Regional variation in mortality impact of the 2009 A (H1N1) influenza pandemic in China

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Background Laboratory-confirmed deaths grossly underestimate influenza mortality burden, so that reliable burden estimates are derived from indirect statistical studies, which are scarce in low- and middle-income settings.

Objectives Here, we used statistical excess mortality models to estimate the burden of seasonal and pandemic influenza in China.

Methods We modeled data from a nationally representative population-based death registration system, combined with influenza virological surveillance data, to estimate influenza-associated excess mortality for the 2004–2005 through 2009–2010 seasons, by age and region.

Results The A(H1N1) pandemic was associated with 11·4–12·1 excess respiratory and circulatory (R&C) deaths per 100 000 population in rural sites of northern and southern China during 2009–2010; these rates were 2·2–2·8 times higher than those of urban sites ($P < 0.01$). Influenza B accounted for a larger proportion of deaths than pandemic A(H1N1) in 2009–2010 in some regions. Nationally, we attribute 126 200 (95% CI, 61 000–248 400) excess R&C deaths (rate of 9·4/100 000) and 2 323 000 (1 166 000–4 533 000) years of life lost (YLL) to the first year of A (H1N1)pdm circulation.

Conclusions The A(H1N1) pandemic posed a mortality and YLL burden comparable to that of interpandemic influenza in China. Our high burden estimates in rural areas highlight the need to enhance epidemiological surveillance and healthcare services, in underdeveloped and remote areas.

Keywords A(H1N1) pandemic, China, influenza, mortality, negative binomial model, regional variation.

Introduction

In June 2009, widespread transmission of a novel influenza A (H1N1)pdm virus led the World Health Organization (WHO) to declare a Phase 6 pandemic, the first in over 40 years. As of August 2010, the global number of reported laboratory-confirmed A(H1N1)pdm fatalities reported to WHO was 18,449.[1] Of these, 805 (4·4%) were from China, even though this country represents 20% of the world population.[2] The number of laboratory-confirmed A(H1N1) pdm deaths is widely considered a gross underestimate of the total pandemic mortality burden for a number of reasons. A limited proportion of individuals suspected of dying from

pandemic influenza are tested, especially in locations with limited access to care. Further, a large fraction of influenza-related deaths are typically classified as deaths due to subsequent complications, particularly among older persons and those with multiple underlying health conditions.[3] A recent global modeling effort estimated that the A(H1N1) pdm virus may be associated with 284 500 respiratory and cardiovascular deaths globally (range 151 700–575 500) in its first year of circulation, indicating that laboratory-confirmed deaths underestimate pandemic mortality burden by 15-fold globally.[4]

China is a middle-income country with a population estimated at about 1·3 billion, with important health and

geographical variation. Reliable estimates of deaths attributable to A(H1N1)pdm are needed to better understand the pandemic impact not only in China but also globally, as information on pandemic burden in low- and middle-income regions remains scarce.[5] Further, comparison of pandemic estimates with data for typical influenza seasons is important to place this pandemic in its historical context. A previous study has estimated that the burden of seasonal influenza in China was similar to that in the United States[6]; however, this study was limited to eight large developed cities and did not cover the pandemic period. A recent global pandemic mortality burden model has projected a burden of 22 816–84 581 deaths in China[4]; however, the model does not use mortality data specific to China. In this study, we modeled vital statistics data derived from a nationally representative population-based death registration system, combined with weekly viral activity surveillance data, to estimate the mortality impact and years of life lost associated with 2009 pandemic and past influenza seasons in China. We explore differences in disease burden by region and age-group.

Methods

Mortality data and population denominators

Mortality and population data were obtained from a timely vital statistics registry—the Disease Surveillance Points (DSP) system—established in China in 1990 (see details in Data S1). The current system consists of 161 sites, covering a population of 72·1 million. The DSP sites were selected to be nationally representative, reflecting regional population distributions in urban and rural areas, age and sex, and comprised sites in eastern, central, and western China.[7] We

identified 128 sites with most reliable mortality data (Data S1) covering a population of 61·1 million, or 4·6% China's population (Figure 1).

The China CDC established an online data management system to collect individual death certificates on a weekly basis based on the underlying cause of death, coded according to International Classification of Diseases, 10th Revision [ICD-10], in all DSP sites. We include mortality data from DSPs from July 2004, when vital statistics registries became established with well-defined population denominators, through June 2010, 13 months after the first A(H1N1)pdm detection in China. We compiled weekly numbers of deaths for respiratory and circulatory diseases (R&C, ICD-10 codes J00-J99 and I00-I99), respiratory diseases (ICD-10 codes J00-J99), as well as total deaths. Mortality was stratified by two age-groups (0–64 years and ≥ 65 years) and four regions (northern urban, northern rural, southern urban, southern rural). Population size denominators were obtained from National Bureau of Statistics of China.

Influenza virological surveillance

Weekly numbers of positive detections for influenza by type and subtype, as well as the total number of specimens tested, were obtained from the national sentinel hospital-based influenza-like illness surveillance network[6] (see details in the Data S1). Surveillance data for the 15 temperate northern provinces and 15 subtropical southern provinces were aggregated to represent the influenza circulation patterns in the northern and southern China, respectively. Because virus isolation was used to detect influenza from 2004 through April 2009 and reverse transcription polymerase chain reaction (RT-PCR) was initiated in May 2009 when the

Figure 1. Locations of rural and urban Disease Surveillance Point sites in Northern and Southern China.

pandemic A(H1N1) began, we adjusted the number of influenza-positive specimens to account for higher sensitivity of RT-PCR over virus isolation methods (Data S1 and Table S1). Specimens reported as influenza A without subtype information (4%) were assigned as A(H1N1), A(H3N2), or A (H1N1)pdm based on the ratio that each virus represented among influenza A viruses subtyped each week. Viral activity data were further standardized by dividing weekly number of positives by the seasonal number of specimens tested. The respiratory season was defined as the 12 consecutive months between July and June. An influenza type or subtype was considered dominant when it accounted for at least 50% of all influenza specimens during the respiratory season.

Estimating Influenza-associated excess mortality

Given overdispersion in mortality data,[6,8,9] we applied negative binomial regression with log link to estimate excess mortality, using weekly mortality counts as the outcome and the standardized weekly proportions of respiratory specimens testing positive for influenza A(H1N1), A(H3N2), A (H1N1)pdm, or B as the predictor variables (Data S1). Models included terms for seasonality (annual harmonics for northern China, annual and semi-annual harmonics for southern China) and time trends and offsets for population size. Models were fit separately for each disease outcome, age-group, and region using a log link.

To limit the effect of demographic noise, we smoothed the mortality and influenza time series using 4-week moving averages. Based on correlation between mortality outcomes and viral surveillance data at different lags (range 0–3 weeks), a 3-week lag was found optimal for mortality models.[6,10] Because respiratory syncytial virus activity is not monitored in China, no term for this pathogen was included in the model.

Weekly excess mortality was estimated as the difference between predicted mortality by the full model and predicted values with the influenza covariates set to zero; weekly excess mortality estimates were summed by season. Standardized all-age seasonal excess mortality rates were derived for each of the four regions using the national Chinese population in 2009–2010 as reference. To check the robustness of our excess mortality estimates, we conducted a number of sensitivity analyses. First, we applied Serfling seasonal regression models[6,11] to mortality data from northern provinces, which experienced clear winter influenza seasonality. Serfling models estimate influenza mortality burden as the mortality increase over a seasonal baseline, with no need for influenza surveillance data.

Further, we tested potential differences in influenza-related excess mortality rates between urban and rural sites by including mortality data for both categories of sites in the same model, using a dummy indicator for urban and rural locations, and interaction terms between the rural/urban term and the four influenza virus covariates. This model allowed for different baseline mortality rates between urban and rural sites and different influenza effects. We also tested the impact of allowing influenza coefficients to vary between years to adjust for potential changes in influenza severity or surveillance. Finally, we assessed the impact of the extended period of influenza surveillance during the pandemic in northern sites, where surveillance is typically limited to October–March, by artificially replacing influenza counts during April–September 2009–2010 with 0.

Extrapolation of DSP-based data to estimate national rates of influenza-associated mortality and years of life lost (YLL)

Next, we extrapolated national influenza-associated mortality rates for China by applying the estimated excess mortality rates for seasonal and pandemic influenza by age-group ($n = 2$) and region ($n = 4$) to the corresponding population sizes of the eight population groups in China. Then, we summed the number of excess deaths in the eight population groups to obtain a national estimate of excess deaths and thereby excess death rates. To control for demographic changes during the study period 2004–2010, we calculated age-standardized death rates for each season between 2004 and 2005 and between 2009 and 2010 based on the 2009–2010 Chinese population structure.

To integrate influenza-associated deaths with the age distribution of these deaths, we used the YLL approach.[12] We multiplied the number of age-specific excess deaths attributable to seasonal influenza or pandemic A(H1N1) by the life expectancy of that age-group (46·3 years for individuals aged 0–64 years and 11·8 years for those ≥ 65 years) in 2008.[13] Age-specific estimates of YLL were summed to give all-age estimates.

Results

Seasonal mortality and influenza virus activity

In the study period 2004–2010, the mean total annual mortality rate per 100 000 population ranged from 507 to 638 across the four regions, with no systematic difference between northern and southern or between rural and urban regions ($P > 0·05$). R&C causes represented 51–59% of all deaths, while individuals aged ≥ 65 years accounted for 62–70% of deaths (Table S2). During the study period, all categories of deaths in all study sites revealed a series of synchronous peaks during November–April each year. A second smaller mortality peak was observed in June–July in the southern region, broadly coinciding with viral surveillance data (Figure 2).

All 3 influenza subtypes cocirculated in the interpandemic seasons 2004–2005 to 2008–2009, with A(H1N1) dominating in two seasons, B and A(H3N2) viruses each dominating in
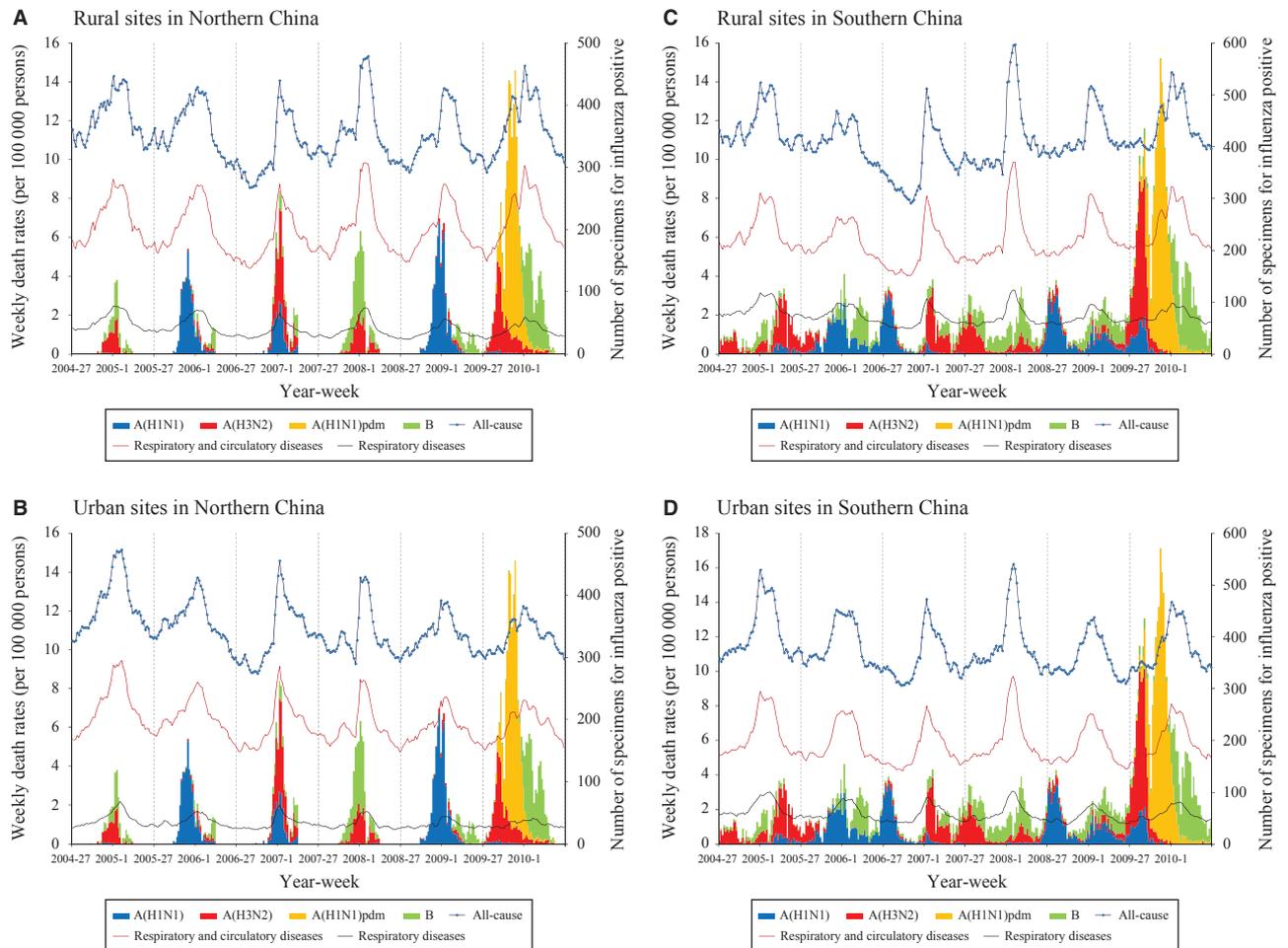
Figure 2. Weekly observed deaths per 100 000 people by underlying causes in the Disease Surveillance Point sites and number of influenza positive specimens, 2004–05 through 2009–10 seasons. Panel (A) Rural sites in Northern China. Panel (B) Urban sites in Northern China. Panel (C) Rural sites in Southern China. Panel (D) Urban sites in Southern China.

one, and no clear dominant subtype in 1 season (Table 1). Dominant subtypes were generally consistent between northern and southern regions. The A(H1N1)pdm virus became the predominant strain circulating in China in September 2009 and remained dominant until January 2010, but represented only 51–56% of influenza-positive samples during the entire pandemic season 2009–2010 (Table 1 and Figure 2). In particular, the period of intense pandemic activity was preceded by an A(H3N2) epidemic and followed by a B epidemic, producing 2 to 3 distinct peaks of mortality, especially pronounced in the rural sites.

Influenza-associated excess deaths

In the pre-pandemic period, mean annual rates of influenza-associated R&C excess deaths per 100 000 were 14·1 (range: 9·4–22·1) and 13·6 (range: 8·4–17·9) for rural and urban sites of northern China, respectively (Wilcoxon signed-rank test, $P > 0·05$). In southern China, rates in urban sites were

significantly lower than in rural sites (7·0 versus 14·3 per 100 000, Wilcoxon signed-rank test, $P < 0·05$). In the pre-pandemic period, the highest mean excess mortality rates were attributed to influenza B virus in all four regions, while rates were lowest for A(H3N2) in the north and for seasonal A(H1N1) in the south (Table 2).

Excess mortality rates associated with A(H1N1)pdm in 2009–2010 were 12·1 and 11·4 per 100 000 for the rural sites in northern and southern China; these rates were 2·2–2·8 times higher than those of urban sites in the same region (Table 2). The A(H1N1)pdm burden was highest in the southern rural regions. During the pandemic season, influenza B accounted for a larger fraction of influenza-related deaths than A(H1N1)pdm in urban sites.

Excess mortality rates for the 2009–2010 season were higher than the pre-pandemic mean for individuals <65 years. Younger individuals living in rural sites were particularly severely hit by the pandemic, with a 2·1- to

Table 1. Annual sum of total specimens tested and specimens positive for influenza by subtypes in northern and southern China, 2004–2005 through 2009–2010 seasons

	Tested specimens	Number (%) of specimens positive for total influenza	Number (%) by subtypes			
			A(H3N2)	A(H1N1)	A(H1N1)pdm	B
Northern China						
2004–2005	6320	782 (12·4)	384 (49·1)	17 (2·2)	–	381 (48·7)
2005–2006	10185	1529 (15·0)	117 (7·7)	1243 (81·3)	–	169 (11·1)
2006–2007	10543	1835 (17·4)	977 (53·2)	582 (31·7)	–	276 (15·0)
2007–2008	11236	1811 (16·1)	585 (32·3)	21 (1·2)	–	1205 (66·5)
2008–2009	18413	2232 (12·1)	142 (6·4)	1759 (78·8)	–	331 (14·8)
2009–2010	62234	6762 (10·9)	1246 (18·4)	65 (1·0)	3773 (55·8)	1677 (24·8)
Total	118931	14952 (12·6)	3451 (23·1)	3687 (24·7)	3773 (25·2)	4040 (27·0)
Southern China						
2004–2005	16261	2281 (14·0)	1513 (66·3)	199 (8·7)	–	569 (24·9)
2005–2006	26223	3007 (11·5)	335 (11·1)	1600 (53·2)	–	1072 (35·7)
2006–2007	31620	2850 (9·0)	1274 (44·7)	998 (35·0)	–	578 (20·3)
2007–2008	32724	2948 (9·0)	1038 (35·2)	167 (5·7)	–	1743 (59·1)
2008–2009	41491	3388 (8·2)	572 (16·9)	1756 (51·8)	1 (0·0)	1059 (31·3)
2009–2010	88914	11339 (12·8)	2335 (20·6)	575 (5·1)	5771 (50·9)	2658 (23·4)
Total	237233	25813 (10·9)	7067 (27·4)	5295 (20·5)	5772 (22·4)	7679 (29·7)

2·7-fold higher burden than that of an average pre-pandemic season. Excess mortality associated with A(H1N1)pdm among people aged 0–64 years represented 15–25% of all-age excess deaths, a minor age shift relative to seasonal epidemics (Table 2 and Figure 3) ($P < 0·05$, chi-square test).

The rates of influenza-associated mortality attributed to all-cause and respiratory diseases showed similar patterns (Table S3–S4). In particular, the excess death rates associated with A(H1N1)pdm in rural sites were 2·1- to 4·0-fold higher than in urban area, while influenza B had higher mortality impact than the other subtypes in the pre-pandemic period.

We present the coefficient estimates for all negative binomial regression models and a number of sensitivity analyses in Tables S5–S6. Sensitivity analyses focused on northern China and excluding viral activity surveillance data in summer months when influenza is not typically monitored did not change estimates for seasonal or pandemic seasons. Sensitivity analyses using a shorter period to fit the model, 2006–2010, where mortality data were less noisy, produced very similar results in most comparison groups except for southern seniors, where estimates were 1·2- to 2·8-fold lower than in the main analysis. Estimates were similar or lower when allowing the influenza coefficients to vary by season. Including data from urban and rural sites in the same model with separate intercepts and interaction terms exacerbated differences between urban and rural populations, relative to the main analysis. Further, the Serfling approach applied to northern China data produced estimates within 0·1–20% of the negative binomial model estimates for seven of the eight comparison groups, with only the pandemic point estimate

in urban seniors being substantially lower than in the main analysis.

Because the ratio of excess R&C to respiratory deaths increased to 3·9 during the pandemic from 2·2 in interpandemic seasons, we checked that this was not an artifact of the modeling approach via perhaps a different timescale between infection and death. We refit the respiratory mortality model with shorter and longer lags for viral activity data, which has little impact on excess mortality estimates (Table S7).

National excess mortality and years of life lost (YLL) extrapolations

Through our extrapolation of DSP data to the national Chinese population, our model attributes 32 500 (14 000–72 000) excess respiratory deaths, 126 200 (61 000–248 400) excess R&C deaths, and 184 500 (84 800–375 400) excess all-cause deaths to A(H1N1)pdm activity in China during July 2009–June 2010. The corresponding excess mortality rates are 2·4, 9·4, and 13·8 deaths per 100 000 population, respectively. The mortality burden associated with A(H1N1)pdm is comparable to that of typical seasonal epidemics and is 66% of the severe influenza B epidemic in 2007–2008 (Table 3).

On the basis of R&C mortality data, we estimate that 2 323 000 YLL (95% CI, 1 166 000–4 533 000 YLL) were associated with A(H1N1)pdm in China in 2009–2010, which is 93% of the YLL burden of an average epidemic season and 74% of the YLL burden of the severe 2007–2008 influenza B epidemic (Table 3). A shift in the age distribution of pandemic-related excess deaths and YLL

Table 2. Influenza-associated excess death rates (per 100 000 people) due to respiratory and circulatory diseases for Northern and Southern Disease Surveillance Point sites

	Rates (95% CI) for all-age*		Rates (%) by virus subtypes				Rates (95% CI) for age ≥ 65 years	Age 0–64 years	
	Age-standardized	Crude rates	A(H1N1)	A(H3N2)	B	A(H1N1)pdm		Rates (95% CI)	% of all-age
Northern sites									
Rural									
2004–2005	14·8 (10·3–44·8)	13·1 (9·1–39·9)	0·3 (2·3)	0·2 (1·6)	12·6 (96·1)	—	161·9 (114·5–465·5)	1·9 (1·1–7·8)	13·4
2005–2006	17·1 (10·6–47·5)	15·3 (9·4–42·6)	12·2 (80·1)	0 (0·1)	3·0 (19·8)	—	184·5 (116·9–492·5)	2·4 (1·2–8·4)	14·3
2006–2007	12·1 (4·5–41·4)	10·8 (4·0–37·4)	5·6 (51·5)	0·3 (2·9)	4·9 (45·7)	—	131·3 (51·5–425·9)	1·6 (0·4–7·7)	13·8
2007–2008	24·4 (18·8–55·1)	22·1 (17·0–50·2)	0·2 (0·7)	0·2 (0·8)	21·7 (98·5)	—	265·2 (207·7–575·6)	3·2 (2·2–9·4)	13·4
2008–2009	10·1 (5·4–35)	9·4 (4·9–32·5)	7·3 (77·8)	0 (0)	2·1 (22·2)	—	108·7 (59·8–357·0)	1·5 (0·6–6·8)	14·7
Mean	15·7 (9·9–44·8)	14·1 (8·9–40·5)	5·1 (36·2)	0·1 (1·0)	8·9 (62·8)	—	170·2 (109·9–462·5)	2·1 (1·1–8·0)	13·8
2009–2010	24·5 (15·4–61·4)	23·0 (14·5–57·7)	0·1 (0·6)	0·1 (0·5)	10·7 (46·5)	12·1 (52·4)	253·6 (159·9–623·3)	4·4 (2·7–12·1)	17·8
Urban									
2004–2005	11·8 (6·5–35·5)	13·1 (7·3–39·1)	0·2 (1·8)	3·9 (29·7)	8·9 (68·5)	—	125·2 (73·4–346·3)	1·8 (0·7–8·2)	12·5
2005–2006	12·9 (7·7–35·8)	14·5 (8·7–40·1)	11·7 (80·6)	0·7 (4·9)	2·1 (14·6)	—	130·5 (80·1–342·3)	2·6 (1·4–8·9)	16·0
2006–2007	12·7 (5·1–34·9)	14·9 (5·9–40·3)	5·7 (38·1)	5·6 (37·7)	3·6 (24·2)	—	125·7 (50·3–327·1)	2·8 (1·1–9·2)	17·1
2007–2008	14·5 (8·6–36·3)	17·9 (10·7–43·7)	0·1 (0·7)	3·1 (17·4)	14·6 (81·9)	—	155·9 (99·6–353·3)	2·1 (0·6–8·4)	10·7
2008–2009	6·9 (3·6–24·4)	8·4 (4·4–29·4)	6·7 (79·5)	0·2 (2·9)	1·5 (17·6)	—	69·1 (36·9–226·5)	1·4 (0·7–6·7)	14·9
Mean	11·8 (6·3–33·4)	13·6 (7·4–38·4)	4·9 (35·9)	2·7 (19·5)	6·1 (44·6)	—	119·9 (67·3–316·0)	2·1 (0·9–8·3)	14·0
2009–2010	11·6 (5·2–35·5)	14·1 (6·4–42·8)	0·1 (0·7)	1·8 (13·1)	6·7 (47·2)	5·5 (39·0)	113·9 (53·5–330·4)	2·6 (0·9–9·6)	16·7
Southern sites									
Rural									
2004–2005	9·8 (1·1–47·6)	9·7 (1·1–47·4)	0 (0)	3·6 (37·4)	6·1 (62·6)	—	104·0 (13·3–495·4)	1·5 (0–8·3)	14·3
2005–2006	6·9 (1·4–40·1)	6·8 (1·4–39·8)	0 (0)	0·6 (8·5)	6·3 (91·5)	—	75·1 (16·1–420·9)	0·9 (0·1–6·6)	12·1
2006–2007	4·2 (0–36·7)	4·3 (0–37·2)	0 (0)	1·6 (38·3)	2·6 (61·7)	—	44·9 (0–383·3)	0·6 (0–6·2)	13·2
2007–2008	9·5 (1·4–42·2)	9·8 (1·4–43·3)	0 (0)	1·3 (13·7)	8·4 (86·3)	—	103·6 (16·4–444·3)	1·3 (0·1–6·9)	11·7
2008–2009	4·4 (0·1–33)	4·5 (0·1–33·3)	0 (0)	0·5 (10·7)	4·0 (89·3)	—	48·7 (1·4–347·8)	0·6 (0–5·3)	11·4
Mean	7·0 (0·8–39·9)	7·0 (0·8–40·2)	0 (0)	1·5 (21·8)	5·5 (78·2)	—	75·2 (9·4–418·0)	1·0 (0–6·7)	12·6
2009–2010	17·7 (6–62·2)	17·8 (6·0–62·4)	0 (0)	1·1 (6·2)	5·3 (29·7)	11·4 (64·2)	188·7 (63·3–657·3)	2·7 (0·9–10·0)	14·1
Urban									
2004–2005	17·9 (8·1–44·5)	19·7 (9·0–48·8)	0·1 (0·4)	6·7 (34·1)	12·9 (65·4)	—	184·2 (86·2–439·3)	3·3 (1·3–9·8)	15·3
2005–2006	13·4 (7·2–36·1)	14·7 (7·9–39·6)	0·5 (3·5)	1·0 (7·1)	13·2 (89·4)	—	130·2 (73·6–340·8)	3·2 (1·3–9·4)	19·4
2006–2007	7·7 (1·4–30·3)	8·5 (1·5–33·4)	0·2 (2·6)	2·9 (34·4)	5·4 (63·0)	—	76·9 (15·3–290·9)	1·6 (0·1–7·4)	17·5
2007–2008	17·4 (9·8–40·3)	19·8 (11·1–45·4)	0 (0)	2·5 (12·4)	17·3 (87·6)	—	178·3 (101·4–398·3)	3·3 (1·7–8·8)	15·2
2008–2009	8·0 (3·2–26·3)	9·2 (3·7–29·9)	0·3 (3·7)	0·7 (8·1)	8·1 (88·2)	—	78·9 (33·4–247·7)	1·8 (0·6–6·8)	17·6
Mean	12·9 (5·9–35·5)	14·3 (6·6–39·3)	0·2 (1·6)	2·7 (19·1)	11·3 (79·2)	—	128·6 (61·5–341·1)	2·6 (1·0–8·4)	16·7
2009–2010	13·7 (5·4–40·1)	15·8 (6·3–46·2)	0·0 (0·1)	1·9 (11·9)	9·9 (62·3)	4·1 (25·7)	136·0 (54·7–391·0)	2·9 (1·1–9·3)	16·8

*The sum of the estimates of excess influenza-associated deaths for the age-group of 0–64 years and ≥ 65 years.
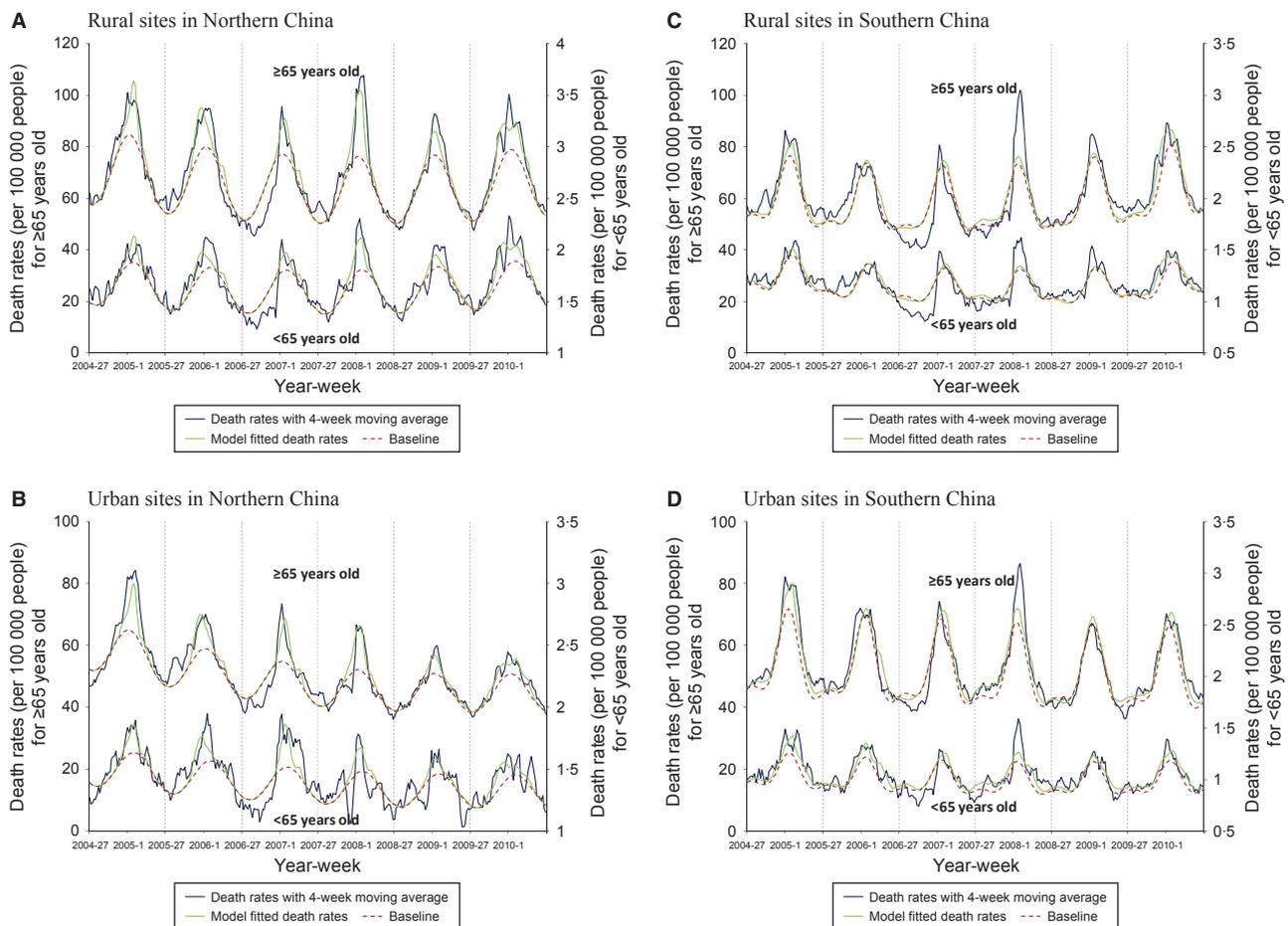
Figure 3. Observed, predicted, and baseline respiratory and circulatory mortality by the negative binomial regression models. Deaths are per 100 000 people for ≥ 65 years and 0–64 years. Panel (A) Rural sites in Northern China. Panel (B) Urban sites in Northern China. Panel (C) Rural sites in Southern China. Panel (D) Urban sites in Southern China.

toward younger populations was observed in all causes of deaths.

Discussion

This is the first study to estimate the mortality burden of the 2009 pandemic in China, based on a unique and nationally representative surveillance system for mortality and viral activity, covering a population of 61 million in 128 study sites in China. We estimate that approximately 126 000 excess respiratory and circulatory deaths (rate of 9·4 deaths per 100 000) and approximately 2 323 000 YLL were attributable to the A(H1N1)pdm circulation in 2009–2010 in China—a middle-income country representing 20% of the world's population and diverse climatic and economic patterns. The pandemic impact was similar to that of an average pre-pandemic influenza season and milder than the severe influenza B epidemic experienced by China in 2007–2008. Remarkably, the 2009–2010 pandemic season was associated with cocirculation of influenza A(H3N2), A(H1N1)pdm, and B subtypes in China, with a higher burden for influenza B than A(H1N1)pdm in urban sites. We noted a marked difference in pandemic impact between urban and rural communities, with rural sites experiencing influenza-associated mortality rates > twofold higher than urban sites. The pandemic experience was particularly severe among people under 65 years living in rural communities, relative to their typical experience with seasonal influenza.

Our A(H1N1)pdm excess mortality estimates derived from all-cause mortality (13·8 per 100 000) can be compared with those derived from similar approaches in other countries/areas (Table 4). Our estimate for China is higher than that for the United States (4·1–4·8),[14,15] Europe (United Kingdom (7·4),[16] Denmark (9·8),[17] France (0·98) and the Netherlands (3·7)[18,19]), Hong Kong SAR (1·8), Brazil (1·5), and Australia (−6·0),[20–22] but lower than that of Mexico (24·6)[23] Estimates of per capita YLL are comparable for the United States and China, even though the age distribution of

Table 3. Number and age distribution of excess deaths and years of life lost associated with A(H1N1)pdm and seasonal influenza in China

	Death cause	Excess deaths		Rates for age ≥65 years (95% CI)	Rates for age 0–64 years (95% CI)	Percentages in age 0–64 years	Years of life lost (adjusted to 2008 population)	
		No. for all-age (95% CI)	Rates for all-age (95% CI)				No. in thousands (95% CI)	Percentages in age 0–64 years
A(H1N1)pdm in 2009–2010	R&C	126 242 (61 002–248 383)	9·4 (4·6–18·6)	94·6 (44·5–187·1)	2·0 (1·0–3·8)	19·1	2323 (1166–4533)	48·0
	Respiratory	32 501 (14 052–72 033)	2·4 (1·1–5·4)	23·8 (9·6–54·0)	0·6 (0·3–1·1)	21·0	620 (295–1324)	51·0
	All-cause	184 453 (84 785–375 433)	13·8 (6·3–28·1)	125·8 (59·3–250·2)	3·9 (1·7–8·6)	26·3	3856 (1716–8066)	58·3
Seasonal epidemics*	R&C	148 694 (66 966–430 665)	11·1 (5·0–32·2)	117·8 (54·8–329·3)	1·7 (0·6–6·1)	14·5	2500 (1060–7678)	39·8
	Respiratory	66 382 (32 022–168 536)	5·0 (2·4–12·6)	53·9 (26·4–131·9)	0·7 (0·3–2·1)	12·3	1067 (499–2892)	35·5
	All-cause	202 357 (84 465–653 765)	15·1 (6·3–48·9)	145·5 (64·5–436·4)	3·7 (1·2–14·8)	22·4	3953 (1510–14 021)	53·0
B epidemic in 2007–2008	R&C	192 210 (116 644–288 725)	14·4 (8·7–21·6)	154·5 (95·8–227·3)	2·1 (1·1–3·5)	13·2	3147 (1832–4906)	37·3
	Respiratory	76 787 (49 173–109 744)	5·7 (3·7–8·2)	63·3 (41·6–88·8)	0·7 (0·3–1·1)	10·9	1198 (729–1775)	32·5
	All-cause	251 919 (147 781–405 597)	18·8 (11·0–30·3)	192·2 (114·8–291·3)	3·6 (1·9–9·4)	17·6	4508 (2567–7935)	45·5

*Average of five interpandemic seasons 2004–2005 through 2008–2009.

pandemic excess deaths differed between the two countries (Table 4).

Regarding more specific death outcomes, our estimate for respiratory diseases is about twofold lower than that of Mexico,[23] but our R&C rate is fivefold higher than that of Hong Kong SAR.[20] Interestingly, our R&C estimate is twofold higher than the Chinese estimate derived from a global disease burden model, which does not include influenza epidemiological data specific to China, and assumes that few pandemic deaths were circulatory.[4] Overall, caution is needed in interpreting differences in cause-specific estimates, due to variation in coding practices between countries,[24,25] especially as the faction of deaths coded as respiratory is lower in China than in the United States or Mexico. A thorough study of death coding practices in different countries, along with a comparison of pandemic and seasonal influenza excess mortality estimates, would be worthwhile in the future to provide a better understanding of geographical differences in disease burden estimates.

The mortality burden associated with A(H1N1)pdm in persons aged 0–64 years was slightly higher relative to that of seasonal epidemics, consistent with an age shift in the distribution of deaths reported in most countries.[14–16,23] Persons under 65 years accounted for 19–26% of pandemic-related excess deaths in our study, consistent with estimates from European countries and Hong Kong SAR (9–30%),[16–20] but substantially lower than estimates based on laboratory-confirmed deaths in China (87%).[26–28] Age biases in testing propensity toward younger cases and increased difficulties in detection of influenza viruses in older people with underlying conditions could account for such discrepancies.[23] The relatively high pandemic burden estimate for Chinese seniors is consistent with a 10% seropositive rate for A(H1N1)pdm reported in this population in January 2010 and a particularly high case fatality rate associated with influenza A (H1N1)pdm infection in this age-group.[26,29]

This study also provides national estimates of excess mortality for seasonal influenza (15·1 all-cause excess deaths per 100 000), which are comparable to those of the United States.[30,31] Further, our estimates are consistent with those of a previous study using a more limited geographical sample comprising eight Chinese cities.[6] Importantly, the present study confirms the large burden of influenza B epidemics in northern and southern China in the pre-pandemic period. The reasons for the particularly high influenza B burden in China, including at the tail end of the 2009–2010 pandemic season, remain unresolved but could be related to subtype differences in case fatality rates[32] or unusual transmission dynamics and immunity patterns to influenza B in China.

Our study reveals a higher pandemic burden in rural areas of China, relative to the pandemic experience in urban communities, and data from northern China suggest this was specific to the pandemic season. Although artifact of data

Table 4. Between-country comparison of excess death rates and years of life lost associated with A(H1N1)pdm influenza. Estimates are based on a literature review of studies using an excess mortality modeling approach

Country/area	Approach	Mortality outcome	Excess death		Years of life lost	
			Rates per 100 000 (95% CI)	% in 0–64 years	No. per 100 000 (95% CI)	% in 0–64 years
China (this study)	Negative binomial model	R&C	9·4 (4·6–18·6)	19	174 (87–339)	48
United States[14]	Probability model	All-cause	4·1 (2·9–6·0)	87	–	–
United States[15]	Quasi-Poisson model	R&C	4·8 (3·3–6·4)	79	154 (104–204)*	90
Mexico[23]	Serfling model	R&C	15·4 (12·7–18·1)	40**	358 (293–426)*	72**
Brazil[22]	Serfling model***	Respiratory	1·5	–	–	–
United Kingdom[16]	Poisson model	All-cause	7·4	9	–	–
France[18]	Poisson model	Respiratory	0·98 (0·2–1·9)	30	19 (8–33)	–
Denmark[17]	Poisson model	All-cause	9·8 (7·4–12·1)	11	–	–
The Netherlands[19]	Poisson model	All-cause	3·7 (1·6–5·8)	30	–	–
Australia[21]	Serfling model	All-cause	−6·0 (−12; −0·6)	–	–	–
Hong Kong SAR, China[20]	Poisson model	R&C	1·6 (0·4–2·9)	15	–	–

*YLL per 100 000 were calculated by dividing the estimated number of YLL by population size.
**Percent in <60 years was presented.
***Using a Serfling methodology to estimate baseline mortality, not excluding deaths associated with seasonal influenza. In this case, pandemic influenza mortality represents the estimated burden above and beyond that of seasonal epidemics and provides an underestimate of the true pandemic burden.

collection or modeling could affect our results, these urbanization differences were independently found in northern and southern China study sites, and patterns were consistent across all model sensitivity analyses and mortality outcomes. Differences between urban and rural sites may be related to access to medical care and socioeconomic status and also reflect regional difference in public health response and interventions strategies, including case finding and treatment, health education, vaccine and antiviral distribution during the pandemic.[27,33] Pandemic vaccination campaigns were initiated at the end of September 2009, but only 7·3% of the population had been vaccinated by April 2010. Cross-sectional surveys undertaken by China CDC during pandemic peak showed that farmers had lower pandemic vaccination uptake compared with healthcare workers, students, teachers, and office staff in urban areas.[34] A better understanding of these differences would be particularly useful, as 70% of the Chinese population still leaves in rural communities.

We used negative binomial models that provide subtype-specific mortality estimates. Several sensitivity analyses using different model assumptions and structures produced similar estimates for mortality associated with R&C diseases, demonstrating the robustness of our results. Further, Serfling model estimates were in line with those of negative binomial models for northern sites, where we could apply both approaches.

Our study has several potential limitations. First, mortality data for 2006–2010 were not adjusted for underreporting rates. The average underreporting rate for the 161 DSP sites was estimated 17·4% in 2006–2008, with slightly higher rates in rural than urban areas (18·1 versus 16·1, $P < 0·01$[35]). Underreporting and misclassification of causes of registered deaths could lead to underestimation of influenza-associated excess mortality rates; hence, our estimates should be considered as conservative. Second, year-to-year variations in virological surveillance coverage and diagnostics methods may have influenced our estimates, despite our attempts to adjust for such biases. However, Serfling model estimates do not rely on viral surveillance data and confirm results of the negative binomial model. Third, our YLL estimates are likely overestimated given that persons who die from influenza usually have underlying comorbidities and thereby shorter life expectancy than the rest of the population. However, we provide fair comparisons of YLL between seasons and countries. Fourth, our estimates are limited to two broad age-groups; unfortunately, modeling of more refined age categories produced unreliable results due to low death counts. A fifth important caveat relates to the crude geographical scale of our analysis, which was limited by the resolution of the surveillance and mortality data. We considered four broad regions corresponding to rural and urban areas of northern and southern China and used a weighted average method to extrapolate national estimates representing a population of 1·3 billion. This extrapolation was an effort to strike balance between demographic noise and health differences worth accounting for, and we hope that future studies will be able to explore differences in

influenza activity and disease burden at higher spatial resolution. Finally, we could not account for the impact of respiratory syncytial virus and other respiratory pathogens in our model, due to lack of surveillance data. Intensified surveillance for respiratory pathogens will be useful to improve excess mortality estimates in the future.[36]

Compared with the 805 laboratory-confirmed A(H1N1) pdm deaths, our relatively conservative estimate of 32 500 pandemic excess respiratory deaths suggests that only 1 in 40 A(H1N1)pdm-related deaths was laboratory confirmed in China, in a period where testing was considerably strengthened. Laboratory confirmation was more intense in other areas, as one in seven influenza-related deaths was laboratory confirmed in Mexico[23] and one in 2·4 in Hong Kong SAR.[20] We do not have any information on how testing practices varied geographically, but assume that there was little testing in rural sites where access to care is poorer.

This study demonstrates that the A(H1N1)pdm pandemic, which is considered a mild pandemic in high-income settings, posed a mortality and YLL burden comparable to that of interpandemic influenza in China. Rural areas of China were hit hardest in 2009 and experienced a subsequent influenza B epidemic in winter 2010, resulting in an unusually high cumulative influenza death toll for the 2009–2010 respiratory season. Differences in health care, perhaps exacerbated during pandemic seasons, and in dominance of influenza subtypes could explain variation in disease burden between regions and countries. In China as in other countries, the pandemic was unusually severe in persons aged 0–64 years, who accounted for half of the YLL burden.

Understanding regional and age variation in pandemic burden is useful to guide intervention strategies and to define high-risk priority groups for vaccination in resource-limited settings. The high pandemic mortality burden estimated for rural areas of China in our study highlights the need to enhance influenza surveillance, healthcare service, and vital statistics collection, in underdeveloped and remote areas. Differences in the seasonal characteristics of mortality and influenza virus circulation in southern China resulted in poorer model fits in this region—a better understanding of the biological mechanisms responsible for such asynchrony to provide more geographically resolved estimates is an interesting area for future studies. Overall, while our study provides useful data to understand regional variation in influenza mortality burden, more information from low- and middle-income regions is required to fully elucidate the relationships between influenza-related mortality and socio-economic and health conditions.

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Author contributions

HY, LF, CV, DKS, and SN designed the analysis; YJ, MZ, and NH provided the data used in this analysis. LF, HZ, ZX, and WY did the data analysis. HY and LF wrote the first draft of the manuscript, and all authors contributed to the interpretation of the results of the analysis and to the revision and final preparation of the manuscript for submission.

Conflict of interests

All authors declared that there are no conflict of interests.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Mortality Data.

Table S1. Adjustment ratio of specimens positive for influenza using virus culture to assay of polymerase chain reaction (PCR).

Table S2. Annual deaths rates (per 100 000 people) by cause of death, region, and season, 2004-05 through 2009-10.

Table S3. Influenza-associated excess death rates (per 100,000 people) due to all-cause for Northern and Sothern Disease Surveillance Point sites.

Table S4. Influenza-associated excess death rates (per 100,000 people) due to respiratory diseases for Northern and Sothern Disease Surveillance Point sites.

Table S5. Coefficients of negative binomial regression models used to derived excess mortality estimates, by age and region.

Table S6. Comparison of influenza-associated excess death rates (per 100 000 people) due to respiratory and circulatory diseases by negative binomial (NB) models and Serfling models.

Table S7. Influenza-associated excess death rates (per 100,000 people) due to respiratory diseases in persons ≥ 65 years old by negative binomial models with different lags between virological data and respiratory death outcomes.

Figure S1. Weekly number of specimens tested and percentage of influenza positive in Northern and Southern China.