BMJ Open

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

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ABSTRACT

Objectives Negative estimates can be produced when statistical modelling techniques are 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 (2621 787, from 1 July 2013), and with influenza-like illness (ILI) outpatient visits (342 149) between 4 January 2010 and 31 December 2017.

Primary outcome measures Influenza-associated disease burden (mortality, hospitalisation 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% credibility interval (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 798.51–1023.66) 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) virus, and its severities were 1.65-fold to 3.54-fold and 1.47-fold to 2.16-fold higher than that for influenza A(H1N1) and B viruses, respectively.

Conclusions The proposed Bayesian approach with reasonable prior information improved estimates of influenza-associated disease burden. Influenza A(H3N2) virus was generally associated with higher morbidity and mortality, and was relatively more severe compared with influenza A(H1N1) and B viruses. 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 risks between layers, provided key parameters for handy estimation of influenza-associated disease burden in Shanghai as well as in other high-income 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 cocirculating respiratory viruses which were not included in the national virological 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 admissions and deaths.[5] The 'influenza pyramid' provides a full perspective of the disease burden associated with influenza and allows identification of 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 (P&I), respiratory and circulatory disease (R&C) and all-cause are often chosen as outcome variables in modelling methods. P&I is deemed to be the most specific outcome measure, but this category excludes other respiratory and circulatory diseases exacerbated by influenza. All-cause is too broad and sacrifices specificity; thus, R&C optimises the balance between sensitivity and specificity.[12–14]

Negative estimates can be produced when statistical modelling techniques are 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 R&C,[3 4 18] we have 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 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. 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) (online supplemental 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 (Hukou) system.[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. Weekly inpatient data from 2013 to 2017 were obtained from the Shanghai Municipal Health and Family Planning Commission. All medical institutions in Shanghai are required to apply the new edition of the inpatient medical record home page where full indicators were collected since 1 January 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 editions of inpatient electronic medical record. We only included inpatients from secondary and tertiary hospitals which had 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 weeks.[21]

We retrieved underlying causes of death and primary discharge diagnoses coded as respiratory disease (J00–J99), circulatory disease (I00–I99) and R&C (J00–J99 and I00–I99) in the International Classification of Diseases Codes V.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 and ≥65 years; 0–5, 6–17, 18–64 and ≥65 years, respectively).

Population and meteorological data

Age-specific annual population sizes, 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 paediatrics) were obtained from China's Health and Family Planning Statistical Yearbook.[23] Daily temperature and dew point temperature data 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 dew point temperature.

Statistical analysis

Negative binomial regression models were fitted separately to weekly deaths, hospitalisations and ILI outpatient visits by age groups and diseases in a Bayesian framework

using the 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 lagged by 0–3 weeks. We selected the dfs and lag weeks based on the minimum deviance information criterion[25] and curve fitting (online supplemental 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 online supplemental 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 paediatric 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 online supplemental appendix S2).[28]

Each model was run in 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 (CrIs) 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% CrIs were also based on these posterior samples.

Analyses were performed using the 'rjags' package of R software V.3.5.2 (R Foundation for Statistical Computing, Vienna, Austria), an interface between R and JAGS software V.4.3.0.[29]

Patient and public involvement

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

RESULTS
Descriptive statistics
During the study period of 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 shifted to A(H3N2) virus in 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, 2407.98 and 5247.92 per 100 000 population, respectively (table 1).

Influenza-associated disease burden
During the study period, we estimated an annual average of 2223 (95% CrI 1300–3164) 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, and 914.95 (95% CrI 798.51–1023.66) and 974.65 (855.22–1100.21) excess ILI outpatient visits, respectively (table 2). The pyramids of influenza-associated disease burden in Shanghai are 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 396.31–1026.38), 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 (1430.91, 95% CrI 1096.85–1773.40 per 100 000 population), followed by people aged ≥65 (1096.79, 95% CrI 914.25–1261.59 per 100 000 population) and 15–64 years (781.92, 95% CrI 664.68–894.82 per 100 000 population). Among people aged ≥65 years, 97.23% of excess R&C deaths and 80.24% of excess R&C hospitalisations occurred, whereas of excess ILI outpatient visits, only 13.13% 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

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*	26.73	22.31	20.99	23.00	23.94	25.85	25.00	32.18
ILI outpatient visit rate†	4681.27	4120.52	4152.99	4633.98	5173.12	5889.30	5685.84	7577.41
Hospitalisations rate‡								
R&C	–	–	–	1897.31	2131.63	2396.44	2557.96	2801.40
Respiratory disease	–	–	–	672.00	776.21	850.69	877.10	971.29
Circulatory disease	–	–	–	1225.31	1355.42	1545.75	1680.86	1830.12
Mortality rate§								
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	14123202	14193600	14269319	14323391	14386900	14429676	14499990	14551300
Permanent population	23019196	23474591	23804303	24151500	24256797	24152700	24197001	24197001

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 consultation rate per 1000 outpatient visits.
†ILI outpatient visit rate per 100 000 permanent population.
‡Hospitalisation rate per 100 000 permanent population.
§Mortality rate per 100 000 registered population.
ILI, influenza-like illness; R&C, respiratory and circulatory disease.

visits per 100 000 population, respectively (table 2 and 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, 95% CrI 27.78–44.16, per 100 000 population) were 1.40-fold to 1.48-fold lower than those for circulatory disease (9.64, 95% CrI 5.05–14.51, and 52.81, 95% CrI 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, 95% CrI 406.51–600.23, per 100 000 population) were 2.39-fold to

2.40-fold higher than those for circulatory disease (30.20, 95% CrI 9.61–60.12, and 210.20, 95% CrI 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%),
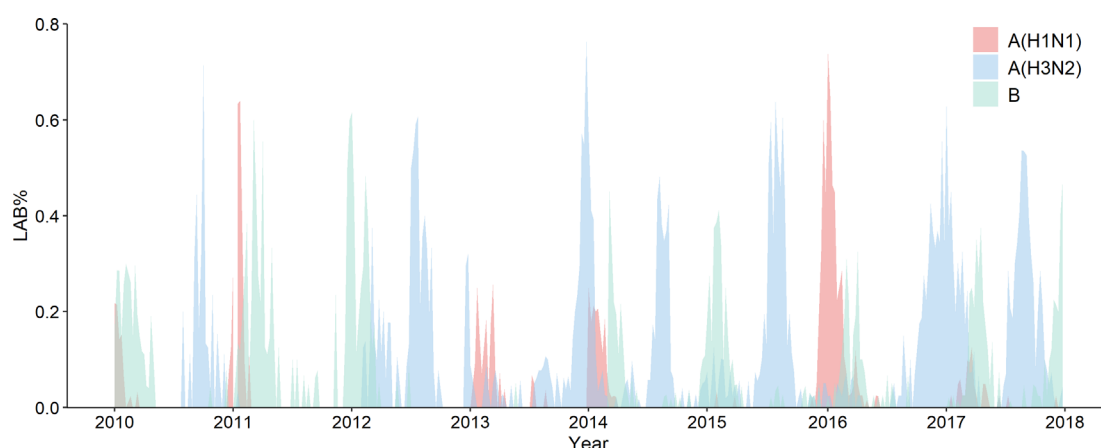

Figure 1 Influenza activity by type/subtype in Pudong New Area, Shanghai, 2010–2017. LAB%, weekly positive proportion of laboratory-confirmed influenza.

Table 2 Mean annual influenza-associated excess mortality rates and hospitalisation rates due to R&Cs, and ILI 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 (208.84–687.51)	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 (243.86–400.31)	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 (340.90–510.55)	224.37 (158.26–284.61)
0–14 years	1430.91 (1,096.85–1,773.40)	482.20 (370.05–605.77)	382.26 (156.64–607.09)	586.25 (360.05–818.06)
15–64 years	781.92 (664.68–894.82)	284.84 (240.37–328.79)	389.71 (299.27–480.25)	134.60 (76.48–196.58)
≥65 years	1096.79 (914.25–1,261.59)	228.14 (169.99–281.51)	722.65 (575.04–868.30)	177.45 (88.86–268.13)

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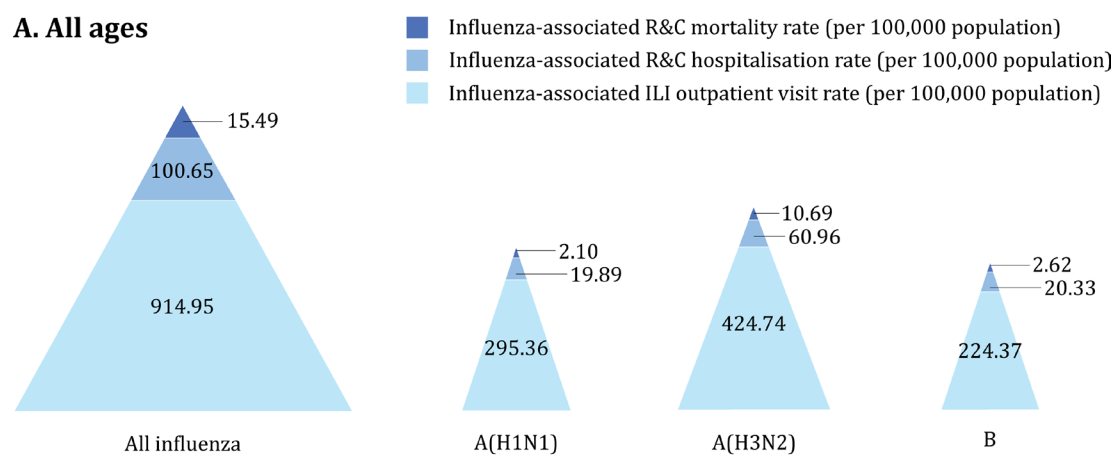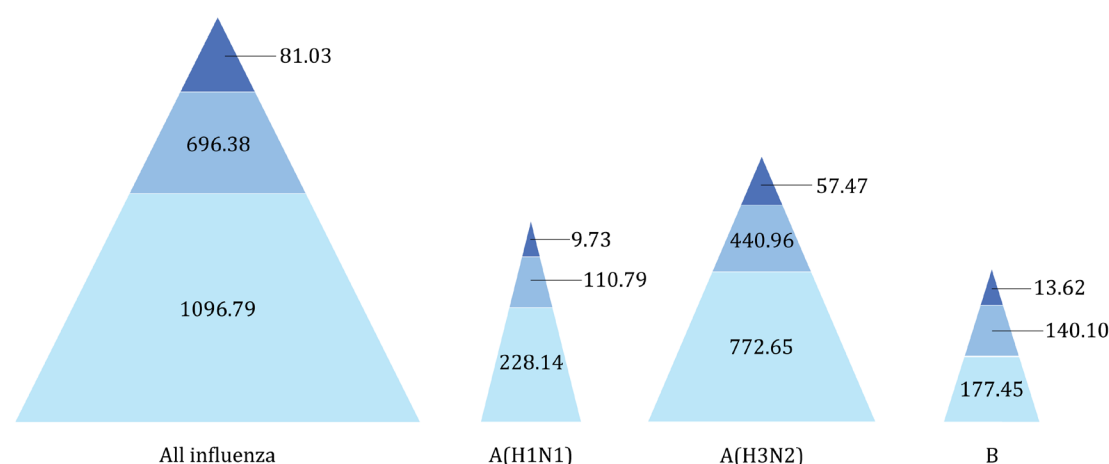
Figure 2 Pyramid of influenza burden by influenza virus types/subtypes and age groups in Shanghai, 2010–2017. ILI, influenza-like illness; R&C, respiratory and circulatory disease.

11.09% (95% CrI 5.23%–17.39%) and 15.29% (95% CrI 7.68%–34.85%), respectively (online supplemental 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 those 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-fold to 3.54-fold and 1.47-fold to 2.16-fold higher than those for influenza A(H1N1) and B viruses, respectively (online supplemental table S2). However, the difference did not reach statistical significance. Also, we presented separately
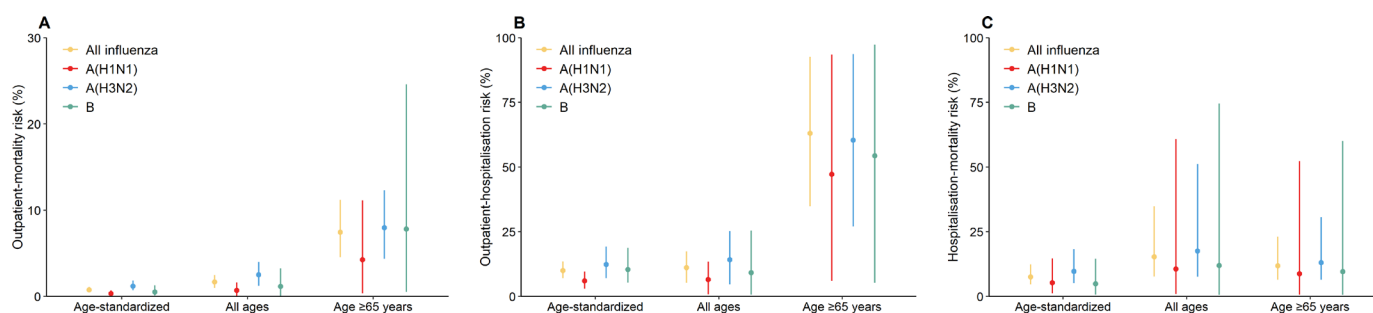

Figure 3 Clinical severity of influenza with different influenza virus types/subtypes and age groups. (A) Outpatient–mortality risk, (B) outpatient–hospitalisation risk and (C) hospitalisation–mortality risk.

the influenza-associated hospitalisation–mortality risks for respiratory disease and circulatory disease (online supplemental figure S5). People with the circulatory disease had a 3.22-fold higher hospitalisation–mortality risk than those with respiratory disease (online supplemental 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 798.51–1023.66) 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 USA (R&C death: 9.9 per 100 000 population,[30] R&C hospitalisation: 88.4 per 100 000 population[4] and ILI outpatient visit: 755–870 per 100 000 population)[31 32]; Argentina (R&C death: 21.3 per 100 000 population and R&C hospitalisation: 57 per 100 000 population)[14]; Hong Kong SAR (R&C death: 7.7 per 100 000 population)[33]; and five southern Chinese cities (R&C death: 8.8 per 100 000 population).[34] In particular, Hong Kong SAR reported an approximately twofold higher hospitalisation burden than our estimates,[33] which could be explained by the result of expanding health service capacities and lowering admission criteria due to the ageing population of Hong Kong in recent years.[13 24 35] 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 36] Influenza A(H3N2) virus is believed to have more frequent antigen drift and higher virulence than seasonal influenza A(H1N1) and B viruses.[37 38] Additionally, our study revealed that influenza A(H3N2) virus was relatively more severe as well.

The elderly people were 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 ageing 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 standardisation 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 had lower hospitalisation–mortality risks than for all ages. A possible explanation might be that young adults are less likely to be hospitalised compared with elderly people, but some of them do develop serious illnesses and require hospitalisation, and thus have a greater risk of death.

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,[39 40] Jiangsu[41–45] and Hubei.[46] 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 high-income countries/regions/cities.

Performing regression analyses in a Bayesian framework had 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% CrIs 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%.[47] 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 ILI 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[48] 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. However, 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 49]

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%). Replacement of 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, R&C 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 cocirculating respiratory viruses, such as respiratory syncytial virus, which may have confounded the results.

In conclusion, the proposed Bayesian approach with reasonable prior information improved estimates of influenza-associated disease burden. 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 was relatively more severe compared with influenza A(H1N1) and B viruses. Targeted influenza prevention and control strategies for the elderly in Shanghai may substantially impact the disease burden.

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Supplementary appendix

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

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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.

$$\frac{Influenza-associated\ ILI\ outpatient\ visits\ in\ Shanghai}{Total\ general\ population\ in\ Shanghai}$$
$$=\frac{Total\ medicine\ and\ pediatric\ outpatient\ visits\ in\ Shanghai}{Total\ general\ population\ in\ Shanghai}$$
$$\times\frac{Total\ influenza-associated\ ILI\ outpatient\ visits\ in\ surveillance\ hospitals}{Total\ medicine\ and\ pediatric\ outpatient\ visits\ in\ surveillance\ hospitals}$$
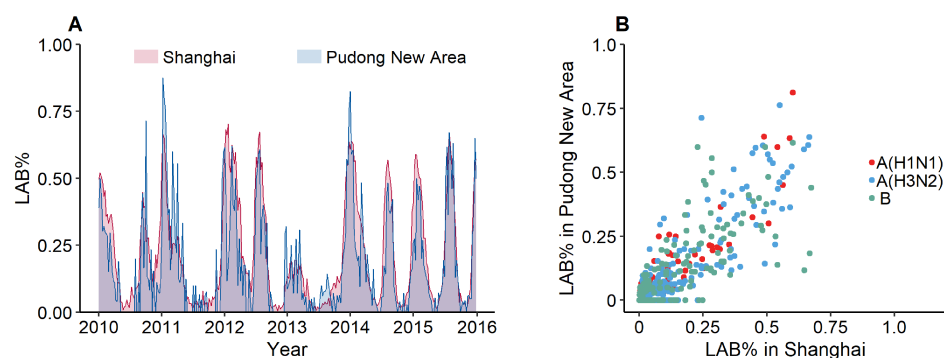
Figure S1. Weekly LAB% in Shanghai and Pudong New Area, 2010-2015.

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.
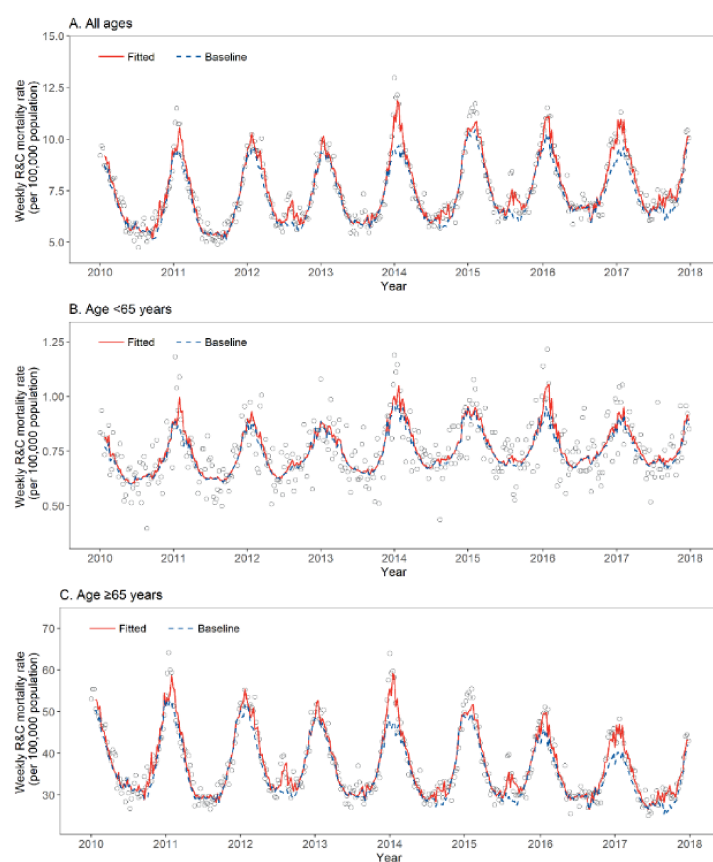
Figure S2. Weekly observed, fitted, and baseline respiratory and circulatory mortality rates by negative binomial regression model in Shanghai, 2010-2017. R&C, respiratory and circulatory disease.
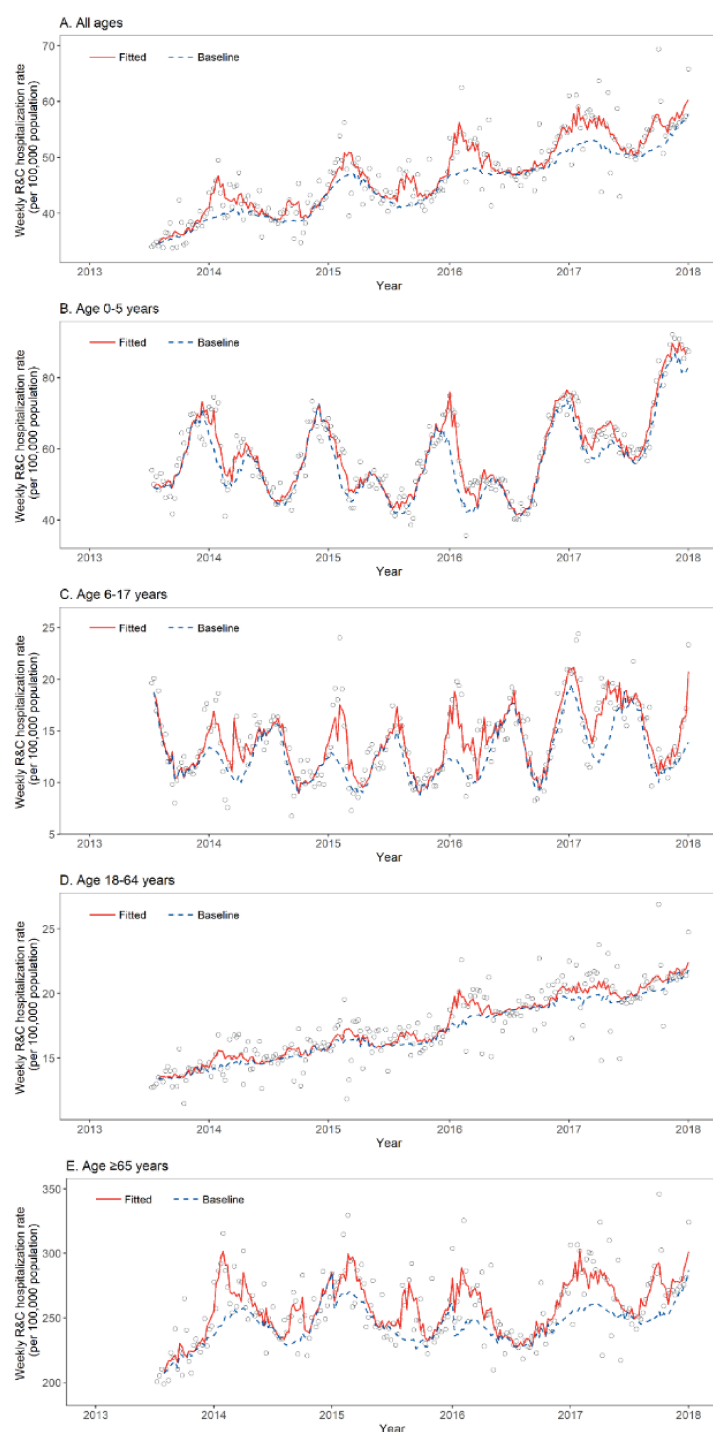
Figure S3. Weekly observed, fitted, and baseline respiratory and circulatory hospitalisation rates by negative binomial regression model in Shanghai, 2013-2017. R&C, respiratory and circulatory disease.

Supplemental material

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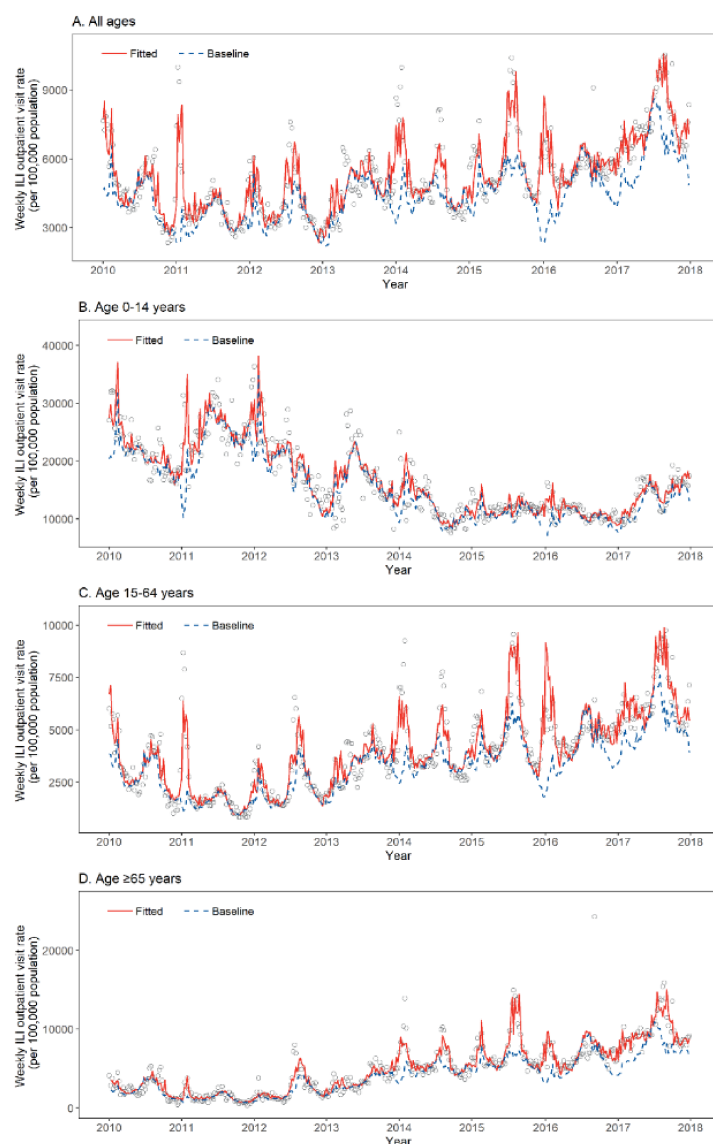**Figure S4. Weekly observed, fitted, and baseline influenza-like illness outpatient visit rates by negative binomial regression model in Shanghai, 2010-2017.** ILI, influenza-like illness.
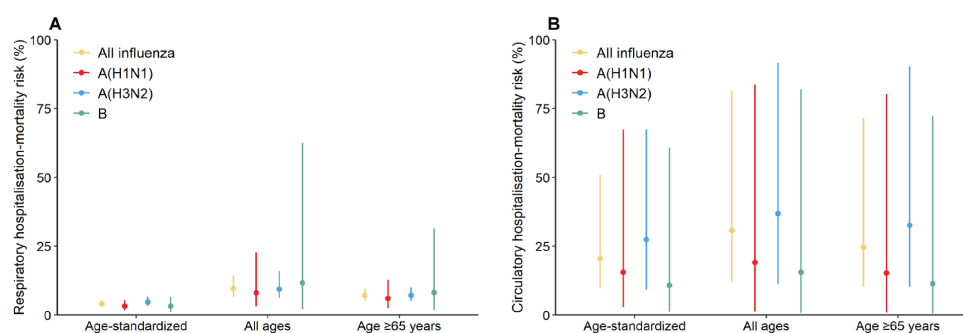
Figure S5. Clinical severity of influenza with different influenza virus types/subtypes and age groups. (A) Respiratory hospitalisation-mortality risk; (B) Circulatory hospitalisation-mortality risk.

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	5239.731	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	5332.93	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	5403.211	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	5435.554	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 (26.97, 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 (10.17, 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.