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Complete List of Authors:	Li, Jing; Fudan University, School of Public Health Wang, Chunfang; Shanghai Municipal Center for Disease Control and Prevention, Department of Vital Statistics Ruan, Luanqi; Shanghai Pudong New Area Center for Disease Control and Prevention, Research Base of Key Laboratory of Surveillance and Early Warning on Infectious Disease in China CDC Jin, Shan; Shanghai Municipal Center for Disease Control and Prevention, Department of Vital Statistics Ye, Chuchu; Shanghai Pudong New Area Center for Disease Control and Prevention, Research Base of Key Laboratory of Surveillance and Early Warning on Infectious Disease in China CDC Yu, Hui-Ting; Shanghai Municipal Center for Disease Control and Prevention, Department of Vital Statistics Zhu, Weiping; Shanghai Pudong New Area Center for Disease Control and Prevention, Research Base of Key Laboratory of Surveillance and Early Warning on Infectious Disease in China CDC Wang, Xi-Ling; Fudan University, School of Public Health
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Development of influenza-associated disease burden pyramid in a Bayesian framework in Shanghai, China, 2010–2017

Jing Li[1#], Chunfang Wang[2#], Luanqi Ruan[3], Shan Jin[2], Chuchu Ye[3], Huiting Yu[2], Weiping Zhu[3†], Xiling Wang[1,4†]

Author Affiliations:

1. School of Public Health, Fudan University, Key Laboratory of Public Health Safety, Ministry of Education, Shanghai, China
2. Department of Vital Statistics, Division of Health Information, Shanghai Municipal Center for Disease Control and Prevention, Shanghai, China
3. Research Base of Key Laboratory of Surveillance and Early Warning on Infectious Disease in China CDC, Shanghai Pudong New Area Center for Disease Control and Prevention, Shanghai, China
4. Shanghai Key Laboratory of Meteorology and Health, Shanghai, China

[#] These authors are joint first authors and contributed equally to this work

[†] These authors are joint senior authors and contributed equally to this work.

Corresponding Authors:

Xiling Wang, School of Public Health, Fudan University, Key Laboratory of Public Health Safety, Ministry of Education, Xuhui District, 200231, Shanghai, China (erinwang@fudan.edu.cn); Weiping Zhu, Research Base of Key Laboratory of Surveillance and Early Warning on Infectious Disease in China CDC, Shanghai Pudong New Area Center for Disease Control and Prevention, Pudong New Area, 200136, Shanghai, China (wpzhu@pdcdc.sh.cn)

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ABSTRACT

Objectives: Negative estimates could be produced when statistical modelling techniques were applied to estimate morbidity and mortality attributable to influenza. Based on the prior knowledge that influenza viruses are hazardous pathogens and have adverse health outcomes of both respiratory and circulatory diseases, we developed an improved model incorporating Bayes' Theorem to construct the influenza burden pyramid in Shanghai, China.

Methods: We obtained weekly numbers on deaths, hospitalisations, outpatient visits, and influenza virological surveillance data in Shanghai from 2010-2017. We used negative binomial regression models to estimate the influenza-associated excess rates by setting prior distributions of regression coefficients for influenza activity truncated at zero. The clinical severities of influenza were assessed by the influenza-associated outpatient-mortality risks, outpatient-hospitalisation risks, and hospitalisation-mortality risks.

Results: Influenza was associated with an annual average of 15.49 (95% CrI 9.06-22.06) excess respiratory and circulatory disease (R&C) deaths, 100.65 (48.79-156.78) excess R&C hospitalisations, and 914.95 (798.51-1,023.66) excess influenza-like illness outpatient visits per 100,000 population in Shanghai. 97.23% and 80.24% excess R&C deaths and hospitalisations occurred in people aged ≥65 years. More than half of excess morbidity and mortality were associated with influenza A(H3N2), and its severities were 1.65- to 3.54-fold and 1.47- to 2.16-fold higher than that for influenza A(H1N1) and B, respectively.

Conclusions: The proposed Bayesian approach with reasonable prior information improved our estimates. Influenza A(H3N2) was generally associated with higher morbidity and mortality, and relatively more severe compared to influenza A(H1N1) and B. Targeted influenza prevention and control strategies for the elderly in Shanghai may substantially reduce the disease burden.

Keywords: Influenza; disease burden; Bayesian regression

Strengths and limitations of this study

- We comprehensively assessed the impact of influenza on both morbidity and mortality in subtropical Shanghai by integrating multiple data sources of influenza surveillance, hospital records, and death registration.
- The developed 'influenza pyramid', together with the risk between layers, provided key parameters for handy estimation of influenza-associated disease burden in Shanghai as well as in other developed countries/regions/cities.
- The proposed Bayesian approach with reasonable prior information improved statistical estimates of influenza-associated disease burden.
- Our results may be confounded by other co-circulating respiratory viruses which were not included in national virologic surveillance scheme in China.

INTRODUCTION

Annual influenza epidemics result in substantial morbidity and mortality. Influenza virus infections can cause a wide spectrum of diseases, from mild to severe illness requiring hospitalisation, and at times even death.[1-4] The influenza burden can be presented using the disease pyramid with multiple tiers including asymptomatic infections, non-medically attended illnesses, medically attended illnesses, hospitalisations, intensive care unit (ICU) admissions, and deaths.[5] The 'influenza pyramid' provides a full perspective of the disease burden associated with influenza and allows to identify relationships between each layer of the outcome. However, the construction of the pyramid may require merging data gathered from different surveillance systems. Considering the availability of time series data, very few studies have attempted to assess the overall burden of influenza and the estimation tended to focus on only one or two particular levels of the pyramid.[6-9]

The disease burden of influenza is difficult to quantify directly because influenza infections are rarely laboratory-confirmed, or specifically coded as influenza-related in hospital discharge records or death certificates. Statistical modelling techniques have been developed to estimate morbidity and mortality attributable to influenza.[3 10 11] 'Pneumonia and influenza', 'respiratory and circulatory disease', and 'all-cause' are often chosen as outcome variables in modelling methods. 'Pneumonia and influenza' is deemed to be the most specific outcome measures, but this category excludes other respiratory and circulatory diseases exacerbated by influenza. The outcome category 'all-cause' is too broad and sacrifices specificity, thus 'respiratory and circulatory disease' optimizes the balance between sensitivity and specificity.[12-14]

Negative estimates could be produced when statistical modelling techniques were applied to estimate morbidity and mortality attributable to influenza. Based on the prior knowledge that influenza viruses are hazardous pathogens and have

adverse health outcomes of both respiratory and circulatory diseases,[15] we developed an improved model incorporating Bayes' Theorem to construct the pyramid of influenza-associated disease burden. We presented the estimates of influenza-associated deaths and hospitalisations due to respiratory and circulatory diseases, and influenza-like illness (ILI) outpatient visits in Shanghai, China from 2010 to 2017.

METHODS

Influenza surveillance data

Weekly ILI surveillance and influenza virological surveillance data from 2010 to 2017 were obtained from the Pudong New Area Center for Disease Control and Prevention (PDCDC). Four hospitals conducted year-round surveillance of influenza, including two national sentinel hospitals (Dongfang Hospital and Zhoupu Hospital) and two municipal sentinel hospitals (Pudong Hospital and Eastern Division of Renji Hospital) in Pudong New Area, Shanghai. Weekly positive proportions of laboratory-confirmed influenza (LAB%) in Shanghai from 2010 to 2015 was obtained by digitalizing the time series plot of influenza activity from published literature.[16] As we do not have access to influenza surveillance data in Shanghai from 2016 to 2017, we used influenza virus activity in Pudong New Area as an alternative for that of Shanghai because we found a strong correlation of LAB% between the two data sources ($r = 0.80$-0.93, all $P < 0.001$) (**Figure S1**). ILI surveillance data included weekly numbers of total outpatient visits and age-specific ILI consultations (0-4, 5-14, 15-24, 25-59, and ≥60 years). As the elderly people with an age cutpoint of ≥65 years were used in our study, we reclassified these five age groups into 0-14, 15-64, and ≥65 years according to the age distribution of the permanent population in Pudong New Area. Influenza virological surveillance data included weekly numbers of total specimens tested and specimens positive for influenza A(H1N1) (referring to the 2009 pandemic strain A(H1N1)pdm09), A(H3N2), and B viruses.

Mortality and hospitalisation data

The death registration system of Shanghai is based on its household registration system (Hukou).[17] We obtained the weekly mortality data for registered residents in Shanghai for the years 2010-2017 from the Shanghai Center for Disease Control and Prevention (SCDC). Weekly inpatient data from 2013 to 2017 were obtained from the Shanghai Municipal Health and Family Planning Commission. All medical institutions in Shanghai have been required to apply the new edition of the inpatient medical record home page where full indicators were collected since January 1, 2013. We excluded the data for the first half of the year (from the 1st week of 2013 to the 26th week of 2013) at this pilot stage. We only included inpatients from secondary and tertiary hospitals and whose current residence in Shanghai. Hospital admissions were greatly reduced around the traditional Chinese Spring Festival and National Day, which cannot reflect patients' true healthcare needs, and thus we replaced the week containing the holidays with the average value of the previous and next week.[18]

We retrieved underlying causes of death and primary discharge diagnoses coded as respiratory disease (J00-J99), circulatory disease (I00-I99), and respiratory and circulatory disease (R&C, J00-J99 and I00-I99), in the International Classification of Diseases Codes, version 10 (ICD-10). We assumed that the excess R&C deaths or hospitalisations approximate the totality of the influenza-associated deaths or hospitalisations. Data for death and hospitalisation were stratified by age groups (<65 years and ≥65 years; 0-5 years, 6-17 years, 18-64 years, and ≥65 years, respectively).

Population and meteorological data

Age-specific annual population size including registered population and permanent population were obtained from the Shanghai Statistical Yearbook[19] and National Bureau of Statistics of China, respectively. Annual outpatient visits (medicine and pediatrics) were obtained from China's Health and Family Planning

Statistical Yearbook.[20] Daily temperature and dew point temperature from 2010 to 2017 were obtained from the Shanghai Meteorological Bureau and were averaged into a weekly level. Absolute humidity was derived from temperature and relative humidity.

Statistical analysis

Negative binomial regression models were fitted separately to weekly deaths, hospitalisations, and ILI outpatient visits by age groups and causes of disease in a Bayesian framework using Markov Chain Monte Carlo approach. We used LAB% as a proxy variable for influenza activity in the models and assumed a multiplicative association between weekly influenza activity and counts of deaths, hospitalisations or ILI outpatient visits, which has been widely applied in previous literature.[3 4 21] Natural cubic splines of the calendar week and absolute humidity were added to adjust for time-varying confounders. Viral surveillance data were lagged by 0 to 3 weeks. We selected the degrees of freedom and lag weeks based on the minimum deviance information criterion (DIC)[22] and curve fitting (**Table S1, Figure S2-S4**). We constrained the regression coefficients for influenza activity to be positive by truncating the Normal priors at zero as previous studies have demonstrated a positive association between influenza and R&C morbidity and mortality.[3 4] More details of the statistical model are available in **Appendix S1**.

The influenza-associated excess deaths, hospitalisations, and ILI outpatient visits were estimated as the difference between the predicted numbers under the model and the baseline numbers when influenza activity proxies were assumed to be zero. The influenza-associated excess mortality rates, hospitalisation rates, and ILI outpatient visit rates were estimated as the numbers of excess deaths, hospitalisations, and ILI outpatient visits per 100,000 population. Age-standardized rates were derived using the World (WHO 2000-2025) Standard Population as the reference.[23] With the assumption that the proportion of ILI

outpatient visits among medicine and pediatric outpatient visits in the surveillance hospitals of Pudong New Area is representative of Shanghai, we extrapolated the influenza-associated ILI outpatient visits in surveillance hospitals to the general population in Shanghai (see details in **Appendix S2**).[24]

Each model was run 60,000 Markov Chain Monte Carlo iterations with the first 30,000 iterations discarded as burn-in. We estimated the clinical severity of influenza with different influenza virus types/subtypes and age groups, including outpatient-mortality risks, outpatient-hospitalisation risks, and hospitalisation-mortality risks, as the ratios of influenza-associated excess mortality rates to ILI outpatient visit rates, hospitalisation rates to ILI outpatient visit rates, and mortality rates to hospitalisation rates. The 95% credibility intervals (95% CrI) for excess crude and age-standardized rates were based on the samples drawn from the posterior distributions. Estimates of the outpatient-mortality risks, outpatient-hospitalisation risks, hospitalisation-mortality risks, and their 95% credibility intervals, were also based on these posterior samples.

Analyses were performed using the '*rjags*' package of R software, version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria), an interface between R and JAGS software, version 4.3.0 (Plummer 2003).

Patient and public involvement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Descriptive statistics

During the study period 2010-2017, Pudong New Area tested 12,283 specimens for influenza viruses, of which 409 were positive for influenza A(H1N1) virus, 1427 for influenza A(H3N2) virus, and 812 for influenza B virus (**Table 1**).

Influenza B virus was the predominant circulating virus in 2010-2011 and a shift to the influenza A(H3N2) virus in the subsequent years (**Figure 1**). In general, R&C mortality rates, R&C hospitalisation rates, and ILI outpatient visit rates increased from 2010 to 2017 in Shanghai, with annual average rates of 392.32, 2,444.94, and 5,247.92 per 100,000 population, respectively (**Table 1**).

Influenza-associated disease burden

During the study period, we estimated an annual average of 2,223 (95% CrI 1,300-3,164) excess R&C deaths, 24,353 (95% CrI 11,805-37,934) excess R&C hospitalisations, and 218,733 (95% CrI 190,897-244,722) excess ILI outpatient visits, attributable to influenza in Shanghai, corresponding to 3.95%, 4.12%, and 17.43% of all R&C deaths, R&C hospitalisations, and ILI outpatient visits, respectively. Accordingly, the estimated crude and age-standardized rates per 100,000 population were 15.49 (95% CrI 9.06-22.06) and 7.36 (4.76-10.25) excess R&C deaths, 100.65 (95% CrI 48.79-156.78) and 97.90 (70.74-129.02) excess R&C hospitalisations, 914.95 (95% CrI 798.51-1,023.66) and 974.65 (855.22-1,100.21) excess ILI outpatient visits, respectively (**Table 2**). The pyramids of influenza-associated disease burden in Shanghai were shown in **Figure 2**.

Influenza-associated R&C mortality rate for people aged ≥65 years was 81.03 (95% CrI 50.41-116.99) per 100,000 population, which was substantially higher than that for those aged <65 years (0.70 [95% CrI 0.23-1.37] per 100,000 population) (**Table 2**). The age-specific influenza-associated R&C hospitalisation rates per 100,000 population showed a J-shaped pattern: highest among people aged ≥65 years (696.38 [95% CrI 396.31-1,026.38]), second highest among children aged 0-5 years (123.21 [95% CrI 46.56-212.08]), followed by children aged 6-17 years (69.19 [46.65-91.48]), and lowest among people aged 18-64 years (20.73 [95% CrI 7.02-39.76]). Children aged 0-14 years had the highest rate of influenza-associated ILI outpatient visits (1,430.91 [95% CrI 1,096.85-1,773.40] per

100,000 population), followed by people aged ≥65 (1,096.79 [95% CrI 914.25-1,261.59] per 100,000 population) and 15-64 years (781.92 [664.68-894.82] per 100,000 population). 97.23% of excess R&C deaths and 80.24% of excess R&C hospitalisations occurred among people aged ≥65 years, whereas only 13.13% of excess ILI outpatient visits occurred in this age group.

Influenza A(H3N2) virus was generally associated with the highest rates of influenza-associated deaths, hospitalisations, and ILI outpatient visits (**Table 2, Figure 2**). Of all these influenza-associated excess estimates, more than half were associated with the influenza A(H3N2) virus. When broken down by respiratory disease and circulatory disease, for all ages, the respiratory death rate was 1.40-fold lower than that of circulatory death, while the respiratory hospitalisation rate was 2.40-fold higher than that of circulatory hospitalisation (**Table 2**). Influenza-associated respiratory hospitalisation rates showed a similar age pattern to R&C hospitalisation, while for circulatory hospitalisation, the estimated rates increased with age.

Influenza-associated clinical severity

Influenza-associated outpatient-mortality risk, outpatient-hospitalisation risk, and hospitalisation-mortality risk were estimated to be 1.69% (95% CrI 0.97-2.48%), 11.09% (5.23-17.39%), 15.29% (7.68-34.85%), respectively (**Table S2**). That is to say, we estimated that there were 1.69 excess deaths and 11.09 excess hospitalisations for every 100 excess ILI outpatient visits, and 15.29 excess deaths for every 100 excess hospitalisations in Shanghai. The estimated risks for people aged ≥65 years were higher than that for all ages except for hospitalisation-mortality risks (**Figure 3**). When comparing these risks between different types/subtypes of the influenza viruses, we found that influenza A(H3N2) virus had the greatest outpatient-mortality risks, outpatient-hospitalisation risks, and hospitalisation-mortality risks across different age groups. Its severities were 1.65- to 3.54-fold and 1.47- to 2.16-fold higher than that for influenza A(H1N1)

and B viruses, respectively. But the difference did not reach statistical significance. Also, we presented separately the influenza-associated hospitalisation-mortality risks for respiratory disease and circulatory disease (**Figure S5**). People with the circulatory disease had a 3.22- to 5.08-fold higher hospitalisation-mortality risk than that of respiratory disease (**Table S2**).

DISCUSSION

Performing regression analyses in a Bayesian framework has two advantages in our study. First, positive priors truncated the posterior distributions of regression coefficients for influenza activity to ensure the positivity of the generated samples. Otherwise, it is unable to explain that influenza is negatively associated with health outcomes of both respiratory and circulatory diseases, especially deaths in young age groups. Second, posterior samples allow us to estimate the 95% credibility intervals for these ratios, which can be challenging in a frequentist framework.

Although there were great year-to-year variations in excess mortality and morbidity, we estimated that influenza contributed to an average of 15.49 (95% CrI 9.06-22.06) excess R&C deaths, 100.65 (95% CrI 48.79-156.78) excess R&C hospitalisations, and 914.95 (95% CrI 798.51-1,023.66) excess ILI outpatient visits per 100,000 population in Shanghai. Our estimates of influenza-associated mortality and morbidity are comparable with the corresponding estimates published for the United States,[4 25 26] Hong Kong SAR,[27] and five southern Chinese cities.[28] In particular, Hong Kong SAR reported an approximately twofold higher hospitalisation burden than our estimates,[27] which could be explained by the result of expanding health service capacities and lowering admission criteria due to the aging population of Hong Kong in recent years.[13 21 29] However, caution is needed when comparing these estimates between countries/areas/cities due to variations in the age structure of populations. Influenza A(H3N2) virus accounted for the highest disease burden than the other two types, which has also been

demonstrated by other studies.[4 14 30] Influenza A(H3N2) virus is believed to have more frequent antigen drift than seasonal influenza A(H1N1) and B viruses.[31 32] Additionally, our study revealed that influenza A(H3N2) virus was relatively more severe as well.

The elderly people are most severely affected by influenza, with the highest influenza-associated mortality rate and hospitalisation rate, the second highest influenza-associated ILI outpatient visit rate. The aging of the Shanghai population is an important contributor to the high rates of influenza-associated mortality and morbidity. For example, the excess mortality rates after age standardization decreased by more than half. Between 2010 and 2017, the registered population aged ≥65 years in Shanghai increased by 28.70%, of about 3.18 million by 2017, accounting for 21.83% of the total population. Interestingly, people aged ≥65 years have lower hospitalisation-mortality risks than for all ages. A possible explanation might be that young adults are less likely to be hospitalized compared to elderly people, but some of them do develop serious illnesses and require hospitalisation, and thus have a greater risk of dying.

Currently, population-based studies of influenza-associated mortality and morbidity have been increasingly reported in mainland China. Of these, two nationally representative studies estimated province-level influenza-associated respiratory mortality rates and ILI outpatient visit rates. However, studies on influenza-associated hospitalisation burden are limited to several cities/districts of Beijing,[33 34] Jiangsu,[35-39] and Hubei.[40] Our study produces a comprehensive assessment of the impact of influenza in Shanghai, especially the hospitalisation burden, which has never been assessed. Our estimated ratios between each layer of the 'influenza pyramid' provided important parameters for the estimation of influenza-associated disease burden.

Nevertheless, our study had several limitations. First, although there was a strong

correlation of influenza virus activity between Pudong New Area and Shanghai, the difference between the two may slightly affect the estimates of influenza burden. Second, national ILI surveillance were aggregated data with defined age groups and cannot be unified into the age groups used for inpatient data. When extrapolating influenza-associated ILI outpatient visits and reclassifying ILI consultations, we were based on representativeness assumptions, but further evaluation is still needed. Third, our estimates of mortality burden and morbidity burden are not exactly based on the same population. We could not rule out the possibility that the mortality burden may be underestimated or overestimated. Fourth, we did not have data on co-circulating respiratory viruses, such as respiratory syncytial virus, which may have confounded the results.

In conclusion, the proposed Bayesian approach with reasonable prior information improved our estimates. Our study highlighted the substantial morbidity and mortality burden attributed to influenza in Shanghai. Influenza A(H3N2) virus was generally associated with more morbidity and mortality, and relatively more severe compared to influenza A(H1N1) and B viruses. Targeted influenza prevention and control strategies for the elderly in Shanghai may substantially impact the disease burden.

Contributors

X.W. and W.Z. conceived, designed, and supervised the study. J.L., C.W., W.Z., L.R., S.J., C.Y., and H.Y. participated in data collection. J.L., X.W., and S.J. conducted statistical analyses. J.L. and C.W. drafted the manuscript. X.W. and W.Z. commented on the data and its interpretation, revised the content critically. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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Table 1. Annual summary of influenza activity, ILI outpatient visit rate, hospitalisation rate, and mortality rate in Shanghai, 2010-2017.

	2010	2011	2012	2013	2014	2015	2016	2017
Influenza A(H1N1) (%)	30 (17.24)	54 (40.00)	0 (0.00)	32 (19.88)	56 (15.34)	68 (14.17)	138 (30.53)	31 (5.09)
Influenza A(H3N2) (%)	45 (25.86)	1 (0.74)	155 (56.99)	128 (79.50)	220 (60.27)	272 (56.67)	226 (50.00)	380 (62.40)
Influenza B (%)	99 (56.90)	80 (59.26)	117 (43.01)	1 (0.62)	89 (24.38)	140 (29.17)	88 (19.47)	198 (32.51)
Total specimens tested	974	755	1026	1231	1935	2127	2093	2142
ILI consultation rate[a]	26.73	22.31	20.99	23.00	23.94	25.85	25.00	32.18
ILI outpatient visit rate[b]	4681.27	4120.52	4152.99	4633.98	5173.12	5889.31	5685.84	7577.41
Hospitalisations rate[c]								
R&C	-	-	-	1922.47	2151.03	2415.85	2612.58	2861.75
Respiratory disease	-	-	-	677.56	782.49	853.14	892.45	987.28
Circulatory disease	-	-	-	1244.91	1368.54	1560.79	1720.12	1874.46
Mortality rate[d]								
R&C	351.16	359.94	385.52	381.45	399.40	428.57	414.33	416.38
Respiratory disease	82.15	79.42	85.13	78.70	80.80	83.19	74.40	71.13
Circulatory disease	269.01	280.51	300.39	302.74	318.60	345.38	339.93	345.25
Registered population	14,123,202	14,193,600	14,269,319	14,323,391	14,386,900	14,429,476	14,499,990	14,551,300
Permanent population	23,019,196	23,474,591	23,804,303	24,151,500	24,256,797	24,152,700	24,197,001	24,197,001

Influenza surveillance data were recorded in Pudong New Area, including specimens positive for influenza by type/subtype, total specimens tested, ILI consultations, and total outpatient visits. ILI, influenza-like illness; R&C, respiratory and circulatory disease.

[a] ILI consultation rate per 1,000 outpatient visits.

[b] ILI outpatient visit rate per 100,000 permanent population.

[c] Hospitalisation rate per 100,000 permanent population.

[d] Mortality rate per 100,000 registered population.

Table 2. Mean annual influenza-associated excess mortality rates and hospitalisation rates due to respiratory and circulatory diseases, and influenza-like illness outpatient visit rates (per 100,000 population) by influenza type/subtype and age group in Shanghai, 2010-2017.

	All influenza	A(H1N1)	A(H3N2)	B
Influenza-associated excess mortality rate				
R&C				
Age-standardized	7.36 (4.76, 10.25)	1.07 (0.27, 2.21)	4.97 (2.90, 7.17)	1.31 (0.21, 3.09)
All ages	15.49 (9.06, 22.06)	2.10 (0.17, 4.66)	10.69 (5.42, 15.80)	2.62 (0.16, 6.86)
<65 years	0.70 (0.23, 1.37)	0.26 (0.02, 0.57)	0.22 (0.01, 0.74)	0.16 (0.01, 0.59)
≥65 years	81.03 (50.41, 116.99)	9.73 (0.86, 23.83)	57.47 (31.71, 82.58)	13.62 (0.93, 34.48)
Respiratory disease				
Age-standardized	3.40 (2.73, 4.13)	0.65 (0.37, 0.95)	2.16 (1.70, 2.61)	0.65 (0.20, 1.09)
All ages	6.90 (5.27, 8.39)	1.16 (0.53, 1.83)	4.50 (3.41, 5.51)	1.29 (0.27, 2.39)
<65 years	0.51 (0.34, 0.69)	0.18 (0.10, 0.26)	0.27 (0.14, 0.40)	0.06 (0, 0.18)
≥65 years	35.70 (27.78, 44.16)	5.90 (2.49, 9.39)	23.13 (18.04, 27.84)	7.21 (1. 71, 12.58)
Circulatory disease				
Age-standardized	4.82 (2.81, 7.04)	0.78 (0.16, 1.66)	3.18 (1.41, 4.76)	0.77 (0.10, 1.99)
All ages	9.64 (5.05, 14.51)	1.43 (0.10, 3.59)	6.56 (2.64, 10.66)	1.48 (0.07, 4.35)
<65 years	0.50 (0.17, 1.01)	0.20 (0.02, 0.47)	0.14 (0.01, 0.56)	0.11 (0.01, 0.44)
≥65 years	52.81 (28.66, 79.37)	7.00 (0.31, 17.29)	36.78 (15.03, 56.76)	7.78 (0.36, 22.57)
Influenza-associated excess hospitalisation rate				
R&C				
Age-standardized	97.90 (70.74, 129.02)	19.89 (9.82, 31.10)	51.22 (30.34, 73.87)	26.69 (14.29, 43.22)
All ages	100.65 (48.79, 156.78)	19.89 (2.38, 38.93)	60.96 (19.95, 100.85)	20.33 (1.62, 53.10)

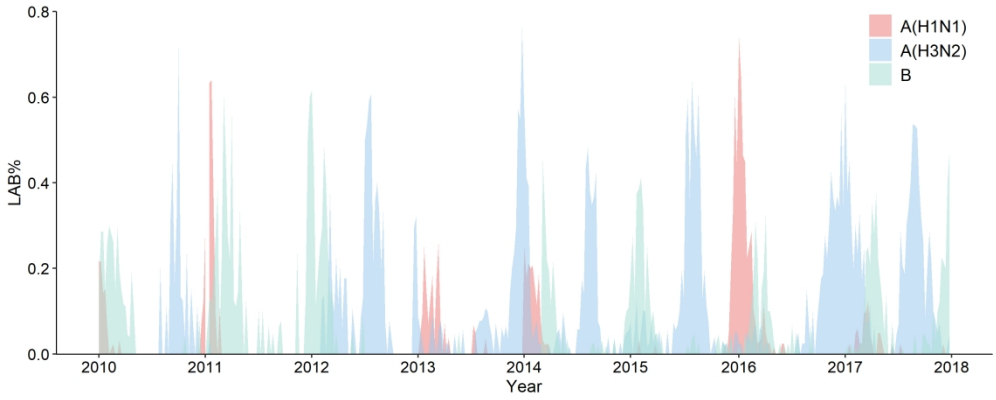
0-5 years	123.21 (46.56, 212.08)	38.04 (8.59, 70.90)	38.19 (1.49, 100.54)	44.47 (4.86, 93.90)
6-17 years	69.19 (46.65, 91.48)	14.13 (5.24, 22.53)	19.49 (2.93, 37.55)	36.15 (24.95, 48.42)
18-64 years	20.73 (7.02, 39.76)	5.87 (0.54, 12.78)	10.02 (0.73, 24.30)	4.24 (0.21, 12.87)
≥65 years	696.38 (396.31, 1026.38)	110.79 (14.68, 237.24)	440.96 (208.84, 687.52)	140.10 (11.93, 326.64)
Respiratory disease				
Age-standardized	84.22 (70.58, 100.36)	20.08 (13.89, 25.93)	45.87 (34.88, 58.36)	19.93 (12.20, 28.69)
All ages	72.48 (51.34, 95.11)	14.46 (5.63, 23.41)	47.89 (29.01, 66.75)	10.52 (1.13, 23.15)
0-5 years	171.40 (78.58, 277.30)	50.95 (15.35, 84.07)	78.11 (9.17, 159.17)	40.15 (4.60, 94.86)
6-17 years	77.07 (50.02, 103.71)	18.88 (7.59, 29.43)	26.72 (7.02, 47.51)	32.95 (20.01, 45.33)
18-64 years	15.46 (8.98, 22.11)	4.31 (1.69, 6.94)	8.77 (3.78, 13.74)	2.31 (0.21, 5.76)
≥65 years	501.90 (406.51, 600.23)	97.86 (53.77, 146.64)	323.59 (243.86, 400.37)	87.29 (22.88, 153.14)
Circulatory disease				
Age-standardized	23.42 (10.38, 41.41)	4.77 (1.06, 11.18)	10.94 (2.56, 23.71)	6.96 (1.42, 16.36)
All ages	30.20 (9.61, 60.12)	6.10 (0.40, 17.24)	14.23 (0.88, 36.60)	8.55 (0.47, 24.98)
0-5 years	1.03 (0.30, 2.32)	0.17 (0.01, 0.68)	0.36 (0.02, 1.51)	0.35 (0.01, 1.24)
6-17 years	2.30 (0.91, 3.98)	0.78 (0.14, 1.44)	0.93 (0.09, 2.25)	0.54 (0.04, 1.41)
18-64 years	8.44 (2.28, 19.89)	1.66 (0.06, 5.78)	4.23 (0.19, 13.01)	1.89 (0.09, 7.35)
≥65 years	210.20 (63.08, 404.70)	41.37 (2.78, 114.16)	95.80 (6.27, 237.28)	65.85 (4.36, 173.23)
Influenza-associated excess ILI outpatient visit rate				
Age-standardized	974.65 (855.22, 1100.21)	332.17 (292.83, 375.69)	414.98 (329.49, 505.67)	256.89 (186.71, 326.45)
All ages	914.95 (798.51, 1023.66)	295.36 (253.86, 338.55)	424.74 (340.90, 510.52)	224.37 (158.26, 284.61)
0-14 years	1430.91 (1096.85, 1773.40)	482.20 (370.05, 605.77)	382.26 (156.64, 607.05)	586.25 (360.05, 818.06)
15-64 years	781.92 (664.68, 894.82)	284.84 (240.37, 328.79)	389.71 (299.27, 480.45)	134.60 (76.48, 196.58)
≥65 years	1096.79 (914.25, 1261.59)	228.14 (169.99, 281.51)	722.65 (575.04, 868.30)	177.45 (88.86, 268.13)

R&C, respiratory and circulatory disease; ILI, influenza like illness.

Figure 1. Influenza activity by type/subtype in Pudong New Area, Shanghai, 2010-2017. LAB%, weekly positive proportions of laboratory-confirmed influenza.

Figure 2. The pyramid of influenza burden by influenza virus types/subtypes and age groups in Shanghai, 2010-2017. R&C, respiratory and circulatory disease; ILI, influenza-like illness.

Figure 3. Clinical severity of influenza with different influenza virus types/subtypes and age groups. (A) Outpatient-mortality risk; (B) Outpatient-hospitalisation risk; (C) Hospitalisation-mortality risk.



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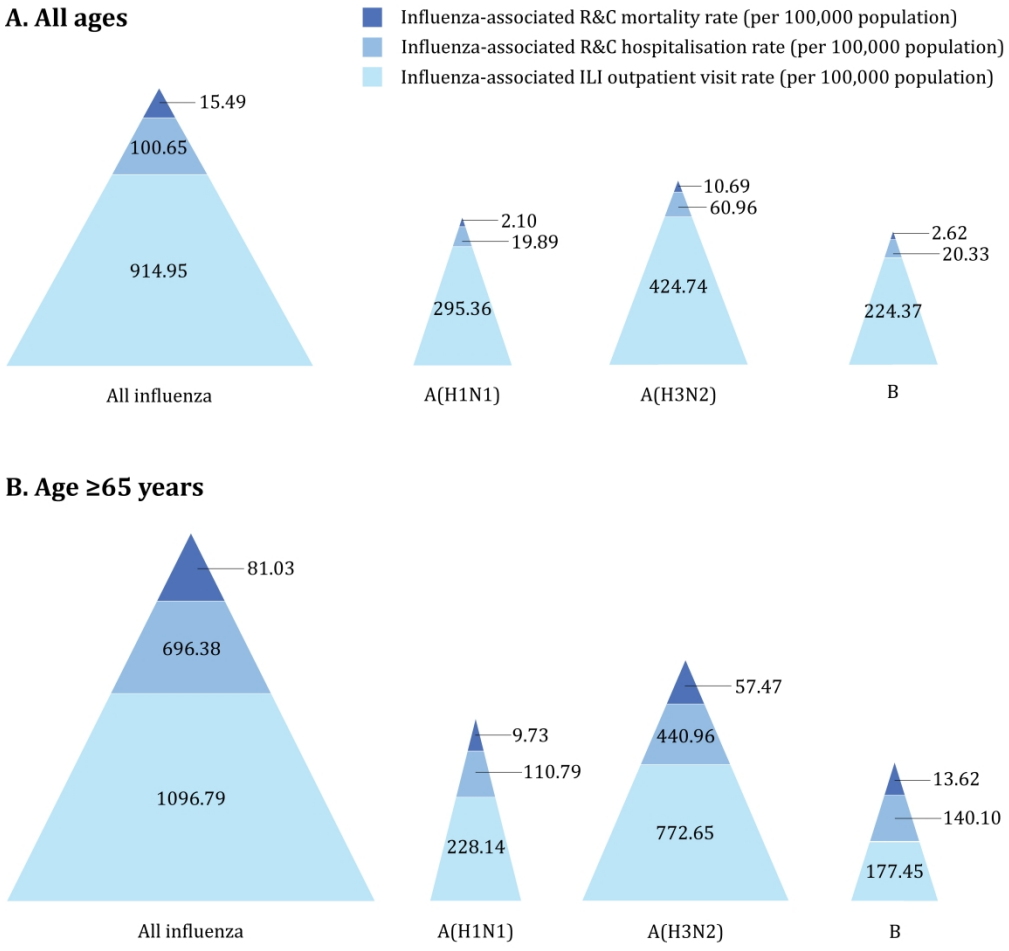

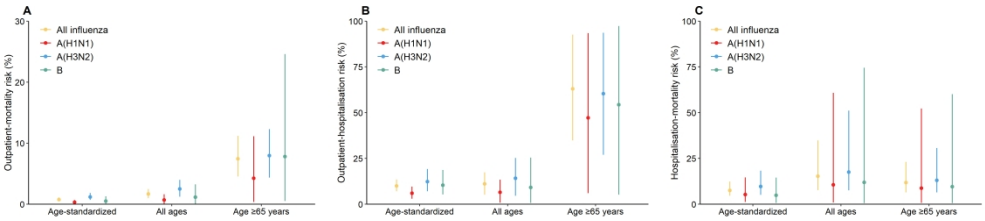

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Supplementary appendix

Development of influenza-associated disease burden pyramid in a Bayesian framework in Shanghai, China, 2010–2017

Jing Li[1#], Chunfang Wang[2#], Luanqi Ruan[3], Shan Jin[2], Chuchu Ye[3], Huiting Yu[2], Weiping Zhu[3†], Xiling Wang[1,4†]

S1. Negative binomial regression models in a Bayesian framework.

We used negative binomial regression models in a Bayesian framework to estimate the influenza-associated mortality rate, hospitalisation rate, and ILI outpatient visit rate across different age groups and causes of disease from 2010 to 2017 in Shanghai. The basic models were as follow:

$$\begin{cases} Y_t \sim NB(r, r/(r+\mu_t)) \\ log(\mu_t) = \beta_0 + \beta_1[A(H1N1)]_{t-i} + \beta_2[A(H3N2)]_{t-i} + \beta_3[B]_{t-i} + ns(t) + ns(AH_t) \end{cases}$$

We used the matrix product of a design matrix $x[,k]$ and a vector of unknown parameters b_k to describe $ns(x)$:

$$ns(t) = \sum_{k=1}^{K} b_{1k} t[,k]$$

$$ns(AH_t) = \sum_{k=1}^{4} b_{2k} AH_t[,k]$$

Where,

- Y_t is the observed number of deaths, hospitalisations, or ILI outpatient visits at week t. The variable Y_t is assumed to follow a negative binomial distribution with size parameter r and probability parameter $r/(r+\mu_t)$.
- $A(H1N1)_{t-i}$, $A(H3N2)_{t-i}$ and B_{t-i} denote the influenza activity proxies (LAB%) for influenza $A(H1N1)$, $A(H3N2)$ and B viruses, respectively, at week $t-i$, i denotes the lag time between influenza infection and health outcome, which varies from 0 to 3 weeks.
- $ns(t)$ and $ns(AH_t)$ denote the smooth functions of calendar week and absolute humidity respectively.

The priors specified in the Bayesian model were the following:

- $\beta_0 \sim Normal(0, 10^6)$
- $\beta_i \sim Normal(0, 10^6)^+$, $i = 1, 2, 3$, where $Normal(0, 10^6)^+$ is the truncated Normal distribution restricted to positive values.

- $b_{1k} \sim Normal(0, 10^6)$
- $b_{2k} \sim Normal(0, 10^6)$
- $r \sim uniform(0, 50)$

S2. Extrapolation of influenza-associated ILI outpatient visits from surveillance hospitals to general population in Shanghai.

We assumed that the proportion of ILI outpatient visits among medicine and pediatric outpatient visits in the surveillance hospitals of Pudong New Area is representative of Shanghai. Thus, influenza-associated ILI outpatient visit rates were calculated as the product of the proportion of influenza-associated ILI outpatient visit in surveillance hospitals and the proportion of medicine and pediatric outpatient visits in the population.

$$\frac{Influenza-associated\ ILI\ outpatient\ visits\ in\ Shanghai}{Total\ general\ population\ in\ Shanghai} = \frac{Total\ medicine\ and\ pediatric\ outpatient\ visits\ in\ Shanghai}{Total\ general\ population\ in\ Shanghai} \times \frac{Total\ influenza-associated\ ILI\ outpatient\ visits\ in\ surveillance\ hospitals}{Total\ medicine\ and\ pediatric\ outpatient\ visits\ in\ surveillance\ hospitals}$$

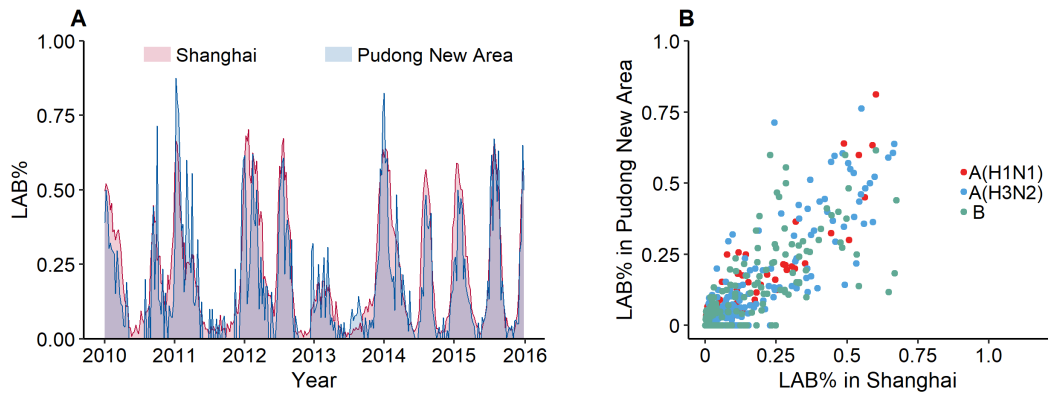

Figure S1. Weekly LAB% in Shanghai and Pudong New Area, 2010-2015. LAB%, weekly positive proportions of laboratory-confirmed influenza. Pearson's correlation coefficients of LAB% between Pudong New Area and Shanghai are 0.93, 0.88 and 0.80 for influenza A(H1N1), A(H3N2), and B, respectively.

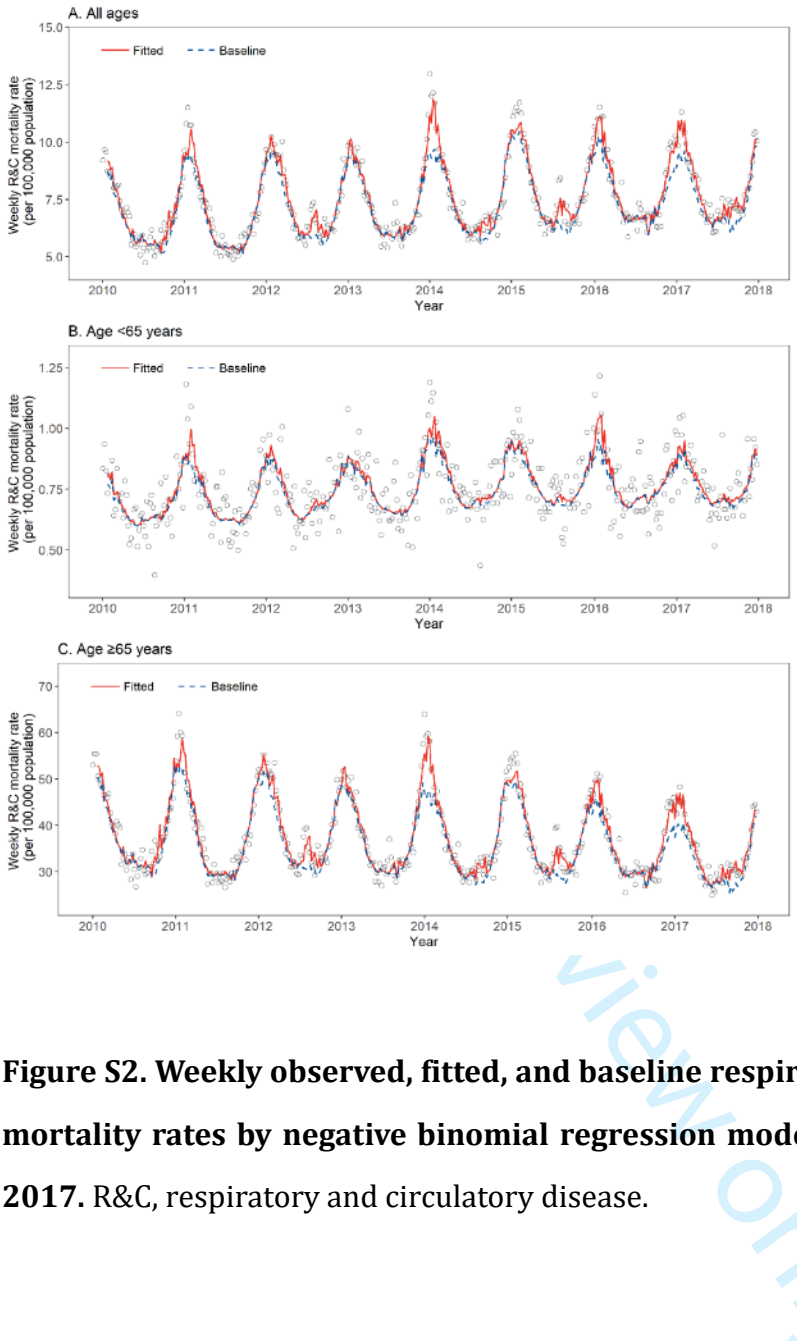

Figure S2. Weekly observed, fitted, and baseline respiratory and circulatory mortality rates by negative binomial regression model in Shanghai, 2010-2017. R&C, respiratory and circulatory disease.

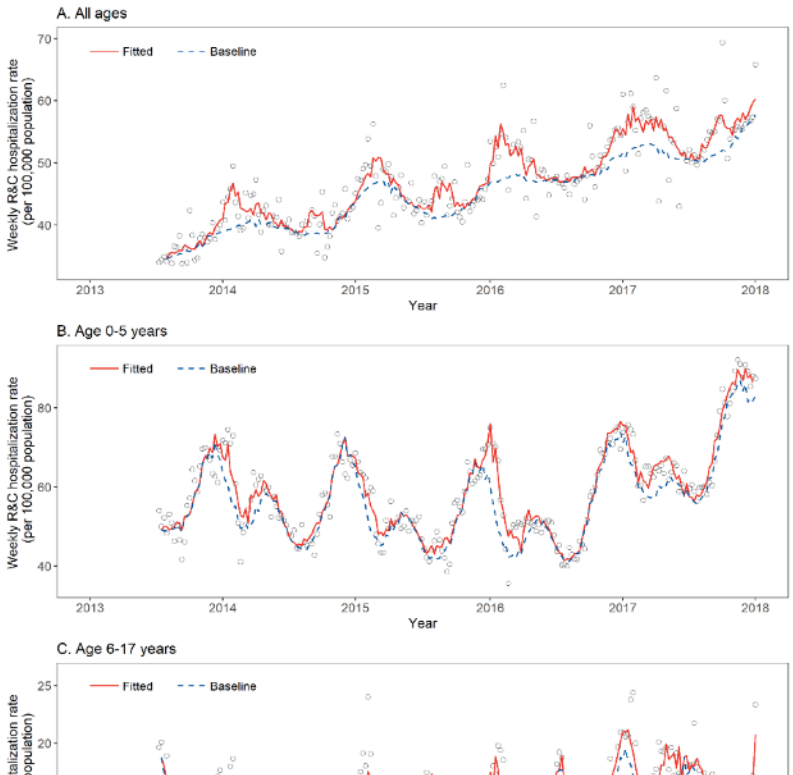

Figure S3. Weekly observed, fitted, and baseline respiratory and circulatory hospitalisation rates by negative binomial regression model in Shanghai, 2013-2017. R&C, respiratory and circulatory disease.

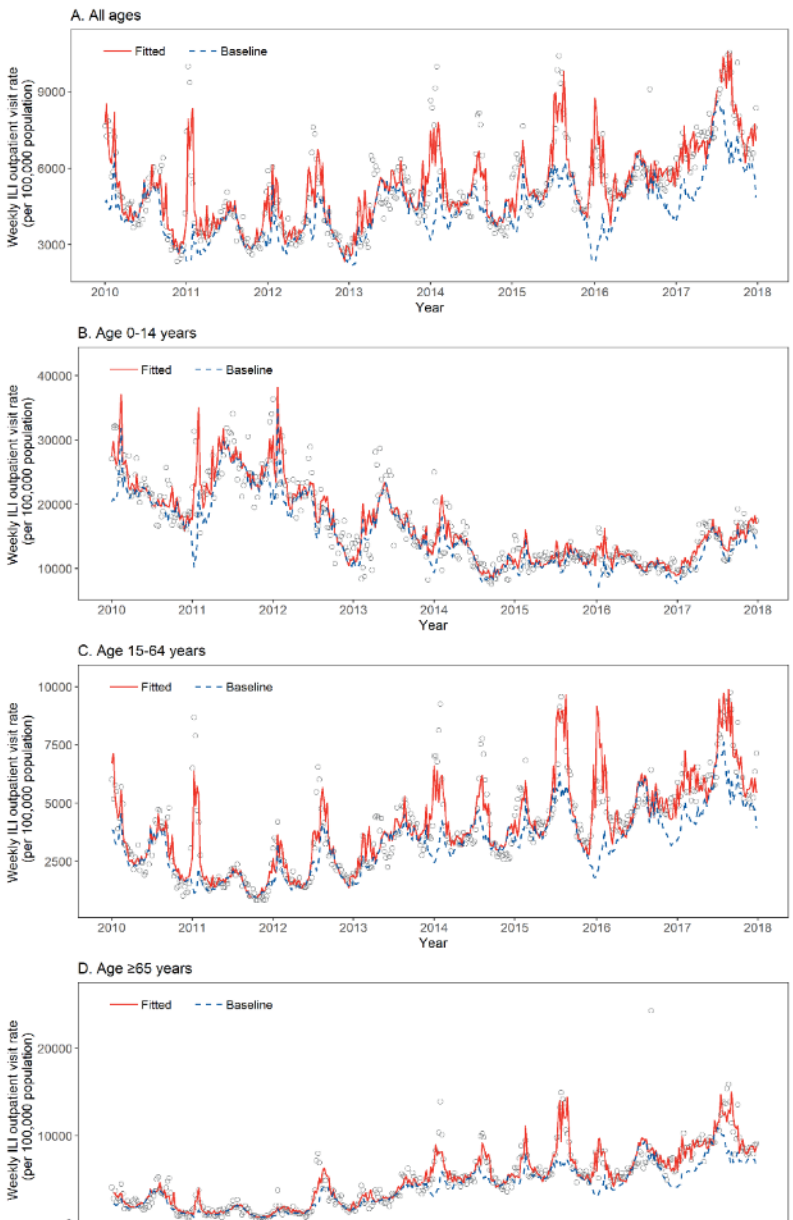

Figure S4. Weekly observed, fitted, and baseline influenza-like illness outpatient visit rates by negative binomial regression model in Shanghai, 2010-2017. ILI, influenza-like illness.

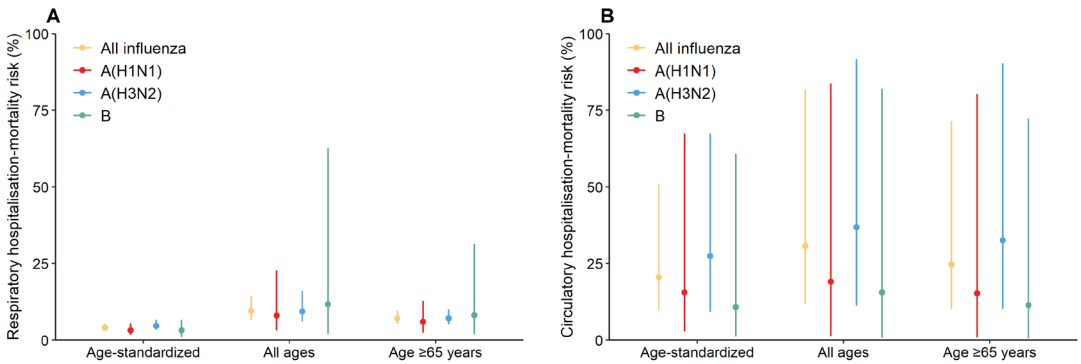

Figure S5. Clinical severity of influenza with different influenza virus types/subtypes and age groups. (A) Respiratory hospitalisation-mortality risk; (B) Circulatory hospitalisation-mortality risk.

Table S1. Posterior parametric coefficients of the influenza activity proxy.

	R&C mortality			R&C hospitalisation					ILI outpatient visit			
	All ages	<65 y	≥65 y	All ages	0-5 y	6-17 y	18-64 y	≥65 y	All ages	0-14 y	15-64 y	≥65 y
Lag0												
β_1	0.314	0.354	0.313	0.168	0.389	0.563	0.121	0.142	1.750	0.970	2.071	1.431
β_2	0.250	0.094	0.270	0.158	0.074	0.231	0.090	0.195	0.733	0.270	0.814	0.921
β_3	0.148	0.075	0.165	0.162	0.287	1.061	0.158	0.160	0.724	0.512	0.601	0.668
DIC	5104.645	3291.688	5044.033	3986.287	2653.707	2381.019	3412.148	3784.309	5239.7[illegible]	4261.237	4979.646	3558.903
Lag1												
β_1	0.247	0.265	0.246	0.236	0.376	0.565	0.168	0.220	1.193	0.381	1.526	1.385
β_2	0.327	0.152	0.345	0.181	0.107	0.212	0.094	0.225	0.794	0.275	0.891	1.089
β_3	0.122	0.048	0.137	0.216	0.285	0.986	0.161	0.227	0.512	0.247	0.566	0.644
DIC	5086.597	3288.968	5019.691	3967.744	2639.012	2370.057	3395.326	3766.228	5332.9[illegible]	4298.581	5054.482	3529.121
Lag2												
β_1	0.214	0.249	0.208	0.209	0.261	0.395	0.163	0.197	0.349	0.042	0.703	0.945
β_2	0.333	0.131	0.351	0.172	0.115	0.167	0.075	0.239	0.775	0.214	0.834	1.067
β_3	0.120	0.066	0.128	0.160	0.276	0.616	0.110	0.174	0.203	0.075	0.307	0.395
DIC	5070.362	3276.906	5008.069	3952.272	2633.324	2380.595	3385.27	3747.855	5403.21[illegible]	4302.206	5127.471	3571.984
Lag3												
β_1	0.139	0.179	0.133	0.228	0.147	0.164	0.195	0.237	0.066	0.028	0.161	0.440
β_2	0.273	0.070	0.297	0.193	0.138	0.133	0.092	0.258	0.519	0.121	0.530	0.529
β_3	0.112	0.081	0.117	0.175	0.189	0.352	0.104	0.210	0.183	0.048	0.346	0.571
DIC	5069.297	3276.217	5002.212	3931.903	2626.978	2387.809	3370.539	3726.269	5435.55[illegible]	4294.45	5161.446	3638.945

β_1, β_2, β_3 are the coefficients of influenza $A(H1N1)$, $A(H3N2)$ and B viruses, respectively.

Table S2. Ratios of influenza-associated excess mortality rates to ILI outpatient visit rates, excess hospitalisation rates to ILI outpatient visit rates, and excess mortality rates to hospitalisation rates by influenza virus types/subtypes and age groups.

	All influenza	A(H1N1)	A(H3N2)	B
Outpatient-mortality risk (%)				
Age-standardized	0.76 (0.48, 1.09)	0.32 (0.08, 0.68)	1.20 (0.69, 1.83)	0.51 (0.08, 1.28)
All ages	1.69 (0.97, 2.48)	0.71 (0.06, 1.63)	2.51 (1.23, 3.99)	1.16 (0.06, 3.26)
≥65 years	7.45 (4.53, 11.18)	4.27 (0.36, 11.14)	7.98 (4.34, 12.28)	7.82 (0.51, 24.61)
Outpatient-hospitalisation risk (%)				
Age-standardized	10.01 (7.04, 13.46)	6.03 (2.94, 9.60)	12.32 (7.03, 19.16)	10.41 (5.33, 18.66)
All ages	11.09 (5.23, 17.39)	6.56 (0.78, 13.40)	14.22 (4.63, 25.20)	9.21 (0.68, 25.49)
≥65 years	63.12 (34.84, 92.66)	47.24 (6.03, 93.48)	60.36 (26.9, 93.64)	54.42 (5.21, 97.30)
Hospitalisation-mortality risk (%)				
R&C				
Age-standardized	7.53 (4.59, 12.31)	5.28 (1.25, 14.64)	9.66 (5.11, 18.27)	4.84 (0.74, 14.46)
All ages	15.29 (7.68, 34.85)	10.61 (0.89, 60.86)	17.55 (7.50, 51.15)	11.93 (0.64, 74.56)
≥65 years	11.79 (6.37, 23.08)	8.76 (0.69, 52.20)	13.04 (6.40, 30.63)	9.56 (0.58, 60.09)
Respiratory disease				
Age-standardized	4.03 (3.06, 5.26)	3.26 (1.74, 5.45)	4.72 (3.35, 6.60)	3.23 (1.01, 6.67)
All ages	9.55 (6.54, 14.36)	8.09 (3.12, 22.68)	9.40 (6.08, 16.06)	11.70 (2.00, 62.60)
≥65 years	7.11 (5.21, 9.58)	6.02 (2.45, 12.77)	7.12 (5.10, 10.05)	8.19 (1.88, 31.38)
Circulatory disease				
Age-standardized	20.49 (9.71, 50.86)	15.65 (2.82, 69.43)	27.51 (9.17, 81.93)	10.78 (1.25, 60.79)
All ages	30.75 (11.97, 81.79)	19.14 (1.27, 83.69)	36.89 (11.21, 91.73)	15.59 (0.67, 82.09)
≥65 years	24.70 (10.17, 71.43)	15.35 (0.78, 80.25)	32.62 (10.15, 90.30)	11.48 (0.49, 72.26)

We assumed that the excess R&C deaths or hospitalisations approximate the totality of the influenza-associated deaths or hospitalisations R&C, respiratory and circulatory disease.

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Development of influenza-associated disease burden pyramid in Shanghai, China, 2010–2017: a Bayesian modelling study

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Development of influenza-associated disease burden pyramid in Shanghai, China, 2010–2017: a Bayesian modelling study

Jing Li[1,2,3#], Chunfang Wang[4#], Luanqi Ruan[5], Shan Jin[4], Chuchu Ye[5], Huiting Yu[4], Weiping Zhu[5†], Xiling Wang[1,6†]

Author Affiliations:

1. School of Public Health, Fudan University, Key Laboratory of Public Health Safety, Ministry of Education, Shanghai, China
2. Renal Division, Peking University Shenzhen Hospital, Peking University, China
3. Clinical Research Academy, Peking University Shenzhen Hospital, Peking University, China
4. Department of Vital Statistics, Division of Health Information, Shanghai Municipal Center for Disease Control and Prevention, Shanghai, China
5. Research Base of Key Laboratory of Surveillance and Early Warning on Infectious Disease in China CDC, Shanghai Pudong New Area Center for Disease Control and Prevention, Shanghai, China
6. Shanghai Key Laboratory of Meteorology and Health, Shanghai, China

[#] These authors are joint first authors and contributed equally to this work.

[†] These authors are joint senior authors and contributed equally to this work.

Corresponding Authors:

Xiling Wang, School of Public Health, Fudan University, Key Laboratory of Public Health Safety, Ministry of Education, Xuhui District, 200231, Shanghai, China (erinwang@fudan.edu.cn); Weiping Zhu, Research Base of Key Laboratory of Surveillance and Early Warning on Infectious Disease in China CDC, Shanghai Pudong New Area Center for Disease Control and Prevention, Pudong New Area, 200136, Shanghai, China (wpzhu@pdcdc.sh.cn)

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ABSTRACT

Objectives: Negative estimates could be produced when statistical modelling techniques were applied to estimate morbidity and mortality attributable to influenza. Based on the prior knowledge that influenza viruses are hazardous pathogens and have adverse health outcomes of respiratory and circulatory disease (R&C), we developed an improved model incorporating Bayes' Theorem to estimate the disease burden of influenza in Shanghai, China from 2010 to 2017.

Design: A modelling study using aggregated data from administrative systems on weekly R&C mortality and hospitalisation, influenza surveillance, and meteorological data. We constrained the regression coefficients for influenza activity to be positive by truncating the prior distributions at zero.

Setting: Shanghai, China.

Participants: People registered with R&C deaths (450,298) and hospitalisations (2,621,787; from July 1, 2013), and with influenza-like illness (ILI) outpatient visits (342,149) between January 4, 2010 and December 31, 2017.

Primary outcome measures: Influenza-associated disease burden (mortality, hospitalization, and outpatient visit rates) and clinical severity (outpatient-mortality, outpatient-hospitalisation, and hospitalisation-mortality risks).

Results: Influenza was associated with an annual average of 15.49 (95% CrI 9.06-22.06) excess R&C deaths, 100.65 (48.79-156.78) excess R&C hospitalisations, and 914.95 (798.51-1,023.66) excess ILI outpatient visits per 100,000 population in Shanghai. 97.23% and 80.24% excess R&C deaths and hospitalisations occurred in people aged ≥65 years. More than half of excess morbidity and mortality were associated with influenza A(H3N2), and its severities were 1.65- to 3.54-fold and 1.47- to 2.16-fold higher than that for influenza A(H1N1) and B, respectively.

Conclusions: The proposed Bayesian approach with reasonable prior information improved estimates of influenza-associated disease burden. Influenza A(H3N2) was generally associated with higher morbidity and mortality, and relatively more severe compared to influenza A(H1N1) and B. Targeted influenza prevention and control strategies for the elderly in Shanghai may substantially

reduce the disease burden.

Strengths and limitations of this study

- We comprehensively assessed the impact of influenza on both morbidity and mortality in subtropical Shanghai by integrating multiple data sources of influenza surveillance, hospital records, and death registration.
- The developed "influenza pyramid", together with the risk between layers, provided key parameters for handy estimation of influenza-associated disease burden in Shanghai as well as in other developed countries/regions/cities.
- The proposed Bayesian approach with reasonable prior information improved statistical estimates of influenza-associated disease burden.
- Our results may be confounded by other co-circulating respiratory viruses which were not included in national virologic surveillance scheme in China.

INTRODUCTION

Annual influenza epidemics result in substantial morbidity and mortality. Influenza virus infections can cause a wide spectrum of diseases, from mild to severe illness requiring hospitalisation, and at times even death.[1-4] The influenza burden can be presented using the disease pyramid with multiple tiers including asymptomatic infections, non-medically attended illnesses, medically attended illnesses, hospitalisations, intensive care unit (ICU) admissions, and deaths.[5] The "influenza pyramid" provides a full perspective of the disease burden associated with influenza and allows to identify relationships between each layer of the outcome. However, the construction of the pyramid may require merging data gathered from different surveillance systems. Considering the availability of time series data, very few studies have attempted to assess the overall burden of influenza and the estimation tended to focus on only one or two particular levels of the pyramid.[6-9]

The disease burden of influenza is difficult to quantify directly because influenza infections are rarely laboratory-confirmed, or specifically coded as influenza-related in hospital discharge records or death certificates. Statistical modelling techniques have been developed to estimate morbidity and mortality attributable to influenza.[3 10 11] "Pneumonia and influenza", "respiratory and circulatory disease", and "all-cause" are often chosen as outcome variables in modelling methods. "Pneumonia and influenza" is deemed to be the most specific outcome measures, but this category excludes other respiratory and circulatory diseases exacerbated by influenza. The outcome category "all-cause" is too broad and sacrifices specificity; thus "respiratory and circulatory disease" optimises the balance between sensitivity and specificity.[12-14]

Negative estimates could be produced when statistical modelling techniques were applied to estimate morbidity and mortality attributable to influenza.[15-17] Based on the prior knowledge that influenza viruses are hazardous pathogens and have

adverse health outcomes of respiratory and circulatory disease,[3 4 18] we developed an improved model incorporating Bayes' Theorem to construct the pyramid of influenza-associated disease burden. We presented the estimates of influenza-associated deaths and hospitalisations due to respiratory and circulatory disease (R&C), and influenza-like illness (ILI) outpatient visits in Shanghai, China from 2010 to 2017.

METHODS

Influenza surveillance data

Weekly ILI surveillance and influenza virological surveillance data from 2010 to 2017 were obtained from the Pudong New Area Center for Disease Control and Prevention (PDCDC). Four hospitals conducted year-round surveillance of influenza, including two national sentinel hospitals (Dongfang Hospital and Zhoupu Hospital) and two municipal sentinel hospitals (Pudong Hospital and Eastern Division of Renji Hospital) in Pudong New Area, Shanghai. As we do not have access to raw influenza surveillance data in Shanghai, we used influenza virus activity in Pudong New Area instead. There was a strong correlation of the weekly positive proportion of laboratory-confirmed influenza (LAB%) between the two data sources from 2010 to 2015 ($r = 0.80$-0.93, all $P < 0.001$) (**Figure S1**). Weekly LAB% data in Shanghai were digitised from the time series plot of influenza activity in published literature[19] using the WebPlotDigitizer software (https://automeris.io/WebPlotDigitizer). ILI surveillance data included weekly numbers of total outpatient visits and age-specific ILI consultations (0-4, 5-14, 15-24, 25-59, and ≥60 years). As the elderly people with an age cutpoint of ≥65 years were used in our study, we reclassified these five age groups into 0-14, 15-64, and ≥65 years according to the age distribution of the permanent population in Pudong New Area. Influenza virological surveillance data included weekly numbers of total specimens tested and specimens positive for influenza A(H1N1) (referring to the 2009 pandemic strain A(H1N1)pdm09), A(H3N2), and B viruses.

Mortality and hospitalisation data

The death registration system of Shanghai is based on its household registration system (Hukou).[20] We obtained the weekly mortality data for registered residents in Shanghai for the years 2010-2017 from the Shanghai Center for Disease Control and Prevention (SCDC). Weekly inpatient data from 2013 to 2017 were obtained from the Shanghai Municipal Health and Family Planning Commission. All medical institutions in Shanghai have been required to apply the new edition of the inpatient medical record home page where full indicators were collected since January 1, 2013. We excluded the unstable data for the first half of the year (from the 1st week of 2013 to the 26th week of 2013) during the transition period between the new and old edition of inpatient electronic medical record. We only included inpatients from secondary and tertiary hospitals which have higher data quality than primary hospitals and they accounted for more than 90% of the total inpatients in Shanghai. Shanghai provided medical treatments to many patients seeking medical care from other provinces, we only used the data of Shanghai residents for representativeness. Hospital admissions were greatly reduced around the traditional Chinese Spring Festival and National Day, which cannot reflect patients' true healthcare needs, and thus we replaced the week containing the holidays with the average value of the previous and next week.[21]

We retrieved underlying causes of death and primary discharge diagnoses coded as respiratory disease (J00-J99), circulatory disease (I00-I99), and respiratory and circulatory disease (R&C, J00-J99 and I00-I99), in the International Classification of Diseases Codes, version 10 (ICD-10). We assumed that the excess R&C deaths or hospitalisations would approximate the totality of the influenza-associated deaths or hospitalisations. Data for death and hospitalisation were stratified by age groups (<65 years and ≥65 years; 0-5 years, 6-17 years, 18-64 years, and ≥65 years, respectively).

Population and meteorological data

Age-specific annual population size including registered population and permanent population were obtained from the Shanghai Statistical Yearbook[22] and National Bureau of Statistics of China, respectively. Annual outpatient visits (medicine and pediatrics) were obtained from China's Health and Family Planning Statistical Yearbook.[23] Daily temperature and dew point temperature from 2010 to 2017 were obtained from the Shanghai Meteorological Bureau and were averaged into a weekly level. Absolute humidity was derived from temperature and relative humidity.

Statistical analysis

Negative binomial regression models were fitted separately to weekly deaths, hospitalisations, and ILI outpatient visits by age groups and causes of disease in a Bayesian framework using Markov Chain Monte Carlo approach. We used LAB% as a proxy variable for influenza activity in the models and assumed a multiplicative association between weekly influenza activity and counts of deaths, hospitalisations or ILI outpatient visits, which has been widely applied in previous literature.[3 4 24] Natural cubic splines of the calendar week and absolute humidity were added to adjust for time-varying confounders. Viral surveillance data were lagged by 0 to 3 weeks. We selected the degrees of freedom and lag weeks based on the minimum deviance information criterion (DIC)[25] and curve fitting (**Table S1, Figure S2-S4**). We constrained the regression coefficients for influenza activity to be positive by truncating the Normal priors at zero as previous studies have demonstrated positive associations between influenza and R&C deaths, hospitalisations and ILI outpatient visits.[3 4 26] More details of the statistical model are available in **Appendix S1**.

The influenza-associated excess deaths, hospitalisations, and ILI outpatient visits were estimated as the difference between the predicted numbers under the model and the baseline numbers when influenza activity proxies were assumed to be zero. The influenza-associated excess mortality rates, hospitalisation rates, and ILI

outpatient visit rates were estimated as the numbers of excess deaths, hospitalisations, and ILI outpatient visits per 100,000 population. Age-standardised rates were derived using the World (WHO 2000-2025) Standard Population as the reference.[27] With the assumption that the proportion of ILI outpatient visits among medicine and pediatric outpatient visits in the surveillance hospitals of Pudong New Area is representative of Shanghai, we extrapolated the influenza-associated ILI outpatient visits in surveillance hospitals to the general population in Shanghai (see details in **Appendix S2**).[28]

Each model was run 60,000 Markov Chain Monte Carlo iterations with the first 30,000 iterations discarded as burn-in. We estimated the clinical severity of influenza with different influenza virus types/subtypes and age groups, including outpatient-mortality risks, outpatient-hospitalisation risks, and hospitalisation-mortality risks, as the ratios of influenza-associated excess mortality rates to ILI outpatient visit rates, hospitalisation rates to ILI outpatient visit rates, and mortality rates to hospitalisation rates. The 95% credibility intervals (95% CrI) for excess crude and age-standardised rates were based on the samples drawn from the posterior distributions. Estimates of the outpatient-mortality risks, outpatient-hospitalisation risks, hospitalisation-mortality risks, and their 95% credibility intervals, were also based on these posterior samples.

Analyses were performed using the "rjags" package of R software, version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria), an interface between R and JAGS software, version 4.3.0 (Plummer 2003).

Patient and public involvement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Descriptive statistics

During the study period 2010-2017, Pudong New Area tested 12,283 specimens for influenza viruses, of which 409 were positive for influenza A(H1N1) virus, 1,427 for influenza A(H3N2) virus, and 812 for influenza B virus (**Table 1**). Influenza B virus was the predominant circulating virus in 2010-2011 and a shift to the influenza A(H3N2) virus in the subsequent years (**Figure 1**). In general, R&C mortality rates, R&C hospitalisation rates, and ILI outpatient visit rates increased from 2010 to 2017 in Shanghai, with annual average rates of 392.32, 2,407.98, and 5,247.92 per 100,000 population, respectively (**Table 1**).

Influenza-associated disease burden

During the study period, we estimated an annual average of 2,223 (95% CrI 1,300-3,164) excess R&C deaths, 24,353 (95% CrI 11,805-37,934) excess R&C hospitalisations, and 218,733 (95% CrI 190,897-244,722) excess ILI outpatient visits, attributable to influenza in Shanghai, corresponding to 3.95%, 4.18%, and 17.43% of all R&C deaths, R&C hospitalisations, and ILI outpatient visits, respectively. Accordingly, the estimated crude and age-standardised rates per 100,000 population were 15.49 (95% CrI 9.06-22.06) and 7.36 (4.76-10.25) excess R&C deaths, 100.65 (95% CrI 48.79-156.78) and 97.90 (70.74-129.02) excess R&C hospitalisations, 914.95 (95% CrI 798.51-1,023.66) and 974.65 (855.22-1,100.21) excess ILI outpatient visits, respectively (**Table 2**). The pyramids of influenza-associated disease burden in Shanghai were shown in **Figure 2**.

Influenza-associated R&C mortality rate for people aged ≥65 years was 81.03 (95% CrI 50.41-116.99) per 100,000 population, which was substantially higher than that for those aged <65 years (0.70 [95% CrI 0.23-1.37] per 100,000 population) (**Table 2**). The age-specific influenza-associated R&C hospitalisation rates per 100,000 population showed a J-shaped pattern: highest among people aged ≥65 years (696.38 [95% CrI 396.31-1,026.38]), second highest among children aged

0-5 years (123.21 [95% CrI 46.56-212.08]), followed by children aged 6-17 years (69.19 [95% CrI 46.65-91.48]), and lowest among people aged 18-64 years (20.73 [95% CrI 7.02-39.76]). Children aged 0-14 years had the highest rate of influenza-associated ILI outpatient visits (1,430.91 [95% CrI 1,096.85-1,773.40] per 100,000 population), followed by people aged ≥65 (1,096.79 [95% CrI 914.25-1,261.59] per 100,000 population) and 15-64 years (781.92 [664.68-894.82] per 100,000 population). 97.23% of excess R&C deaths and 80.24% of excess R&C hospitalisations occurred among people aged ≥65 years, whereas only 13.13% of excess ILI outpatient visits occurred in this age group.

Influenza A(H3N2) virus was generally associated with the highest rates of influenza infections, with all-age annual average rates of 10.69 (95% CrI 5.42-15.80) R&C deaths, 60.96 (95% CrI 19.95-100.85) R&C hospitalisations, and 424.74 (95% CrI 340.90-510.55) ILI outpatient visits per 100,000 population, respectively (**Table 2, Figure 2**). When broken down by diseases, for all ages and ≥65 years, the influenza-associated mortality rates for respiratory disease (6.90 [95% CrI 5.27-8.39] and 35.70 [27.78-44.16] per 100,000 population) were 1.40- to 1.48-fold lower than that for circulatory disease (9.64 [95% CrI 5.05-14.51] and 52.81 [28.66-79.37] per 100,000 population), while the influenza-associated hospitalisation rates for respiratory disease (72.48 [95% CrI 51.34-95.11] and 501.90 [406.51-600.23] per 100,000 population) were 2.39- to 2.40-fold higher than that for circulatory disease (30.20 [95% CrI 9.61-60.12] and 210.20 [63.08-404.70] per 100,000 population) (**Table 2**). A similar J-shaped age pattern was also observed in influenza-associated respiratory hospitalisation rates, while for circulatory hospitalisation, the estimated rates increased with age.

Influenza-associated clinical severity

Influenza-associated outpatient-mortality risk, outpatient-hospitalisation risk, and hospitalisation-mortality risk were estimated to be 1.69% (95% CrI 0.97-2.48%), 11.09% (5.23-17.39%), and 15.29% (7.68-34.85%), respectively (**Table**

S2). That is to say, we estimated that there were 1.69 excess R&C deaths and 11.09 excess R&C hospitalisations for every 100 excess ILI outpatient visits, and 15.29 excess R&C deaths for every 100 excess R&C hospitalisations in Shanghai. The estimated risks for people aged ≥65 years were higher than that for all ages except for hospitalisation-mortality risks (**Figure 3**). When comparing these risks between different types/subtypes of influenza viruses, we found that influenza A(H3N2) virus had the greatest outpatient-mortality risks, outpatient-hospitalisation risks, and hospitalisation-mortality risks across different age groups. Its severities were 1.65- to 3.54-fold and 1.47- to 2.16-fold higher than that for influenza A(H1N1) and B viruses, respectively (**Table S2**). But the difference did not reach statistical significance. Also, we presented separately the influenza-associated hospitalisation-mortality risks for respiratory disease and circulatory disease (**Figure S5**). People with the circulatory disease had a 3.22-fold higher hospitalisation-mortality risk than that of respiratory disease (**Table S2**).

DISCUSSION

Although there were great year-to-year variations in influenza-associated mortality and morbidity from 2010 to 2017, we estimated that influenza contributed to an annual average of 15.49 (95% CrI 9.06-22.06) excess R&C deaths, 100.65 (95% CrI 48.79-156.78) excess R&C hospitalisations, and 914.95 (95% CrI 798.51-1,023.66) excess ILI outpatient visits per 100,000 population in Shanghai. Our crude or age-standardised estimates of influenza-associated mortality and morbidity are comparable with the corresponding estimates published for the United States (R&C death: 9.9 per 100,000 population;[29] R&C hospitalisation: 88.4 per 100,000 population;[4] ILI outpatient visit: 755-870 per 100,000 population),[30 31] Argentina (R&C death: 21.3 per 100,000 population; R&C hospitalisation: 57 per 100,000 population),[14] Hong Kong SAR (R&C death: 7.7 per 100,000 population),[32] and five southern Chinese cities (R&C death: 8.8 per 100,000 population).[33] In particular, Hong Kong SAR reported an approximately

twofold higher hospitalisation burden than our estimates,[32] which could be explained by the result of expanding health service capacities and lowering admission criteria due to the aging population of Hong Kong in recent years.[13 24 34] However, caution is needed when comparing these estimates between countries/regions/cities due to variations in the study period, predominant circulating influenza virus, age structure of population, influenza vaccination coverage, and statistical model used. Influenza A(H3N2) virus accounted for the highest disease burden than the other two types, which has also been demonstrated by other studies.[4 14 35] Influenza A(H3N2) virus is believed to have more frequent antigen drift and higher virulence than seasonal influenza A(H1N1) and B viruses.[36 37] Additionally, our study revealed that influenza A(H3N2) virus was relatively more severe as well.

The elderly people are most severely affected by influenza, with the highest influenza-associated mortality and hospitalisation rates, and the second highest influenza-associated ILI outpatient visit rates. The aging of the Shanghai population is an important contributor to the high rates of influenza-associated mortality and morbidity. For example, the influenza-associated mortality rates after age standardization decreased by more than half. Between 2010 and 2017, the registered population aged ≥65 years in Shanghai increased by 28.70%, of about 3.18 million by 2017, accounting for 21.83% of the total population. Interestingly, people aged ≥65 years have lower hospitalisation-mortality risks than for all ages. A possible explanation might be that young adults are less likely to be hospitalised compared to elderly people, but some of them do develop serious illnesses and require hospitalisation, and thus have a greater risk of dying.

Currently, population-based studies of influenza-associated mortality and morbidity have been increasingly reported in mainland China. Of these, two nationally representative studies estimated province-level influenza-associated respiratory mortality rates and ILI outpatient visit rates. However, studies on

influenza-associated hospitalisation burden were limited to Beijing,[38 39] Jiangsu,[40-44] and Hubei.[45] Our study comprehensively assessed the impact of influenza in Shanghai, especially the hospitalisation burden, which has never been assessed before. The estimated ratios between each layer of the "influenza pyramid" provided key parameters for handy estimation of influenza-associated disease burden in Shanghai as well as in other developed countries/regions/cities.

Performing regression analyses in a Bayesian framework has two advantages in our study. First, positive priors truncated the posterior distributions of regression coefficients for influenza activity to ensure the positivity of the generated samples. Otherwise, it was difficult to explain that influenza was protective to human health. Second, Bayesian posterior samples allowed us to estimate the 95% credibility intervals for these ratios, which could be challenging in a frequentist framework. Various proxies for influenza activity have been developed and the most commonly used proxy variable was LAB%.[46] Yu, et al.[19] estimated influenza-associated P&I mortality considering three different proxies for influenza activity: LAB number (positive number of laboratory-confirmed influenza), LAB%, and LAB × ILI% (the product of positive proportion of laboratory-confirmed influenza and influenza-like illness consultation rate). The results of this study demonstrated that LAB% proxy produced slightly higher estimates of influenza-associated mortality than LAB number and LAB% × ILI% proxies. Another study by Chan, et al.[47] evaluated the performance of various virus proxy variables in estimating excess hospitalisation, and concluded that LAB × ILI% proxy provided more reliable estimates if age-specific virus data were not available. But in general, different influenza activity proxies provided comparable estimates for influenza disease burden. We used LAB% proxy in this study which has been adopted to link influenza and health outcomes in previous literature.[3 4 48]

Nevertheless, our study had several limitations. First, despite a strong correlation of influenza virus activity between Pudong New Area and Shanghai, LAB% in

Shanghai was slightly higher than that in Pudong New Area (median difference: 6.12%). Replaced by influenza activity in Pudong New Area may lead to an underestimation of the influenza burden in Shanghai from 2010 to 2017. Second, national ILI surveillance data were recorded by five predefined age groups; thus, influenza burden estimates for ILI outpatient visits and hospitalisations were difficult to compare across different age groups. Additionally, when extrapolating influenza-associated ILI outpatient visits and reclassifying ILI consultations, we were based on representativeness assumptions, but further evaluation may be needed. Third, "respiratory and circulatory disease" was chosen to optimise sensitivity-specificity balance, but influenza-associated R&C events may be slightly lower than the totality of the influenza-associated events. Fourth, we excluded hospitalisation data of inpatients from primary hospitals and with non-Shanghai residential addresses considering the study's quality and population representativeness. The former may underestimate and the latter may overestimate the influenza-associated hospitalisation burden. Fifth, our estimates of influenza-associated mortality and morbidity burden were not exactly based on the same population (registered population and permanent population respectively). Deaths of permanent population without Shanghai Hukou are usually registered at their place of household registration. Using the permanent population as the denominator may underestimate the influenza-associated mortality burden. Finally, we did not have data on co-circulating respiratory viruses, such as respiratory syncytial virus, which may have confounded the results.

In conclusion, the proposed Bayesian approach with reasonable prior information improved our estimates. Our study highlighted the substantial morbidity and mortality burden attributed to influenza in Shanghai. Influenza A(H3N2) virus was generally associated with more morbidity and mortality, and relatively more severe compared to influenza A(H1N1) and B viruses. Targeted influenza prevention and control strategies for the elderly in Shanghai may substantially

impact the disease burden.

Contributors

X.W. and W.Z. conceived, designed, and supervised the study. J.L., C.W., W.Z., L.R., S.J., C.Y., and H.Y. participated in data collection. J.L., X.W., and S.J. conducted statistical analyses. J.L. and C.W. drafted the manuscript. X.W. and W.Z. commented on the data and its interpretation, revised the content critically. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Ethics approval

This study did not require ethical approval because the data accessed were aggregated and anonymised.

Data availability statement

Data are available upon reasonable request to the corresponding author.

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Table 1. Annual summary of influenza activity, ILI outpatient visit rate, hospitalisation rate, and mortality rate in Shanghai, 2010-2017.

	2010	2011	2012	2013	2014	2015	2016	2017
Influenza A(H1N1) (%)	30 (17.24)	54 (40.00)	0 (0.00)	32 (19.88)	56 (15.34)	68 (14.17)	138 (30.53)	31 (5.09)
Influenza A(H3N2) (%)	45 (25.86)	1 (0.74)	155 (56.99)	128 (79.50)	220 (60.27)	272 (56.67)	226 (50.00)	380 (62.40)
Influenza B (%)	99 (56.90)	80 (59.26)	117 (43.01)	1 (0.62)	89 (24.38)	140 (29.17)	88 (19.47)	198 (32.51)
Total specimens tested	974	755	1,026	1,231	1,935	2,127	2,093	2,142
ILI consultation rate[a]	26.73	22.31	20.99	23.00	23.94	25.85	25.00	32.18
ILI outpatient visit rate[b]	4,681.27	4,120.52	4,152.99	4,633.98	5,173.12	5,889.36	5,685.84	7,577.41
Hospitalisations rate[c]								
R&C	-	-	-	1,897.31	2,131.63	2,396.44	2,557.96	2,801.40
Respiratory disease	-	-	-	672.00	776.21	850.69	877.10	971.29
Circulatory disease	-	-	-	1,225.31	1,355.42	1,545.75	1,680.86	1,830.12
Mortality rate[d]								
R&C	351.16	359.94	385.52	381.45	399.40	428.57	414.33	416.38
Respiratory disease	82.15	79.42	85.13	78.70	80.80	83.19	74.40	71.13
Circulatory disease	269.01	280.51	300.39	302.74	318.60	345.38	339.93	345.25
Registered population	14,123,202	14,193,600	14,269,319	14,323,391	14,386,900	14,429,876	14,499,990	14,551,300
Permanent population	23,019,196	23,474,591	23,804,303	24,151,500	24,256,797	24,152,700	24,197,001	24,197,001

Influenza surveillance data were recorded in Pudong New Area including specimens positive for influenza by type/subtype, total specimens tested, ILI consultations, and total outpatient visits. ILI, influenza-like illness; R&C, respiratory and circulatory disease.

[a] ILI consultation rate per 1,000 outpatient visits.

[b] ILI outpatient visit rate per 100,000 permanent population.

[c] Hospitalisation rate per 100,000 permanent population.

[d] Mortality rate per 100,000 registered population.

Table 2. Mean annual influenza-associated excess mortality rates and hospitalisation rates due to respiratory and circulatory diseases, and influenza-like illness outpatient visit rates (per 100,000 population) by influenza type/subtype and age group in Shanghai, 2010-2017.

	All influenza	A(H1N1)	A(H3N2)	B
Influenza-associated excess mortality rate				
R&C				
Age-standardised	7.36 (4.76, 10.25)	1.07 (0.27, 2.21)	4.97 (2.90, 7.17)	1.31 (0.21, 3.09)
All ages	15.49 (9.06, 22.06)	2.10 (0.17, 4.66)	10.69 (5.42, 15.80)	2.62 (0.16, 6.86)
<65 years	0.70 (0.23, 1.37)	0.26 (0.02, 0.57)	0.22 (0.01, 0.74)	0.16 (0.01, 0.59)
≥65 years	81.03 (50.41, 116.99)	9.73 (0.86, 23.83)	57.47 (31.71, 82.58)	13.62 (0.93, 34.48)
Respiratory disease				
Age-standardised	3.40 (2.73, 4.13)	0.65 (0.37, 0.95)	2.16 (1.70, 2.61)	0.65 (0.20, 1.09)
All ages	6.90 (5.27, 8.39)	1.16 (0.53, 1.83)	4.50 (3.41, 5.51)	1.29 (0.27, 2.39)
<65 years	0.51 (0.34, 0.69)	0.18 (0.10, 0.26)	0.27 (0.14, 0.40)	0.06 (0, 0.18)
≥65 years	35.70 (27.78, 44.16)	5.90 (2.49, 9.39)	23.13 (18.04, 27.84)	7.21 (1. 71, 12.58)
Circulatory disease				
Age-standardised	4.82 (2.81, 7.04)	0.78 (0.16, 1.66)	3.18 (1.41, 4.76)	0.77 (0.10, 1.99)
All ages	9.64 (5.05, 14.51)	1.43 (0.10, 3.59)	6.56 (2.64, 10.66)	1.48 (0.07, 4.35)
<65 years	0.50 (0.17, 1.01)	0.20 (0.02, 0.47)	0.14 (0.01, 0.56)	0.11 (0.01, 0.44)
≥65 years	52.81 (28.66, 79.37)	7.00 (0.31, 17.29)	36.78 (15.03, 56.76)	7.78 (0.36, 22.57)
Influenza-associated excess hospitalisation rate				
R&C				
Age-standardised	97.90 (70.74, 129.02)	19.89 (9.82, 31.10)	51.22 (30.34, 73.87)	26.69 (14.29, 43.22)
All ages	100.65 (48.79, 156.78)	19.89 (2.38, 38.93)	60.96 (19.95, 100.85)	20.33 (1.62, 53.10)

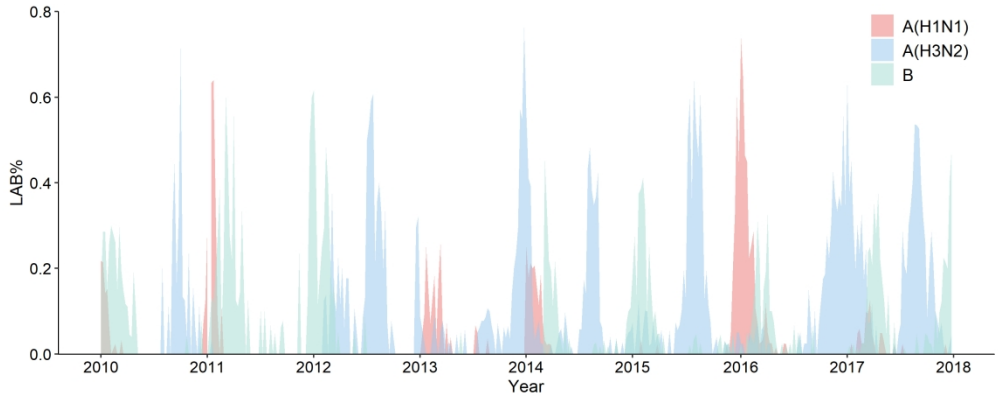
0-5 years	123.21 (46.56, 212.08)	38.04 (8.59, 70.90)	38.19 (1.49, 100.54)	44.47 (4.86, 93.90)
6-17 years	69.19 (46.65, 91.48)	14.13 (5.24, 22.53)	19.49 (2.93, 37.55)	36.15 (24.95, 48.42)
18-64 years	20.73 (7.02, 39.76)	5.87 (0.54, 12.78)	10.02 (0.73, 24.30)	4.24 (0.21, 12.87)
≥65 years	696.38 (396.31, 1026.38)	110.79 (14.68, 237.24)	440.96 (208.84, 687.52)	140.10 (11.93, 326.64)
Respiratory disease				
Age-standardised	84.22 (70.58, 100.36)	20.08 (13.89, 25.93)	45.87 (34.88, 58.36)	19.93 (12.20, 28.69)
All ages	72.48 (51.34, 95.11)	14.46 (5.63, 23.41)	47.89 (29.01, 66.75)	10.52 (1.13, 23.15)
0-5 years	171.40 (78.58, 277.30)	50.95 (15.35, 84.07)	78.11 (9.17, 159.17)	40.15 (4.60, 94.86)
6-17 years	77.07 (50.02, 103.71)	18.88 (7.59, 29.43)	26.72 (7.02, 47.51)	32.95 (20.01, 45.33)
18-64 years	15.46 (8.98, 22.11)	4.31 (1.69, 6.94)	8.77 (3.78, 13.74)	2.31 (0.21, 5.76)
≥65 years	501.90 (406.51, 600.23)	97.86 (53.77, 146.64)	323.59 (243.86, 400.37)	87.29 (22.88, 153.14)
Circulatory disease				
Age-standardised	23.42 (10.38, 41.41)	4.77 (1.06, 11.18)	10.94 (2.56, 23.71)	6.96 (1.42, 16.36)
All ages	30.20 (9.61, 60.12)	6.10 (0.40, 17.24)	14.23 (0.88, 36.60)	8.55 (0.47, 24.98)
0-5 years	1.03 (0.30, 2.32)	0.17 (0.01, 0.68)	0.36 (0.02, 1.51)	0.35 (0.01, 1.24)
6-17 years	2.30 (0.91, 3.98)	0.78 (0.14, 1.44)	0.93 (0.09, 2.25)	0.54 (0.04, 1.41)
18-64 years	8.44 (2.28, 19.89)	1.66 (0.06, 5.78)	4.23 (0.19, 13.01)	1.89 (0.09, 7.35)
≥65 years	210.20 (63.08, 404.70)	41.37 (2.78, 114.16)	95.80 (6.27, 237.28)	65.85 (4.36, 173.23)
Influenza-associated excess ILI outpatient visit rate				
Age-standardised	974.65 (855.22, 1,100.21)	332.17 (292.83, 375.69)	414.98 (329.49, 505.67)	256.89 (186.71, 326.45)
All ages	914.95 (798.51, 1,023.66)	295.36 (253.86, 338.55)	424.74 (340.90, 510.52)	224.37 (158.26, 284.61)
0-14 years	1,430.91 (1,096.85, 1,773.40)	482.20 (370.05, 605.77)	382.26 (156.64, 607.05)	586.25 (360.05, 818.06)
15-64 years	781.92 (664.68, 894.82)	284.84 (240.37, 328.79)	389.71 (299.27, 480.45)	134.60 (76.48, 196.58)
≥65 years	1,096.79 (914.25, 1,261.59)	228.14 (169.99, 281.51)	722.65 (575.04, 868.30)	177.45 (88.86, 268.13)

570 R&C, respiratory and circulatory disease; ILI, influenza like illness.

Figure 1. Influenza activity by type/subtype in Pudong New Area, Shanghai, 2010-2017. LAB%, weekly positive proportion of laboratory-confirmed influenza.

Figure 2. The pyramid of influenza burden by influenza virus types/subtypes and age groups in Shanghai, 2010-2017. R&C, respiratory and circulatory disease; ILI, influenza-like illness.

Figure 3. Clinical severity of influenza with different influenza virus types/subtypes and age groups. (A) Outpatient-mortality risk; (B) Outpatient-hospitalisation risk; (C) Hospitalisation-mortality risk.



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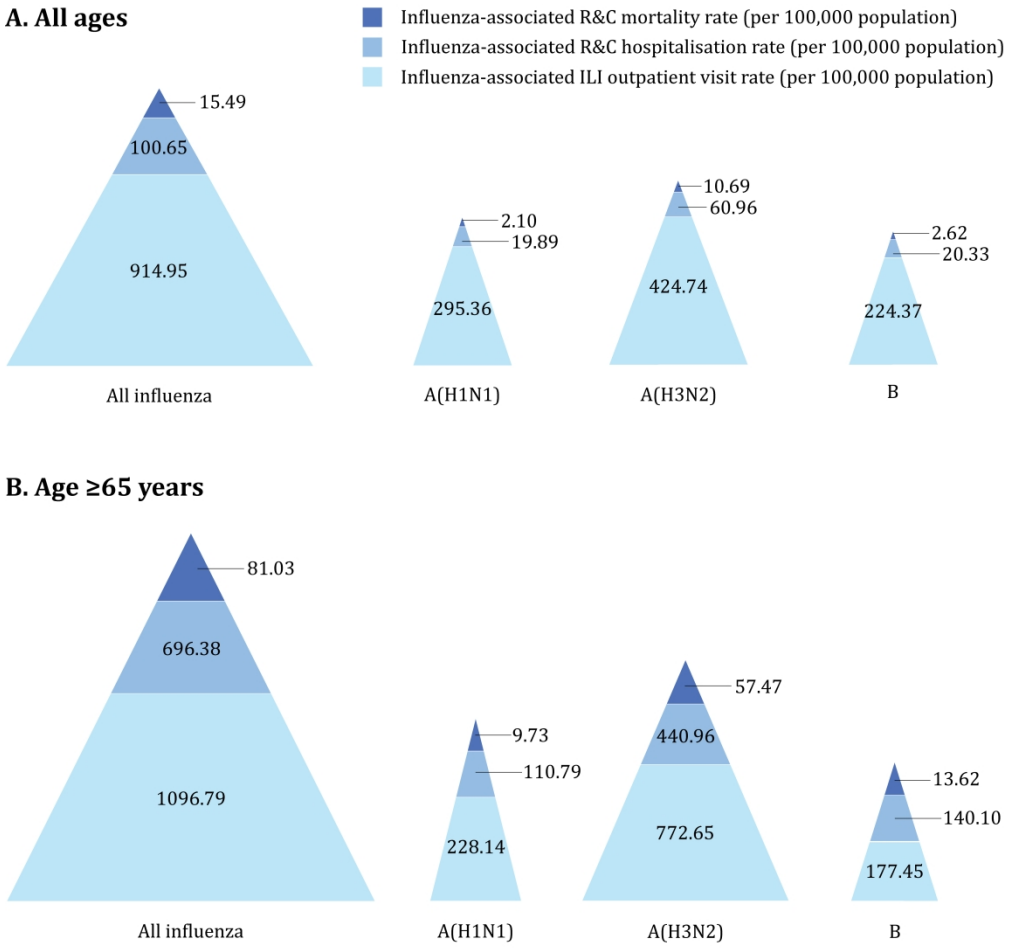

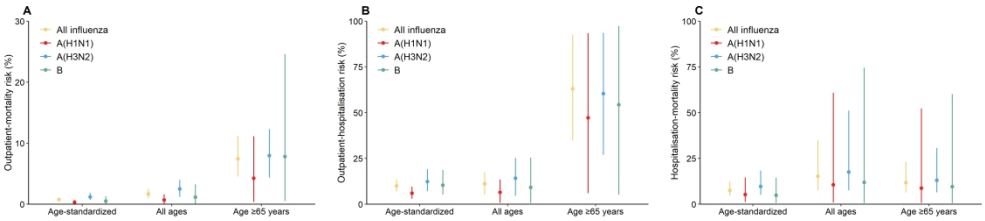

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Supplementary appendix

Development of influenza-associated disease burden pyramid in Shanghai, China, 2010–2017: a Bayesian modelling study

Jing Li[1,2,3#], Chunfang Wang[4#], Luanqi Ruan[5], Shan Jin[4], Chuchu Ye[5], Huiting Yu[4], Weiping Zhu[5†], Xiling Wang[1,6†]

S1. Negative binomial regression models in a Bayesian framework.

We used negative binomial regression models in a Bayesian framework to estimate the influenza-associated mortality rate, hospitalisation rate, and ILI outpatient visit rate across different age groups and causes of disease from 2010 to 2017 in Shanghai. The basic models were as follow:

$$\begin{cases} Y_t \sim NB(r, r/(r+\mu_t)) \\ log(\mu_t) = \beta_0 + \beta_1[A(H1N1)]_{t-i} + \beta_2[A(H3N2)]_{t-i} + \beta_3[B]_{t-i} + ns(t) + ns(AH_t) \end{cases}$$

We used the matrix product of a design matrix $x[,k]$ and a vector of unknown parameters b_k to describe $ns(x)$:

$$ns(t) = \sum_{k=1}^{K} b_{1k} t[,k]$$

$$ns(AH_t) = \sum_{k=1}^{4} b_{2k} AH_t[,k]$$

Where,

- Y_t is the observed number of deaths, hospitalisations, or ILI outpatient visits at week t. The variable Y_t is assumed to follow a negative binomial distribution with size parameter r and probability parameter $r/(r+\mu_t)$.
- $A(H1N1)_{t-i}$, $A(H3N2)_{t-i}$ and B_{t-i} denote the influenza activity proxies (LAB%) for influenza $A(H1N1)$, $A(H3N2)$ and B viruses, respectively, at week $t-i$, i denotes the lag time between influenza infection and health outcome, which varies from 0 to 3 weeks.
- $ns(t)$ and $ns(AH_t)$ denote the smooth functions of calendar week and absolute humidity respectively.

The priors specified in the Bayesian model were the following:

- $\beta_0 \sim Normal(0, 10^6)$
- $\beta_i \sim Normal(0, 10^6)^+$, $i = 1, 2, 3$, where $Normal(0, 10^6)^+$ is the truncated Normal distribution restricted to positive values.

- $b_{1k} \sim Normal(0, 10^6)$
- $b_{2k} \sim Normal(0, 10^6)$
- $r \sim uniform(0, 50)$

S2. Extrapolation of influenza-associated ILI outpatient visits from surveillance hospitals to general population in Shanghai.

We assumed that the proportion of ILI outpatient visits among medicine and pediatric outpatient visits in the surveillance hospitals of Pudong New Area is representative of Shanghai. Thus, influenza-associated ILI outpatient visit rates were calculated as the product of the proportion of influenza-associated ILI outpatient visit in surveillance hospitals and the proportion of medicine and pediatric outpatient visits in the population.

$$\frac{Influenza-associated\ ILI\ outpatient\ visits\ in\ Shanghai}{Total\ general\ population\ in\ Shanghai} = \frac{Total\ medicine\ and\ pediatric\ outpatient\ visits\ in\ Shanghai}{Total\ general\ population\ in\ Shanghai} \times \frac{Total\ influenza-associated\ ILI\ outpatient\ visits\ in\ surveillance\ hospitals}{Total\ medicine\ and\ pediatric\ outpatient\ visits\ in\ surveillance\ hospitals}$$

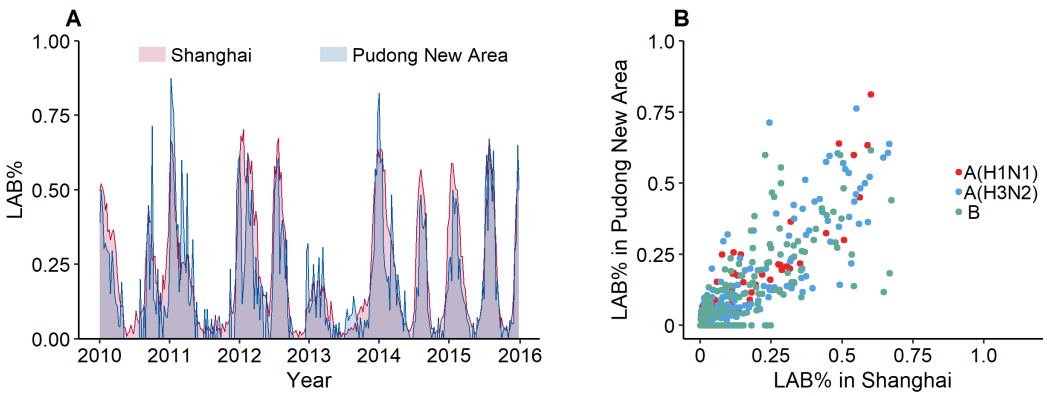

Figure S1. Weekly LAB% in Shanghai and Pudong New Area, 2010-2015. LAB%, weekly positive proportions of laboratory-confirmed influenza. Pearson's correlation coefficients of LAB% between Pudong New Area and Shanghai are 0.93, 0.88 and 0.80 for influenza A(H1N1), A(H3N2), and B, respectively.

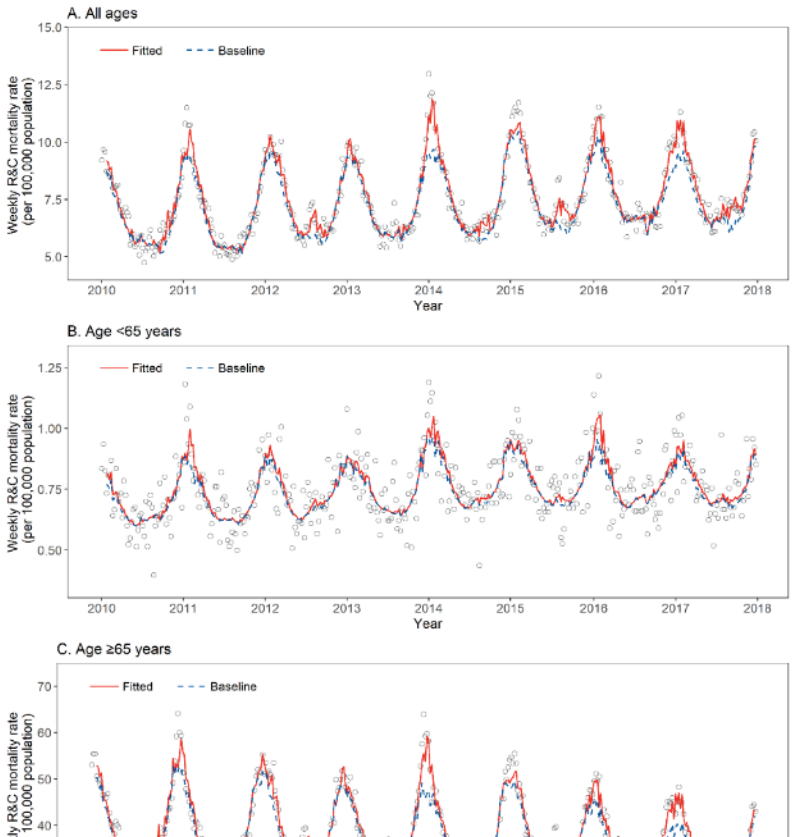

Figure S2. Weekly observed, fitted, and baseline respiratory and circulatory mortality rates by negative binomial regression model in Shanghai, 2010-2017. R&C, respiratory and circulatory disease.

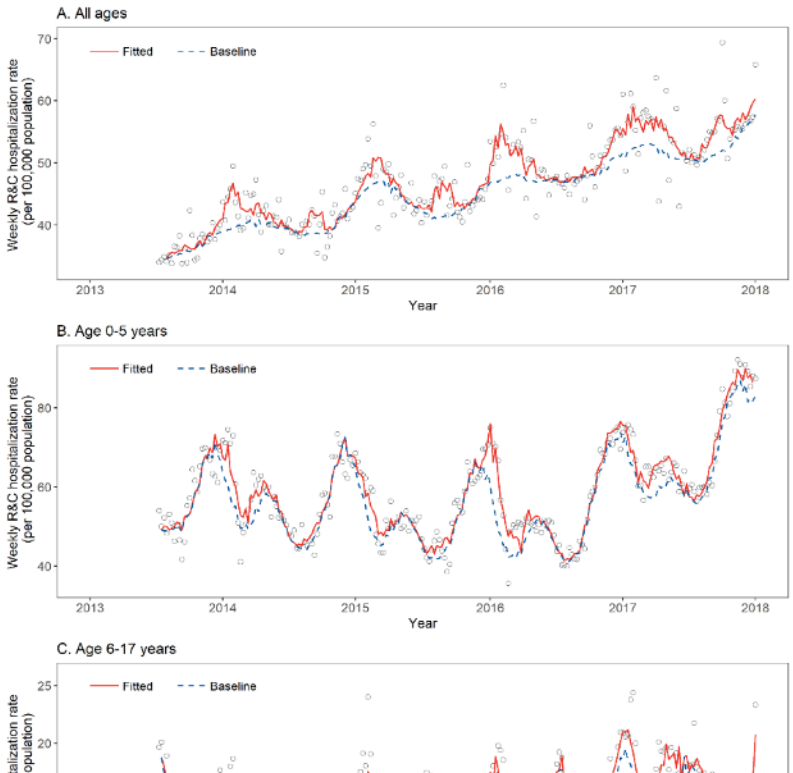

Figure S3. Weekly observed, fitted, and baseline respiratory and circulatory hospitalisation rates by negative binomial regression model in Shanghai, 2013-2017. R&C, respiratory and circulatory disease.

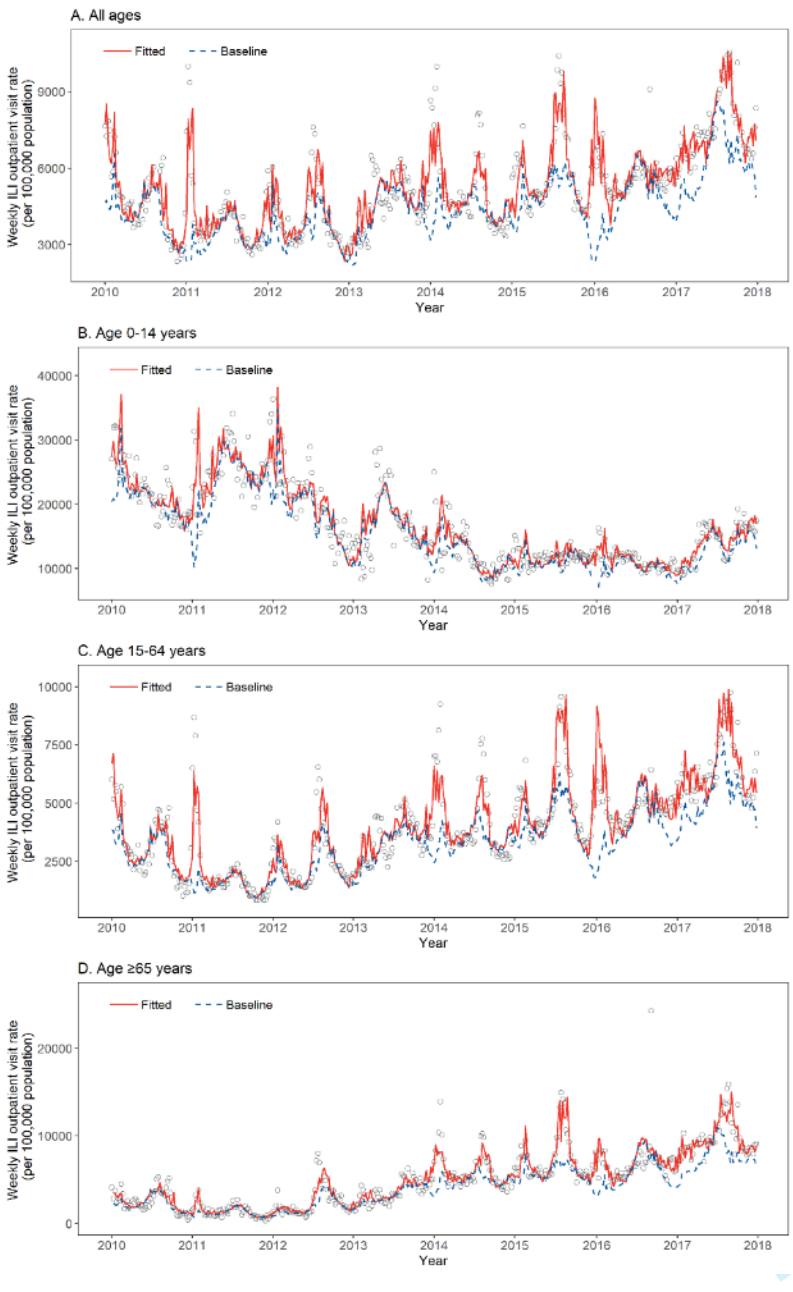

Figure S4. Weekly observed, fitted, and baseline influenza-like illness outpatient visit rates by negative binomial regression model in Shanghai, 2010-2017. ILI, influenza-like illness.

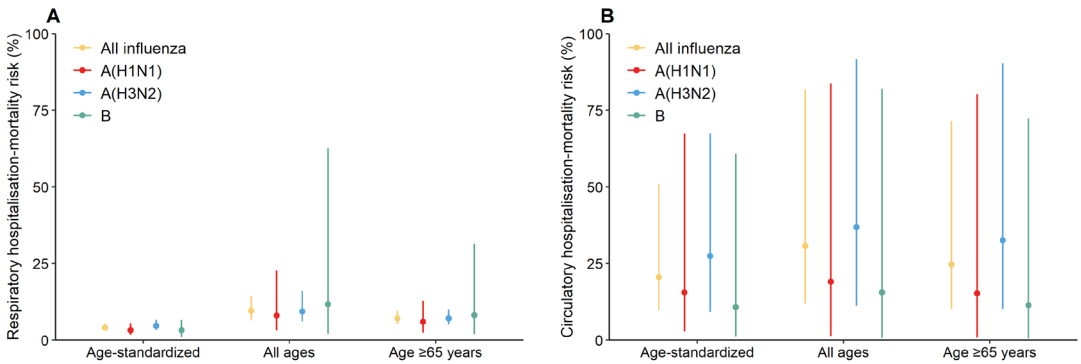

Figure S5. Clinical severity of influenza with different influenza virus types/subtypes and age groups. (A) Respiratory hospitalisation-mortality risk; (B) Circulatory hospitalisation-mortality risk.

Table S1. Posterior parametric coefficients of the influenza activity proxy.

	R&C mortality			R&C hospitalisation					ILI outpatient visit			
	All ages	<65 y	≥65 y	All ages	0-5 y	6-17 y	18-64 y	≥65 y	All ages	0-14 y	15-64 y	≥65 y
Lag0												
β_1	0.314	0.354	0.313	0.168	0.389	0.563	0.121	0.142	1.750	0.970	2.071	1.431
β_2	0.250	0.094	0.270	0.158	0.074	0.231	0.090	0.195	0.733	0.270	0.814	0.921
β_3	0.148	0.075	0.165	0.162	0.287	1.061	0.158	0.160	0.724	0.512	0.601	0.668
DIC	5104.645	3291.688	5044.033	3986.287	2653.707	2381.019	3412.148	3784.309	5239.7[illegible]	4261.237	4979.646	3558.903
Lag1												
β_1	0.247	0.265	0.246	0.236	0.376	0.565	0.168	0.220	1.193	0.381	1.526	1.385
β_2	0.327	0.152	0.345	0.181	0.107	0.212	0.094	0.225	0.794	0.275	0.891	1.089
β_3	0.122	0.048	0.137	0.216	0.285	0.986	0.161	0.227	0.512	0.247	0.566	0.644
DIC	5086.597	3288.968	5019.691	3967.744	2639.012	2370.057	3395.326	3766.228	5332.9[illegible]	4298.581	5054.482	3529.121
Lag2												
β_1	0.214	0.249	0.208	0.209	0.261	0.395	0.163	0.197	0.349	0.042	0.703	0.945
β_2	0.333	0.131	0.351	0.172	0.115	0.167	0.075	0.239	0.775	0.214	0.834	1.067
β_3	0.120	0.066	0.128	0.160	0.276	0.616	0.110	0.174	0.203	0.075	0.307	0.395
DIC	5070.362	3276.906	5008.069	3952.272	2633.324	2380.595	3385.27	3747.855	5403.21[illegible]	4302.206	5127.471	3571.984
Lag3												
β_1	0.139	0.179	0.133	0.228	0.147	0.164	0.195	0.237	0.066	0.028	0.161	0.440
β_2	0.273	0.070	0.297	0.193	0.138	0.133	0.092	0.258	0.519	0.121	0.530	0.529
β_3	0.112	0.081	0.117	0.175	0.189	0.352	0.104	0.210	0.183	0.048	0.346	0.571
DIC	5069.297	3276.217	5002.212	3931.903	2626.978	2387.809	3370.539	3726.269	5435.55[illegible]	4294.45	5161.446	3638.945

β_1, β_2, β_3 are the coefficients of influenza $A(H1N1)$, $A(H3N2)$ and B viruses, respectively.

Table S2. Ratios of influenza-associated excess mortality rates to ILI outpatient visit rates, excess hospitalisation rates to ILI outpatient visit rates, and excess mortality rates to hospitalisation rates by influenza virus types/subtypes and age groups.

	All influenza	A(H1N1)	A(H3N2)	B
Outpatient-mortality risk (%)				
Age-standardised	0.76 (0.48, 1.09)	0.32 (0.08, 0.68)	1.20 (0.69, 1.83)	0.51 (0.08, 1.28)
All ages	1.69 (0.97, 2.48)	0.71 (0.06, 1.63)	2.51 (1.23, 3.99)	1.16 (0.06, 3.26)
≥65 years	7.45 (4.53, 11.18)	4.27 (0.36, 11.14)	7.98 (4.34, 12.28)	7.82 (0.51, 24.61)
Outpatient-hospitalisation risk (%)				
Age-standardised	10.01 (7.04, 13.46)	6.03 (2.94, 9.60)	12.32 (7.03, 19.16)	10.41 (5.33, 18.66)
All ages	11.09 (5.23, 17.39)	6.56 (0.78, 13.40)	14.22 (4.63, 25.20)	9.21 (0.68, 25.49)
≥65 years	63.12 (34.84, 92.66)	47.24 (6.03, 93.48)	60.36 (26.9, 93.64)	54.42 (5.21, 97.30)
Hospitalisation-mortality risk (%)				
R&C				
Age-standardised	7.53 (4.59, 12.31)	5.28 (1.25, 14.64)	9.66 (5.11, 18.27)	4.84 (0.74, 14.46)
All ages	15.29 (7.68, 34.85)	10.61 (0.89, 60.86)	17.55 (7.50, 51.15)	11.93 (0.64, 74.56)
≥65 years	11.79 (6.37, 23.08)	8.76 (0.69, 52.20)	13.04 (6.40, 30.63)	9.56 (0.58, 60.09)
Respiratory disease				
Age-standardised	4.03 (3.06, 5.26)	3.26 (1.74, 5.45)	4.72 (3.35, 6.60)	3.23 (1.01, 6.67)
All ages	9.55 (6.54, 14.36)	8.09 (3.12, 22.68)	9.40 (6.08, 16.06)	11.70 (2.00, 62.60)
≥65 years	7.11 (5.21, 9.58)	6.02 (2.45, 12.77)	7.12 (5.10, 10.05)	8.19 (1.88, 31.38)
Circulatory disease				
Age-standardised	20.49 (9.71, 50.86)	15.65 (2.82, 69.43)	27.51 (9.17, 81.93)	10.78 (1.25, 60.79)
All ages	30.75 (11.97, 81.79)	19.14 (1.27, 83.69)	36.89 (11.21, 91.73)	15.59 (0.67, 82.09)
≥65 years	24.70 (10.17, 71.43)	15.35 (0.78, 80.25)	32.62 (10.15, 90.30)	11.48 (0.49, 72.26)

We assumed that the excess R&C deaths or hospitalisations approximate the totality of the influenza-associated deaths or hospitalisations R&C, respiratory and circulatory disease.

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any pre-specified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	N/A
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	N/A
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	N/A

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-11
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	N/A
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	N/A
		Cross-sectional study—Report numbers of outcome events or summary measures	N/A
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	11-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15-16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.