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Original Contribution

Distribution and Risk Factors of 2009 Pandemic Influenza A (H1N1) in Mainland China

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Data from all reported cases of 2009 pandemic influenza A (H1N1) were obtained from the China Information System for Disease Control and Prevention. The spatiotemporal distribution patterns of cases were characterized through spatial analysis. The impact of travel-related risk factors on invasion of the disease was analyzed using survival analysis, and climatic factors related to local transmission were identified using multilevel Poisson regression, both at the county level. The results showed that the epidemic spanned a large geographic area, with the most affected areas being in western China. Significant differences in incidence were found among age groups, with incidences peaking in school-age children. Overall, the epidemic spread from southeast to northwest. Proximity to airports and being intersected by national highways or freeways but not railways were variables associated with the presence of the disease in a county. Lower temperature and lower relative humidity were the climatic factors facilitating local transmission after correction for the effects of school summer vacation and public holidays, as well as population density and the density of medical facilities. These findings indicate that interventions focused on domestic travel, population density, and climatic factors could play a role in mitigating the public health impact of future influenza pandemics.

China; disease outbreaks; disease transmission, infectious; influenza, human; invasion process; pandemics

Abbreviations: CCDC, Chinese Center for Disease Control and Prevention; CISDCP, China Information System for Disease Control and Prevention.

In early April 2009, human cases of infection with 2009 pandemic influenza A (H1N1) virus were first identified in the United States and Mexico (1). The virus then spread rapidly to other regions of the world. As of January 24, 2010, laboratory-confirmed cases of pandemic influenza (H1N1-2009) were being reported in more than 209 countries or regions worldwide, with 14,711 deaths among confirmed cases (2). Pandemic influenza was introduced to mainland China on May 9, 2009 (3, 4), and then spread across the whole country. By the end of 2009, more than 120,000 confirmed cases were reported to the Chinese Center for Disease Control and Prevention (CCDC), including 648 deaths (5). Information on reported cases was released daily by the Ministry of Health of the People's Republic of China in the early stages of the pandemic and then twice weekly later on.

Analyzing the information gathered and unearthing underlying risk factors provide an opportunity to identify epidemic characteristics and transmission patterns of the pandemic in China, thereby producing useful information for prevention and control measures during future epidemics. In this study, we aimed to characterize the temporal and spatial distribution of pandemic influenza in mainland China, to understand the diffusion pattern of the disease within the country, and to identify risk factors for invasion and local transmission of this disease.

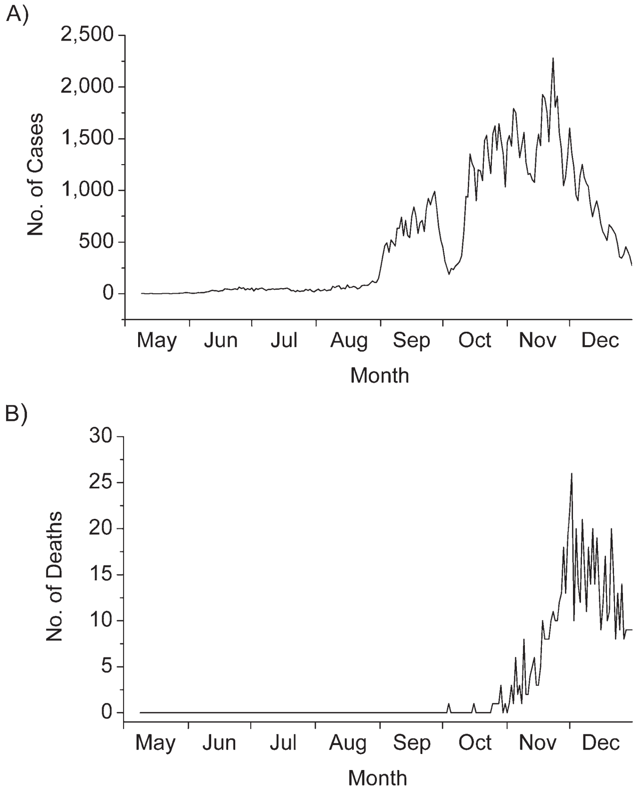

Figure 1. Epidemic curves for pandemic influenza (H1N1-2009) in mainland China, 2009. A) Daily temporal distribution of confirmed cases; B) daily temporal distribution of deaths due to pandemic influenza (H1N1-2009).

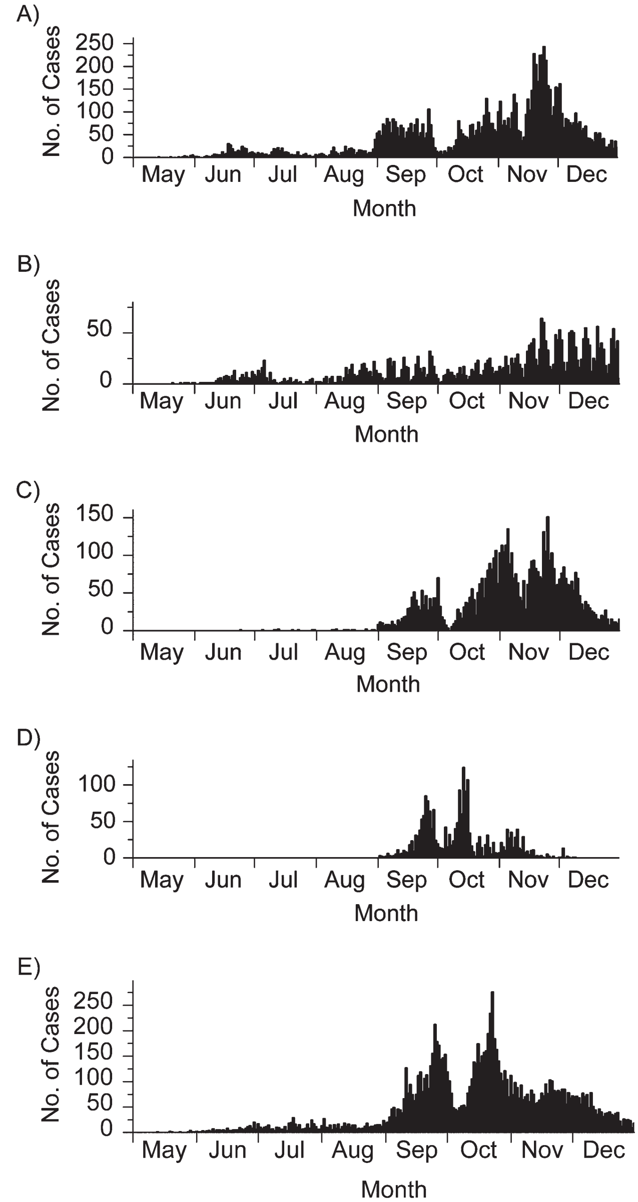

Figure 2. Epidemic curves for pandemic influenza (H1N1-2009) for 5 selected cities/provinces in different regions of mainland China, 2009. A) Guangdong Province in southern China; B) Shanghai City in eastern China; C) Shaanxi Province in central China; D) Tibet Autonomous Region in western China; E) Beijing City in northern China.

MATERIALS AND METHODS

Data collection

We used a database that included all cases of pandemic influenza (H1N1-2009) reported to the China Information System for Disease Control and Prevention (CISDCP) from May 9, 2009, when the first confirmed case in China was reported, to December 31, 2009 (6). The CISDCP covers all provincial, prefectural, and county centers for disease control and prevention, 95.3% of the provincial, prefectural, and county hospitals (9,084 in total), and 84.0% of township clinics (38,175 in total) across mainland China. After the World Health Organization issued an alert about the novel influenza virus (H1N1-2009), pandemic influenza was classified as a class B notifiable infectious disease on April 30, 2009, by the Ministry of Health but was managed according to the criteria for class A notifiable infectious diseases. According to the Law for Prevention and Control of Infectious Diseases in China, information regarding each patient, once identified, must be reported to the CCDC within 2 hours through the Web-based CISDCP system. A suspected case was defined as a person with influenza-like symptoms who had had close contact with a confirmed case within the past 7 days, had a history of travel to affected areas within the past 7 days, or tested positive for influenza A virus, excluding other known subtypes of influenza A. A laboratory-confirmed case was defined according to World Health Organization criteria—that is, a person with influenza-like symptoms and laboratory-confirmed pandemic influenza A virus infection by one or more of the following tests: reverse-transcriptase polymerase chain reaction, real-time reverse-transcriptase polymerase chain reaction, viral culture, or a 4-fold rise in specific antibodies to pandemic influenza A virus (7). Influenza-like symptoms were defined according to World Health Organization criteria: sudden onset of fever greater than 38°C, cough or sore throat, and absence of other diagnoses (8).

Table 1. Association Between Duration of Time (Days) to the First Confirmed Case of Pandemic Influenza A (H1N1-2009) and Travel-related Factors at the County Level[a] in Survival Analysis, People's Republic of China, 2009

Variable and Unit[b]	Median Duration,[c] days (IQR)	Univariate Cox Analysis			Multivariate Cox Analysis		
		Crude HR	95% CI	*P* Value	Adjusted HR	95% CI	*P* Value
Intersected by national highway							
No	172 (130 to >237)	1.00			1.00		
Yes	161 (126–195)	1.32	1.21, 1.44	<0.001	1.25	1.14, 1.37	<0.001
Intersected by railway							
No	173 (133–212)	1.00					
Yes	159 (124–198)	1.19	1.09, 1.29	<0.001	NS (excluded)		
Intersected by freeway							
No	171 (134–215)	1.00					
Yes	140 (118–187)	1.45	1.33, 1.58	<0.001	1.21	1.10, 1.32	<0.001
Distance to the nearest airport (categorical), km							
<40	130 (96–171)						
40–79	168 (128–205)						
80–120	170 (133–204)						
>120	177 (146 to >237)						
Distance to the nearest airport (continuous), 50 km		0.80	0.77, 0.83	<0.001	0.87	0.84, 0.91	<0.001
Population density (categorical), per km^2							
<120	180 (160 to >237)						
120–299	172 (135–203)						
300–700	159 (126–205)						
>700	128 (91–168)						
Population density (continuous), 1,000 persons per km^2		1.08	1.08, 1.09	<0.001	1.08	1.07, 1.09	<0.001
Density of medical facilities (categorical), per 10,000 people							
<0.6	159 (124–199)						
0.6–0.9	165 (127–199)						
1.0–1.4	164 (128–201)						
>1.4	167 (130 to >237)						
Density of medical facilities (continuous), per 10,000 people		0.93	0.91, 0.95	<0.001	0.98	0.95, 1.00	0.068

Abbreviations: CI, confidence interval; HR, hazard ratio; IQR, interquartile range; NS, not significant.
[a] Unaffected counties were considered as right-censored, and results were corrected for population density and the density of medical facilities.
[b] For all continuous variables, categorical results are also reported to allow inspection of the data and assessment of whether or not the assumption regarding continuous variables was justified.
[c] Duration of time to the first confirmed case for all affected counties, starting on May 9, 2009, the date of the first confirmed case in the whole of mainland China; right-censored at 237 days for all unaffected counties.

All laboratory-confirmed cases from 2009 were included in our database, including information about age, sex, occupation, residence address, work address, onset date and location, hospital admission date and address, and clinical outcome. Furthermore, census information was obtained from the National Bureau of Statistics of China (9).

Analyses of temporal and spatial distribution

Epidemic curves were created by plotting the daily number of newly confirmed cases and the number of deaths. Mainland China is divided into 2,925 counties, which are political subdivisions of provinces, usually containing several townships.

The incidences for different sex and age groups were calculated using 2009 census data. As was done previously (10, 11), each case was linked to a digital map of China (1:100,000) according to its onset location. The incidence for each county was calculated and standardized using direct standardization for age and sex according to the overall composition of the 2009 Chinese population, using 5-year age-group categories. To explore the spatial and temporal diffusion trend of pandemic influenza in mainland China, a map of pandemic influenza spread was developed using trend surface analysis, which is a spatial smoothing method that uses polynomials with geographic coordinates, as defined by the central point of each county (12–14). The time delay of the first confirmed case for each county was defined as the duration of time (in days) since May 9, 2009, the date of the first confirmed case in mainland China. A trend surface on these durations was created in ArcGIS 9.2 (ESRI Inc., Redlands, California) using a second-order trend surface model with a local polynomial method to explore the diffusion patterns of pandemic influenza over time. In addition, the epidemic curves were also plotted for 5 selected cities/provinces in different regions of mainland China: Guangdong (southern China), Shanghai (eastern China), Shaanxi (central China), Tibet (western China), and Beijing (northern China).

Statistical analysis of risk factors

To assess the association between the invasion of pandemic influenza and different means of domestic travel, we performed a survival analysis (Cox analysis) of the time delay of the first confirmed case for each affected county, considering unaffected counties as right-censored. The time delay of the first confirmed case was defined as the duration (in days) since May 9, 2009, the date of the first confirmed case in mainland China. Domestic travel was expressed using 4 variables: distance (from the midpoint of each county) to the nearest civil airport and whether or not a county was intersected by national highways, freeways, or railways. This information was obtained from the National Bureau of Statistics of China (9, 15). Spatial analyses were used to extract data on these variables in ArcGIS 9.2 (ESRI Inc.). Since population density is also linked to human activities and may facilitate influenza transmission (16, 17) and since density of medical facilities could be linked to patient reporting, we adjusted for the effects of these variables. In this study, the population density for each county was obtained from the National Bureau of Statistics of China (9, 15), and the densities of medical facilities were based on the CISDCP, including all reporting sectors for notifiable infectious diseases, comprising provincial, prefectural, and county centers for disease control and prevention and provincial, prefectural, and county hospitals and township clinics. Hazard ratios and their 95% confidence intervals and *P* values were estimated using maximum likelihood methods. Hazard ratios for the continuous variables were calculated for the following units: distance to the nearest airport (in 50-km increments), population density (in 1,000 persons per km^2), and density of medical facilities (in number of reporting sectors for pandemic influenza per 10,000 persons).

To explore the effect of climatic factors on local transmission within counties, we performed multilevel Poisson regression. Climatic data (temperature, relative humidity, and precipitation) during May–December 2009 were obtained from the National Meteorological Bureau of China (18). Owing to probable time lags, the climatic variables were processed by calculating the average value for the current day and a lag of 1–3 days, which is the observed incubation period of pandemic influenza (19). Poisson regression deals with the daily number of laboratory-confirmed cases per county. The inclusion of the population size for each county as an offset makes it an analysis of incidence. To account for possible confounding, we included school summer vacation and public holidays, the proportion of the school-age population (ages 6–19 years), population density, and the density of medical facilities as correction factors in the analysis. The percentage change in incidence in response to the change of the variable by a given amount (10°C for temperature, 10% for relative humidity, 1 mm for precipitation, 10% for school-age population, 1,000 persons per km^2 for population density, and number of facilities per 10,000 persons) was used to reflect the impact of each variable. The 95% confidence intervals and corresponding *P* values were estimated after correcting for overdispersion because of the nature of infectious diseases with spatial clustering patterns (20, 21). For temperature, we also included a quadratic term in the analysis.

For all analyses, univariate analysis was performed first to examine the effect of each variable separately. Multivariate analysis was then performed by including all variables with *P* values less than 0.20 in univariate analysis and exclusion of variables with *P* values greater than 0.10, using a standard backward likelihood ratio method. For all continuous variables, we also presented categorical results in 3–5 categories to allow inspection of the data and determine whether or not the assumption regarding continuous variables (quadratic for temperature) was justified. Statistical analyses were performed using the Stata package (StataCorp LP, College Station, Texas) (20). Readers interested in further research can contact the corresponding author to obtain the full data set used in this study.

RESULTS

A total of 121,805 cases of pandemic influenza (H1N1-2009), distributed in all 31 provinces in mainland China, were reported from May 9, 2009, to December 31, 2009. There was much variation in the numbers of confirmed cases in different provinces, ranging from 881 to 12,748, with a median of 2,958 cases, and in the incidence of confirmed cases in different provinces, ranging from 3.94 per 100,000 population to 71.72 per 100,000, with a median of 8.41 per 100,000. From the time profile, we found that the number of confirmed cases increased rapidly beginning at the end of August, when a new term began for school students, and peaked by the end of November. The first death caused by pandemic influenza was reported on October 4, 2009. The number of deaths eventually rose to 648 by the end of the year, and peaked in early December (Figure 1). The age- and sex-standardized incidence map shows that the epidemic spanned a large geographic area, and the most affected areas were in western China (see Web Figure 1, which appears on the *Journal*'s website (http://aje.oxfordjournals.org/)). Significant differences in incidence were found among age groups, with incidences peaking in school-age groups (Web Figure 1). Boys showed a higher incidence than girls (ages <20 years).

Table 2. Association Between Incidence of Pandemic Influenza A (H1N1-2009) and Climatic Factors at the County Level in Multilevel Poisson Regression,[a] People's Republic of China, 2009

Variable and Unit[b]	Daily Average Incidence	No. of Observations	Univariate Analysis			Multivariate Analysis		
			Crude % Change	95% CI	*P* Value	Adjusted % Change	95% CI	*P* Value
Temperature (categorical), °C								
<0	0.076	38,106						
0–9	0.159	66,570						
10–19	0.110	97,800						
20–30	0.027	168,983						
>30	0.009	16,467						
Temperature (continuous), 10°C			74.8	71.7, 77.9	<0.001	76.3	73.2, 79.5	<0.001
Quadratic temperature (continuous), 100°C			−36.7	−37.1, −36.3	<0.001	−34.9	−35.3, −34.5	<0.001
Relative humidity (categorical), %								
<20	0.316	1,770						
20–39	0.164	20,645						
40–59	0.096	67,031						
60–80	0.065	199,565						
>80	0.057	98,915						
Relative humidity (continuous), 10%			−4.4	−4.8, −3.9	<0.001	−1.4	−1.9, −0.9	<0.001
Precipitation (categorical), mm								
0	0.088	208,047						
0.01–1.00	0.063	167,906						
>1.00	0.022	11,973						
Precipitation (continuous), 1 mm			1.0	1.0, 1.0	0.184	NS (excluded)		

Table continues

Web Figure 2 shows the trend of the spatial spread of pandemic influenza over time in mainland China and indicates that the epidemic areas during the first 120 days after May 9, 2009, were limited to the circumferences of cities with international airports, such as Beijing, Shanghai, Guangzhou, Shenzhen, Chengdu, and Changchun. Thereafter, it spread to the rest of mainland China, roughly from southeast to northwest. The largest-scale spread took place 150–180 days after the first case (Web Figure 2). Figure 2 shows the large variation in the temporal patterns of pandemic influenza for the 5 selected cities/provinces, but there was a marked drop in incidence during the first week of October for all locations.

Survival analysis of the duration of time to the first confirmed case in each county indicated that all 4 factors related to domestic travel or human mobility were significantly associated with the invasion of pandemic influenza in the Cox univariate analysis (Table 1). Population density and the density of medical facilities also showed a significant association. The significant effect of being intersected by railways disappeared, and the density of medical facilities showed borderline significance after correction for other factors in multivariate analysis, whereas being intersected by national highways and freeways and proximity to airports and higher population density remained as significant factors, all showing a positive association (Table 1).

Table 2 shows that all climatic factors (except precipitation), school summer vacation and public holidays, proportion of the school-age population, population density, and the density of medical facilities were significantly associated with the extent of local transmission in univariate multilevel Poisson regression. School summer vacation and public holidays showed a significant negative association with the incidence of pandemic influenza. The significant effect of the proportion of school-age children disappeared after correction for other factors; thus, temperature, relative humidity, school summer vacation and public holidays, population density, and the density of medical facilities remained as significant factors in multivariate analysis. Temperature showed a peak pattern, with the highest incidences for the range from 0°C to 10°C, which was also reflected in the statistically significant quadratic term.

DISCUSSION

Our study provides a complete overview of the spatial and temporal characteristics of the pandemic influenza (H1N1-2009) epidemic in mainland China in 2009. The

Table 2. Continued

Variable and Unit[b]	Daily Average Incidence	No. of Observations	Univariate Analysis			Multivariate Analysis		
			Crude % Change	95% CI	*P* Value	Adjusted % Change	95% CI	*P* Value
School summer vacation and public holidays								
No	0.113	187,797	1.0			1.0		
Yes	0.039	200,129	−62.3	−62.8, −61.8	<0.001	−36.4	−37.2, −35.5	<0.001
Proportion of school-age population (categorical), %								
<18	0.094	121,412						
18–22	0.062	132,302						
>22	0.070	134,212						
Proportion of school-age population (continuous), 10%			−19.7	−28.9, −9.4	<0.001	NS (excluded)		
Population density (categorical), per km^2								
<120	0.083	92,787						
120–299	0.039	95,396						
300–700	0.043	96,416						
>700	0.130	103,327						
Population density (continuous), 1,000 persons per km^2			13.1	10.2, 16.1	<0.001	14.8	11.8, 18.0	<0.001
Density of medical facilities (categorical), per 10,000 people								
<0.8	0.028	146,343						
0.8–1.1	0.052	71,734						
>1.1	0.125	169,849						
Density of medical facilities (continuous), per 10,000 people			62.5	52.3, 73.3	<0.001	43.5	35.3, 52.3	<0.001

Abbreviations: CI, confidence interval; NS, not significant.

[a] Results were adjusted for school summer vacation and public holidays, population density, and the density of medical facilities.

[b] For all continuous variables, categorical results are also reported to allow inspection of the data and assessment of whether or not the assumption regarding continuous variables was justified.

epidemic spanned a large geographic area and presented spatial and temporal heterogeneity in different regions of mainland China. Our analyses of the invasion of pandemic influenza indicated that domestic travel by air and by national highways and freeways and population density contributed to the spread of the epidemic. Lower temperatures and lower relative humidity were climatic factors that facilitated local transmission after correction for the effects of school summer vacation and public holidays, as well as population density and the density of medical facilities. The density of medical facilities could have influenced pandemic influenza patient reporting, and this effect seemed more important for the reporting of local transmission (a highly significant positive association) than for reporting of the invasion (borderline significance). This indicates that the CISDCP can be further improved.

In the initial phase of the epidemic, the Chinese government took measures to prevent and control the spread of the novel influenza virus, declaring it a notifiable infectious disease in order to strengthen national surveillance and find newly confirmed cases quickly. In addition, quarantine measures were implemented at the international airports (e.g., Beijing, Shanghai, Guangzhou, and Fuzhou) to identify and isolate probable cases and close contacts in order to decrease the risk of local transmission caused by imported cases. It is possible that these measures were effective in achieving a slower pace of spread in the early stages of the epidemic, but the current evidence is inconclusive (22). However, following the development of the global pandemic and the beginning of the new school term, a rapid spread of the epidemic occurred in mainland China, and local outbreaks increased at the end of August 2009. A reduction in incidence was observed during the first week of October, when there was an 8-day public holiday during the National Days from October 1 to October 8. This drop in incidence was largely due to a lower tendency for patients to visit medical facilities at that time, together with the fact that many hospitals had reduced the open hours of their outpatient clinics during the holidays. This is clearly visible in Figure 1, where we see the drop beginning on September 28, 3 days (i.e., the average duration between onset and seeing a physician) before the start of the holiday period. Thus, the holiday period led to a reduction in the number of people being diagnosed with pandemic influenza. Apparently, most undiagnosed patients recovered in the following days, because there was no marked compensation visible in the days after the holiday period. Additionally, there may have been some reduced transmission because of school closure, as was observed in Japan, where transmission was substantially reduced during school closure (23). In addition, the temporal death curve could reflect the massive rise in confirmed cases with approximately 1 week's delay following the peak of confirmed cases at the end of November.

The direction of the spread of pandemic influenza was from the southeast to the northwest, indicating how the virus benefited from entering the country through international airports in the coastal areas and spreading further along routes of long-distance domestic travel.

With the fast-growing public transportation infrastructure and increasing socioeconomic activities, travel has become an important issue in the prevention of emerging airborne infectious diseases such as influenza, especially during the introduction period. Obviously, the presence of airports and high densities of transportation routes coincide with more developed areas (i.e., those with a higher population density and more medical facilities); however, after we corrected for these factors, proximity to airports and the presence of national highways or freeways remained significantly associated with the spread of the infection.

Geoinformatics plays an important role in the study and control of infectious disease outbreaks, and it includes techniques such as geographic mapping and location-based alert services (16, 24–26). As was recognized previously, the international spread of pandemic influenza and severe acute respiratory syndrome was largely related to air travel (27–29). Our study confirms that air travel and transportation routes accelerated the spread of pandemic influenza between counties in mainland China. Air travel and travel by national highways and freeways especially appeared to play a role, whereas railways were less important. In mainland China, trains are mainly used for occasional long-distance travel, whereas highways are more often used for daily or weekly commuting, especially because bus schedules are more flexible. Our previous study on the geographic spread of the severe acute respiratory syndrome epidemic in China also demonstrated that domestic travel along national highways played a more important role than travel by railway (30). Data from the National Bureau of Statistics of China show that passenger traffic by highways in 2009 was 18.2 times that of railway travel (9). Transportation by highway remains an important mode of travel between Chinese cities and provinces and therefore is a potential target for controlling any future emerging airborne infections.

We also showed that lower temperature and lower relative humidity create a higher risk of local transmission of pandemic influenza. However, much lower temperature (e.g., $<0°C$) did not facilitate local transmission, as indicated by the daily incidence over categorical temperature in Table 2, and required inclusion of a quadratic variable in the model. The observation of an influence of temperature and relative humidity on pandemic influenza is in accordance with animal experiments on seasonal influenza virus (31). In addition, recent studies have suggested that absolute humidity could also play an important role in the transmission of pandemic influenza and seasonal variations in influenza epidemics in temperate regions (32–34). As expected, population density further facilitated both invasion and local transmission, whereas holiday periods reduced spread (16, 17, 35, 36). We also used population size as a correction factor instead of population density, which led to similar results (not shown).

In conclusion, this is the first complete documentation of pandemic influenza in mainland China, to our knowledge. The findings indicate that interventions focused on domestic travel, population density, and climatic factors could play a major role in mitigating the public health impact of future influenza pandemics.

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REFERENCES

1. Dawood FS, Jain S, Finelli L, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team. *N Engl J Med*. 2009;360(25):2605–2615.
2. World Health Organization. *Pandemic (H1N1) 2009—Update 85*. Geneva, Switzerland: World Health Organization; 2010. (http://www.who.int/csr/don/2010_01_29/en/index.html). (Accessed January 29, 2010).
3. Bin C, Xingwang L, Yuelong S, et al. Clinical and epidemiologic characteristics of 3 early cases of influenza A pandemic (H1N1) 2009 virus infection, People's Republic of China, 2009. *Emerg Infect Dis*. 2009;15(9):1418–1422.

4. Cao B, Li XW, Mao Y, et al. Clinical features of the initial cases of 2009 pandemic influenza A (H1N1) virus infection in China. National Influenza A Pandemic (H1N1) 2009 Clinical Investigation Group of China. *N Engl J Med*. 2009;361(26):2507–2517.
5. Ministry of Health of the People's Republic of China. *Announcement of the Situation of Prevention and Control of Pandemic Influenza A (H1N1) in China, 2010* [in Chinese]. Beijing, China: Ministry of Health of the People's Republic of China; 2010. (http://61.49.18.65/publicfiles/business/htmlfiles/mohwsyjbgs/s7863/201001/45434.htm). (Accessed January 2, 2010).
6. Chinese Center for Disease Control and Prevention. *China Information System for Disease Control and Prevention* [database; in Chinese]. Beijing, China: Chinese Center for Disease Control and Prevention; 2010. (http://1.202.129.170/). (Accessed January 2, 2010).
7. Ministry of Health of the People's Republic of China. *Protocol of Diagnosis and Treatment of Pandemic Influenza A (H1N1) (Preliminary Version)* [in Chinese]. Beijing, China: Ministry of Health of the People's Republic of China; 2009. (http://www.moh.gov.cn/publicfiles/business/htmlfiles/mohyzs/s3585/200905/40478.htm). (Accessed January 2, 2010).
8. Department of Communicable Disease Surveillance and Response, World Health Organization. *WHO Recommended Surveillance Standards, Second Edition.* (Document no. WHO/CDS/CSR/ISR/99.2). Geneva, Switzerland: World Health Organization; 1999. (http://www.who.int/csr/resources/publications/surveillance/WHO_CDS_CSR_ISR_99_2_EN/en/). (Accessed August 19, 2009).
9. National Bureau of Statistics of China. *China Statistical Yearbook 2010*. Beijing, China: China Statistics Press; 2009:1–386.
10. Fang LQ, Zhao WJ, de Vlas SJ, et al. Spatiotemporal dynamics of hemorrhagic fever with renal syndrome, Beijing, People's Republic of China. *Emerg Infect Dis*. 2009;15(12):2043–2045.
11. Fang LQ, de Vlas SJ, Liang S, et al. Environmental factors contributing to the spread of H5N1 avian influenza in mainland China. *PLoS ONE*. 2008;3(5):e2268. (doi:10.1371/journal.pone.0002268).
12. Berrang-Ford L, Berke O, Abdelrahman L, et al. Spatial analysis of sleeping sickness, southeastern Uganda, 1970–2003. *Emerg Infect Dis*. 2006;12(5):813–820.
13. Moore DA. Spatial diffusion of raccoon rabies in Pennsylvania, USA. *Prev Vet Med*. 1999;40(1):19–32.
14. Berke O. Estimation and prediction in the spatial linear model. *Water Air Soil Pollut*. 1999;110(3):215–237.
15. All China Data Center. *China Data Online* [database; in Chinese]. Ann Arbor, MI: University of Michigan; 2010. (http://data.acmr.com.cn/). (Accessed April 20, 2010).
16. Viboud C, Bjørnstad ON, Smith DL, et al. Synchrony, waves, and spatial hierarchies in the spread of influenza. *Science*. 2006;312(5772):447–451.
17. Olson DR, Heffernan RT, Paladini M, et al. Monitoring the impact of influenza by age: emergency department fever and respiratory complaint surveillance in New York City. *PLoS Med*. 2007;4(8):e247. (doi:10.1371/journal.pmed.0040247).
18. China Meteorological Administration. *China Meteorological Data Sharing Service System* [database; in Chinese]. Beijing, China: China Meteorological Administration; 2010. (http://cdc.cma.gov.cn/index.jsp). (Accessed January 2, 2010).
19. Yang Y, Sugimoto JD, Halloran ME, et al. The transmissibility and control of pandemic influenza A (H1N1) virus. *Science*. 2009;326(5953):729–733.
20. Rabe-Hesketh S, Everitt B. *A Handbook of Statistical Analyses Using STATA*. 3rd ed. New York, NY: CRC Press; 2006:1–304.
21. Fang LQ, Wang XJ, Liang S, et al. Spatiotemporal trends and climatic factors of hemorrhagic fever with renal syndrome epidemic in Shandong Province, China. *PLoS Negl Trop Dis*. 2010;4(8):e789. (doi:10.1371/journal.pntd.0000789).
22. Wong E. China's tough flu measures appear to be effective. *NY Times (Online)*. 2009;Nov 11. (http://www.nytimes.com/2009/11/12/world/asia/12chinaflu.html?_r=1&ref=asia). (Accessed January 2, 2010).
23. Kawaguchi R, Miyazono M, Noda T, et al. Influenza (H1N1) 2009 outbreak and school closure, Osaka Prefecture, Japan. *Emerg Infect Dis*. 2009;15(10):1685. (doi:10.3201/eid1510.091029).
24. Gething PW, Noor AM, Gikandi PW. Improving imperfect data from health management information systems in Africa using space-time geostatistics. *PLoS Med*. 2006;3(6):e271. (doi:10.1371/journal.pmed.0030271).
25. Eisen L, Eisen RJ. Need for improved methods to collect and present spatial epidemiologic data for vectorborne diseases. *Emerg Infect Dis*. 2007;13(12):1816–1820.
26. Riley S. Large-scale spatial-transmission models of infectious disease. *Science*. 2007;316(5829):1298–1301.
27. Khan K, Arino J, Hu W, et al. Spread of a novel influenza A (H1N1) virus via global airline transportation. *N Engl J Med*. 2009;361(2):212–214.
28. Wilder-Smith A. The severe acute respiratory syndrome: impact on travel and tourism. *Travel Med Infect Dis*. 2006;4(2):53–60.
29. Wilder-Smith A, Paton NI, Goh KT. Experience of severe acute respiratory syndrome in Singapore: importation of cases, and defense strategies at the airport. *J Travel Med*. 2003;10(5):259–262.
30. Fang LQ, de Vlas SJ, Feng D, et al. Geographical spread of SARS in mainland China. *Trop Med Int Health*. 2009;14(suppl 1):14–20.
31. Lowen AC, Mubareka S, Steel J, et al. Influenza virus transmission is dependent on relative humidity and temperature. *PLoS Pathog*. 2007;3(10):1470–1476.
32. Shaman J, Goldstein E, Lipsitch M. Absolute humidity and pandemic versus epidemic influenza. *Am J Epidemiol*. 2011;173(2):127–135.
33. Shaman J, Pitzer VE, Viboud C, et al. Absolute humidity and the seasonal onset of influenza in the continental United States. *PLoS Biol*. 2010;8(2):e1000316. (doi:10.1371/journal.pbio.1000316).
34. Shaman J, Kohn M. Absolute humidity modulates influenza survival, transmission, and seasonality. *Proc Natl Acad Sci U S A*. 2009;106(9):3243–3248.
35. Ferguson NM, Cummings DA, Fraser C, et al. Strategies for mitigating an influenza pandemic. *Nature*. 2006;442(7101):448–452.
36. Cauchemez S, Valleron AJ, Boëlle PY, et al. Estimating the impact of school closure on influenza transmission from sentinel data. *Nature*. 2008;452(7188):750–754.