicates the predicted respiratory death rate; X represents influenza virus activity proxy; and x_obs refers to the observed influenza virus activity proxy. We were not able to directly estimate excess respiratory mortality in children or younger adults because of the smaller numbers of deaths reported and therefore these individuals were incorporated into the estimate for

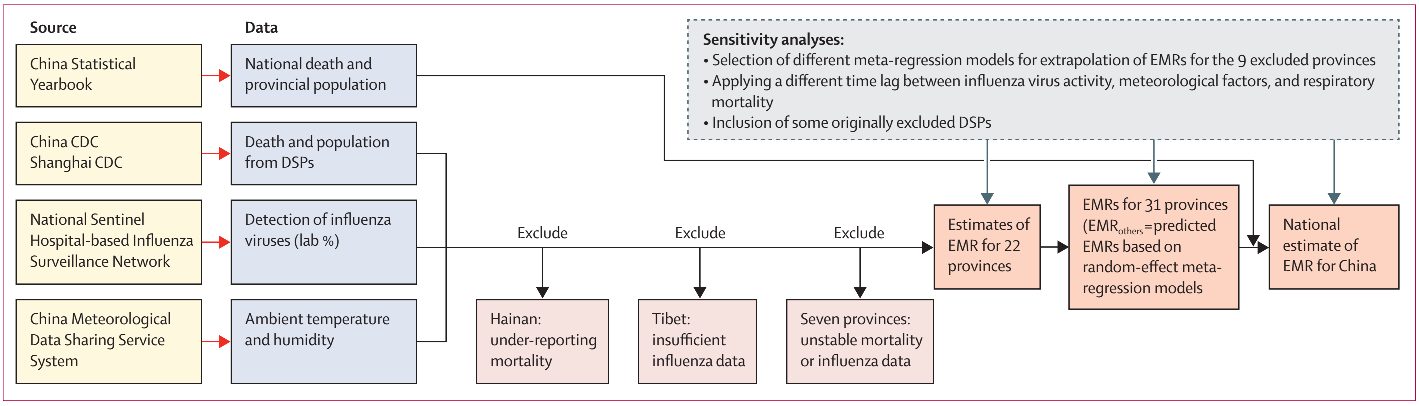

Figure 1: **Data sources and data analysis**
CDC=Center for Disease Control and Prevention. DSP=disease surveillance point. EMR=influenza-associated excess respiratory mortality rate.

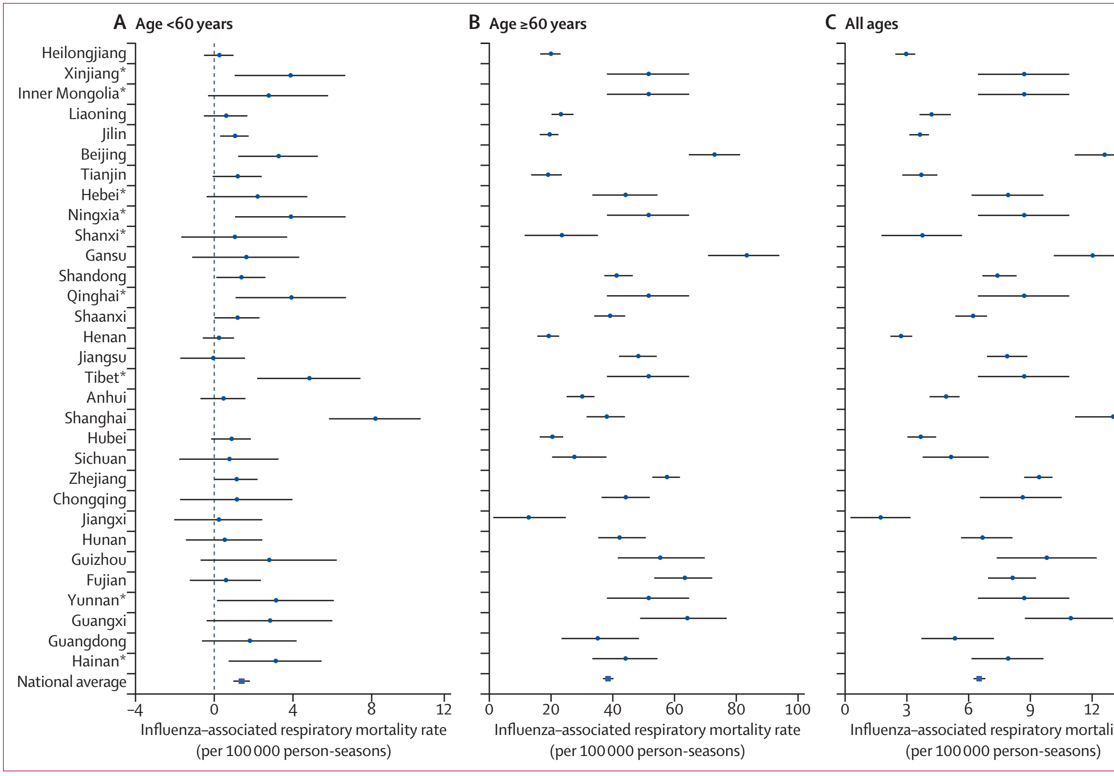

Figure 2: Age-specific influenza-associated excess respiratory mortality rates per 100 000 person-seasons for all influenza in mainland China between the 2010–11 through 2014–15 seasons
Dots indicate the point estimates of excess respiratory mortality rates. Black lines indicate the 95% CIs. *Indicates province excluded from the linear regression modelling analysis. Excess respiratory mortality rate for this province was estimated using a random-effect meta-regression model based on estimates from the remaining 22 provinces.

those younger than 60 years. Influenza-associated excess respiratory deaths were estimated for the population younger than 60 years simply by subtracting the estimate for those aged 60 years or older from the all ages estimate. The excess respiratory mortality rate was estimated as the number of influenza-associated excess respiratory deaths per 100 000 person-seasons. Further technical details on how we estimated single-province mortality are in the appendix (pp 9–11).

For the remaining nine provinces without reliable data for the linear regression analysis, influenza-related excess respiratory mortality was estimated by extrapolation using a random-effects meta-regression model. The model incorporated one group of economy-related variables (ie, gross domestic product per person, population density, and regional classification: west, centre, and east), and one group of variables that indicated health-care infrastructure, access to health-care services, and health-care needs in the population (ie, the number of sentinel hospitals per 100 000 individuals, the number of hospitals per 1000 individuals, the number of hospital beds per 1000 individuals, number of outpatients per 1000 individuals), and the climate-related variable of latitude. We selected the model from those with statistically significant independent variables and based on the value of Akaike Information Criterion (AIC; appendix p 12).

National burden estimates

We estimated national excess respiratory mortality rates by age group, influenza virus type or subtype, and influenza season. The national excess respiratory mortality rates in each season were estimated as the population-weighted mean excess respiratory mortality rate across all 31 provinces. The proportion of annual national respiratory deaths attributable to influenza was also estimated using the national-level output from our estimation models and national death data taken from the China Statistical Yearbook (appendix pp 13–14).

Finally, we did several sensitivity analyses. We extrapolated influenza-associated excess respiratory mortality values for the nine excluded provinces based on the model with the smallest value of AIC, to explore the potential effect of applying meta-regression models with different covariates on the national overall estimate of influenza-associated excess respiratory mortality. We also re-estimated the national influenza-associated excess respiratory mortality assuming a lag of 2 weeks between influenza, climatic factors, and by including additional data from 14 of the originally excluded disease surveillance

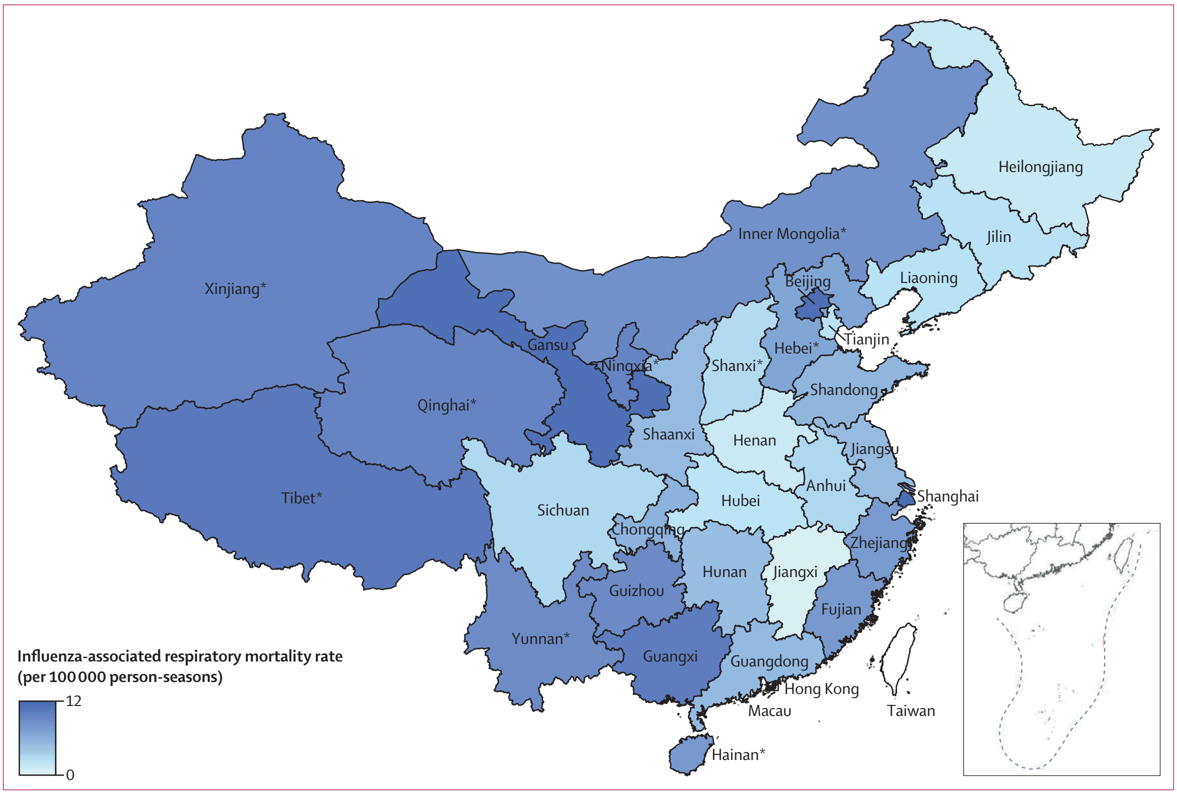

Figure 3: **Age-standardised influenza-associated excess respiratory mortality rates per 100 000 person-seasons for all influenza in China between the 2010–11 through 2014–15 seasons**

*Indicates province excluded from the linear regression modeling analysis. Excess respiratory mortality rate for this province was estimated using a random-effect meta-regression model based on estimates from the remaining 22 provinces.

points (appendix pp 15–18). All analyses were done using R version 3.5.1.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We fitted the linear regression model with the data from 22 of 31 provinces in mainland China, representing 83·0% of the total population. The age-specific estimates of mean excess respiratory mortality rates per season varied across the 22 provinces, with a median of 1·1 (IQR 0·6–1·6) and 38·4 (20·9–53·4) per 100 000 person-seasons for people younger than 60 years and those aged 60 years or older, respectively (figure 2; appendix pp 19–20). The age-standardized excess respiratory mortality rates per season in the 22 provinces ranged between 1·7 (95% CI –0·7 to 4·2) per 100 000 person-seasons in Jiangxi and 11·9 (9·7 to 14·1) per 100 000 person-seasons in Shanghai (figure 3; appendix p 19).

	A(H1N1)pdm09	A(H3N2)	B	All influenza
<60 years	0·4 (0·2–0·5)	0·7 (0·5–1·0)	0·4 (0·1–0·6)	1·5 (1·1–1·9)
≥60 years	9·7 (9·0–10·4)	14·4 (13·3–15·4)	14·4 (13·4–15·5)	38·5 (36·8–40·2)
All ages	1·6 (1·5–1·7)	2·6 (2·4–2·8)	2·3 (2·1–2·5)	6·5 (6·3–6·8)

Data are rates (95% CI) presented by age group and by influenza virus type or subtype in mainland China between the 2010–11 through 2014–15 seasons.

Table: **Mean annual influenza-associated respiratory excess mortality rates per 100 000 person-seasons**

The contributions of infections from different influenza virus types or subtypes to respiratory mortality varied across the 22 provinces, with provincial estimates of median mean excess respiratory mortality rates of 1·6 (IQR 0·9–2·3), 2·9 (1·2–3·8), and 1·9 (0·9–3·4) per 100 000 person-seasons for influenza A(H1N1)pdm09, A(H3N2), and B viruses, respectively (appendix pp 21–22).

Heterogeneity was noted in the estimated all-age annual average excess respiratory mortality rates across the 22 provinces over the seasons (Q=784; p<0·0001; I^2=98%). The random-effects meta-regression model that included regional classification indicated that the annual average excess mortality was higher in the west (Z=3·274; p=0·0011) and east of China (Z=3·109; p=0·0019) than in the centre of China (appendix p 23).

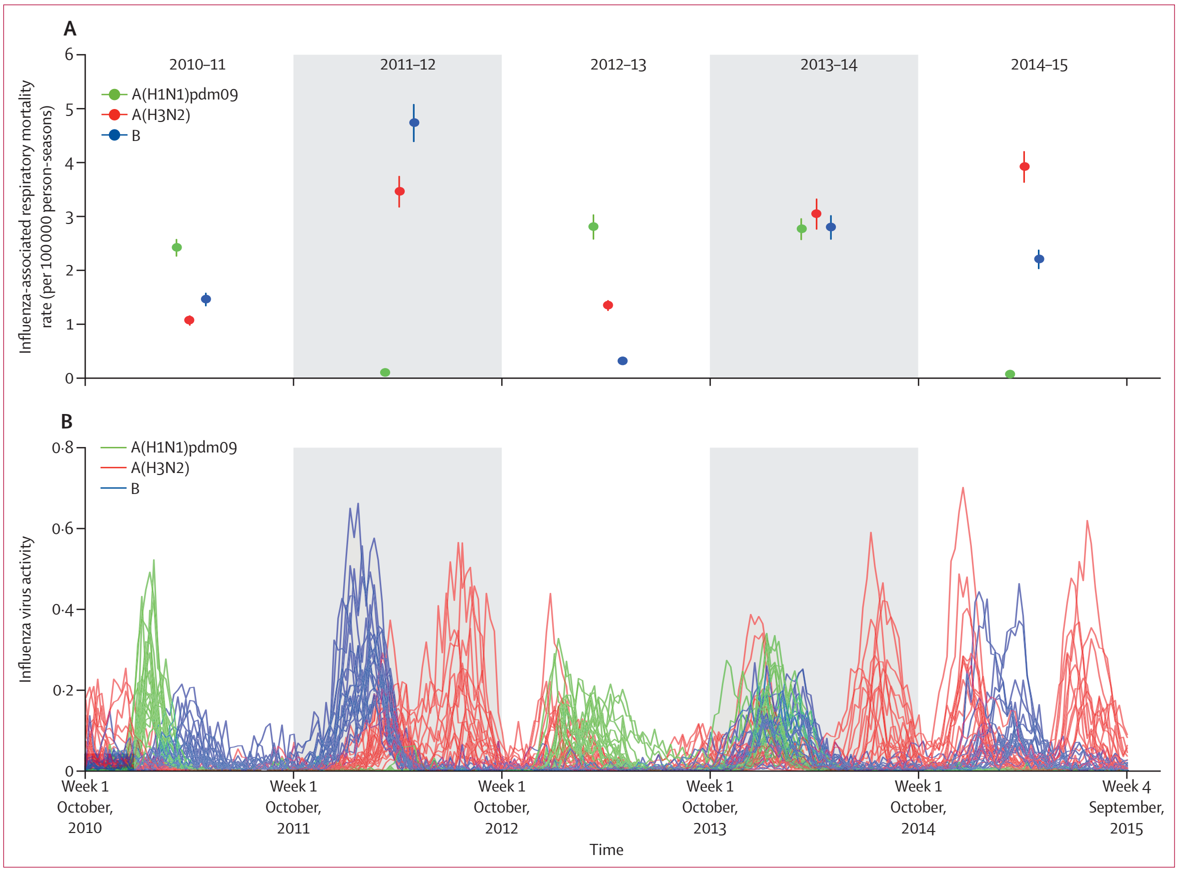

Figure 4: **Annual national estimates of the all-age influenza-associated respiratory excess mortality rates per 100 000 person-seasons in mainland China**
(A) Rates by influenza virus type or subtype from the 2010–11 through 2014–15 seasons. Dots indicate the point estimates of excess respiratory mortality rates. Coloured lines indicate the 95% CI. (B) Weekly detections of influenza viruses from 22 provinces included in the original modelling analysis (each line refers to the virus activity observed in a province).

We estimated that an annual average of 88 100 (95% CI 84 200–92 000) influenza-associated excess respiratory deaths occurred in mainland China between 2010–11 and 2014–15, corresponding to 8·2% (95% CI 7·9–8·6) of all respiratory deaths. Accordingly, the average all-age and age-standardised excess respiratory mortality rates per season were estimated to be 6·5 (95% CI 6·3–6·8) and 5·9 (5·5–6·3; appendix p 20) per 100 000 person-seasons, respectively.

The estimated overall rate of influenza-associated excess respiratory deaths for adults aged 60 years or older was 38·5 (95% CI 36·8–40·2) per 100 000 person-seasons, which was higher than that for individuals younger than 60 years (1·5 [95% CI 1·1–1·9] per 100 000 person-seasons). We estimated that 17 200 (95% CI 12 200–22 000) and 71 000 (67 800–74 100) influenza-associated excess respiratory deaths occurred in individuals younger than 60 years and 60 years or older, respectively, during an influenza season, which corresponded to approximately 20% and 80% of all influenza-associated excess respiratory deaths, respectively.

The national average annual influenza-associated excess respiratory death rates per 100 000 person-seasons are in the table. The average annual mortality burden of influenza A(H3N2) and B virus infections for people 60 years or older was numerically higher than mortality rates attributable to influenza A(H1N1)pdm09 virus infection (table).

Variations occurred in the influenza virus activity and the annual estimated national excess respiratory mortality rates across five influenza seasons (figure 4; appendix p 24). These ranged between 0·1 (95 CI 0·1–0·1) and 2·8 (2·6–3·0) per 100 000 person-seasons for influenza A(H1N1)pdm09, between 1·1 (95% CI 1·0–1·2) and 3·9 (3·6–4·2) per 100 000 person-seasons for A(H3N2) virus, and between 0·3 (95% CI 0·3–0·3) and 4·7 (4·4–5·1) per 100 000 person-seasons for B virus (figure 3; appendix p 24). We estimated that the national excess respiratory mortality rates ranged between 4·5 (95% CI 4·2–4·7) and 8·6 (8·2–9·0) per 100 000 person-seasons in 2012–13 and 2013–14, respectively (appendix p 24).

Results from the sensitivity analysis indicated that there were no substantial variations in the estimates of influenza-associated excess respiratory mortality from different models or from the analysis on a varied set of disease surveillance points. The average annual estimates of influenza-associated excess respiratory mortality rates were robust to the selection of meta-regression models with different independent variables for extrapolation of excess respiratory mortality for the nine provinces excluded from the original modelling analysis. They were also robust for the models with a different time lag between influenza virus activity, climatic factors, and respiratory mortality, and with more disease surveillance points included for the estimation (appendix p 25).

Discussion

We estimated that 88 100 influenza-associated excess respiratory deaths occurred in mainland China during an influenza season, corresponding to 8·2% of annual respiratory deaths. Accordingly, the mean all-age excess respiratory mortality rate in mainland China of 6·5 (95% CI 6·3–6·8) per 100 000 person-seasons fell within the estimate for the Western Pacific region reported in a global study (95% credible interval 3·6–7·5 per 100 000 individuals),[3] despite differences in modelling approaches. Our estimate was also similar to estimates previously published in other countries or regions or cities; eg, our point estimate of the overall influenza-associated excess respiratory mortality rate was similar to that reported for Hong Kong (6·3 per 100 000 person-years),[20] higher than those reported in Yancheng, a subtropical city in eastern China (4·6 per 100 000 person-years),[13] the USA (3·6 per 100 000 person-seasons),[4] and Hefei, a subtropical city in China (2·7 per 100 000 person-years),[17] and lower than that reported in western Kenya (10 per 100 000 person-years).[21] Influenza virus infections might not only cause respiratory deaths, but also lead to deaths by triggering or exacerbating underlying chronic conditions such as cardiovascular diseases.[22] Therefore, the estimated excess respiratory deaths in this study only reflected a fraction of all influenza-associated deaths.[1]

Spatial variations occurred in the estimates of the influenza-associated excess respiratory mortality among the provinces studied. Estimates in provinces located in the west and east of China were higher than those in provinces in the centre of China. The higher mortality burden of influenza in the west of China could be due to a shortage of access to health-care services, especially in rural areas,[23,24] and the higher mortality burden of influenza in the east of China could be due to higher population density, which might increase the risk of influenza transmission. The higher influenza-associated excess respiratory mortality in Shanghai and Beijing might be attributable to their high population densities and high influx of people from other provinces, for migrant work, tourism or seeking health care;[25,26] these factors are likely to increase the risk of influenza transmission in the population and therefore the mortality burden in the cities.

Most of the influenza-associated excess respiratory deaths (around 80%) occurred in people 60 years or older, similar to findings from previous studies.[10,13] Older individuals would be more likely to have underlying health conditions and therefore be at a higher risk of mortality after influenza virus infections.[27] Seasonal influenza vaccination is the most effective intervention in protection against influenza virus infection in outpatients and inpatients.[28] Many high-income countries undertake influenza vaccination programmes in older adults with the goal of reducing influenza-associated mortality in this high-risk group. China in general has low vaccination coverage in the population, although vaccine uptake in some specific age groups is higher in cities such as Beijing, where the local government fully subsidises vaccination in older adults.[7] Further efforts, such as improving health-care services or access for less-developed regions, more targeted interventions for older adults including vaccination, early treatment with antivirals, and improving hand hygiene might also be needed to mitigate the mortality burden of influenza in mainland China.

The virus-specific estimates of excess respiratory mortality rates in our study were higher for A(H3N2) and B viruses compared with influenza A(H1N1)pdm09 virus. A higher excess mortality was also associated with influenza A(H3N2) virus infection compared with other influenza virus types or subtypes in the USA[4] and Hong Kong.[5] Possible explanations are that more severe clinical symptoms caused by seasonal influenza A(H3N2) virus infections are more likely to increase mortality burden;[2,29] there is a higher level of virulence in this subtype;[30] and faster antigenic drift of the virus might lead to a higher incidence of infections in the population and therefore contribute to the higher mortality burden.[31] The varied mortality burden of influenza virus types or subtypes across different study locations could be attributable to the distinct circulating influenza virus types or subtypes during the study period and to transmission dynamics of and population immunity against different influenza virus types or subtypes.[9]

This study had some limitations: first, we estimated the influenza-associated excess respiratory mortality in China based on data from five influenza seasons. The long-term trends of influenza-associated mortality burden should be assessed in the future with data from a longer time span. Second, the analyses were based on data from 22 of 31 provinces in mainland China, which might not fully represent the influenza-associated excess respiratory mortality burden over the country as a whole. Third, the quality of mortality data reported by disease surveillance points varying across provinces might have affected the estimated excess respiratory mortality rates, although our sensitivity analysis did not indicate a substantial effect on the final estimates of this study. Fourth, our analysis only provided combined estimates of the influenza-associated excess respiratory deaths in children and adults collectively as people younger than 60 years instead of two groups separately, because of the small number of deaths reported in each of the age groups. Additionally, we did not include pathogens such as respiratory syncytial virus (RSV) into our model when estimating the excess mortality rates.

RSV was suggested in previous studies to be associated with an increase in mortality of older individuals, although the effect might not be as substantial as that attributable to influenza. The absence of national RSV surveillance data in China did not allow us to investigate the effect of RSV on mortality in this study. Fifth, the potential cluster effect of the estimates from geographically close provinces was not considered in these analyses, which might have led to narrower interval estimates. Finally, we made several statistical choices that should be borne in mind. Although a linear regression model was chosen as the most appropriate to estimate excess mortality rates in 22 provinces, we did not quantitatively assess alternative model fits. Additionally, in both the main analyses and sensitivity analyses, we selected cutoffs to exclude datapoints that we assessed as likely to represent under-reporting; ie, excluding disease surveillance points with an annual average mortality rate of less than 0·4% or an annual mortality rate of less than 0·3% in the main analysis. In the sensitivity analysis to test the effect of under-reporting, we excluded disease surveillance points with annual under-reporting rates of more than 50% (appendix p 15). Different statistical choices around cleaning of the data could have resulted in different numerical outcomes.

In conclusion, human seasonal influenza viruses were associated with substantial mortality burden in population in China, and the burden varied across age groups and provinces. Our estimates of the influenza-associated excess respiratory deaths provide crucial information for optimisation of future public health policy and interventions, such as immunisation campaigns, behavioural campaigns, and targeted treatment strategies in China.

Contributors

PW, BJC, LF, and HY conceived the study. YL, ZP, XW, TC, JuY, LW, JZ, YQ, HJ, SL, JQ, JZ, JiY, YH, MZ, and LF collected data. LL, YL, PW, ZP, JYTW, HSB, YCL, SF, VJF, EHYL, and LF analysed the data. LL, PW, BJC, LF, and HY wrote the first draft of the manuscript. All authors contributed to the interpretation of the results and edited the manuscript.

Declaration of interests

HY has received investigator-initiated research funding from Sanofi Pasteur, GlaxoSmithKline, and Yichang HEC Changjiang Pharmaceutical Company. BJC has received honoraria from Sanofi Pasteur and Roche.

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References

1 Li L, Wong JY, Wu P, et al. Heterogeneity in estimates of the impact of influenza on population mortality: a systematic review. *Am J Epidemiol* 2018; **187:** 378–88.

2 Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. *JAMA* 2004; **292:** 1333–40.

3 Iuliano A, Roguski K, Chang H, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet* 2018; **391:** 1285–300.

4 Goldstein E, Viboud C, Charu V, Lipsitch M. Improving the estimation of influenza-related mortality over a seasonal baseline. *Epidemiology* 2012; **23:** 829–38.

5 Wu P, Goldstein E, Ho LM, et al. Excess mortality associated with influenza A and B virus in Hong Kong, 1998-2009. *J Infect Dis* 2012; **206:** 1862–71.

6 WHO. Influenza (seasonal). 2019. Geneva: World Health Organization. http://www.who.int/mediacentre/factsheets/fs211/en/ (accessed June 21, 2019).

7 Yang J, Atkins KE, Feng L, et al. Seasonal influenza vaccination in China: landscape of diverse regional reimbursement policy, and budget impact analysis. *Vaccine* 2016; **34:** 5724–35.

8 Yu H, Alonso WJ, Feng L, et al. Characterization of regional influenza seasonality patterns in China and implications for vaccination strategies: spatio-temporal modeling of surveillance data. *PLoS Med* 2013; **10:** e1001552.

9 Yu H, Feng L, Viboud CG, et al. Regional variation in mortality impact of the 2009 A(H1N1) influenza pandemic in China. *Influenza Other Respir Viruses* 2013; **7:** 1350–60.

10 Feng L, Shay DK, Jiang Y, et al. Influenza-associated mortality in temperate and subtropical Chinese cities, 2003–2008. *Bull World Health Organ* 2012; **90:** 279–88b.

11 Wu S, Wei Z, Greene CM, et al. Mortality burden from seasonal influenza and 2009 H1N1 pandemic influenza in Beijing, China, 2007–2013. *Influenza Other Respir Viruses* 2018; **12:** 88–97.

12 Yu X, Wang C, Chen T, et al. Excess pneumonia and influenza mortality attributable to seasonal influenza in subtropical Shanghai, China. *BMC Infect Dis* 2017; **17:** 756.

13 Zhang H, Xiong Q, Wu P, Chen Y, Leung NHL, Cowling BJ. Influenza-associated mortality in Yancheng, China, 2011–15. *Influenza Other Respir Viruses* 2018; **12:** 98–103.

14 Wang H, Fu C, Li K, et al. Influenza associated mortality in Southern China, 2010-2012. *Vaccine* 2014; **32:** 973–78.

15 Wong CM, Peiris JS, Yang L, et al. Effect of influenza on cardiorespiratory and all-cause mortality in Hong Kong, Singapore and Guangzhou. *Hong Kong Med J* 2012; **18** (suppl 2): 8–11.

16 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.

17 Liu XX, Qin G, Li X, et al. Excess mortality associated with influenza after the 2009 H1N1 pandemic in a subtropical city in China, 2010–2015. *Int J Infect Dis* 2017; **57:** 54–60.

18 National Center for Chronic and Noncommunicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention. National disease surveillance point system mortality surveillance dataset 2012. Beijing: Popular Science Press. December, 2013: 4.

19 National Meterological Information Center. China Meterological Data Service Center. http://www.cma.gov.cn/2011qxfw/2011qsjgx (accessed August 14, 2019).

20 Wu P, Presanis AM, Bond HS, Lau EHY, Fang VJ, Cowling BJ. A joint analysis of influenza-associated hospitalizations and mortality in Hong Kong, 1998–2013. *Sci Rep* 2017; **7:** 929.

21 Emukule GO, Spreeuwenberg P, Chaves SS, et al. Estimating influenza and respiratory syncytial virus-associated mortality in Western Kenya using health and demographic surveillance system data, 2007–2013. *PLoS One* 2017; **12:** e0180890.

22 Siriwardena AN. Increasing evidence that influenza is a trigger for cardiovascular disease. *J Infect Dis* 2012; **206:** 1636–38.

23 Li J, Shi L, Liang H, Ding G, Xu L. Urban-rural disparities in health care utilization among Chinese adults from 1993 to 2011. *BMC Health Serv Res* 2018; **18:** 102.

24 Zhang T, Xu Y, Ren J, Sun L, Liu C. Inequality in the distribution of health resources and health services in China: hospitals versus primary care institutions. *Int J Equity Health* 2017; **16**: 42.

25 Yuan J, Lau EH, Li K, et al. Effect of live poultry market closure on avian influenza A(H7N9) virus activity in Guangzhou, China, 2014. *Emerg Infect Dis* 2015; **21:** 1784–93.

26 Liu Z. Research on strengthening the management of migrant population in Shanghai. 2013. http://www.gzsk.org.cn/URBAN-INSIGHT/Magazine/2013/201306/201306-145_split_1.pdf (accessed July 21, 2019).

27 Gordon A, Reingold A. The burden of influenza: a complex problem. *Curr Epidemiol Rep* 2018; **5:** 1–9.

28 Castilla J, Godoy P, Dominguez A, et al. Influenza vaccine effectiveness in preventing outpatient, inpatient, and severe cases of laboratory-confirmed influenza. *Clin Infect Dis* 2013; **57:** 167–75.

29 Frank AL, Taber LH, Wells JM. Comparison of infection rats and severity of illness for influenza A subtypes H1N1 and H3N2. *J Infect Dis* 1985; **151:** 73–80.

30 Wright PF, Thompson J, Karzon DT. Differing virulence of H1N1 and H3N2 influenza strains. *Am J Epidemiol* 1980; **112:** 814–19.

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:** 615–19.