Transmission Dynamics, Border Entry Screening, and School Holidays during the 2009 Influenza A (H1N1) Pandemic, China

Hongjie Yu,[1] Simon Cauchemez,[1] Christl A. Donnelly, Lei Zhou, Luzhao Feng, Nijuan Xiang, Jiandong Zheng, Min Ye, Yang Huai, Qiaohong Liao, Zhibin Peng, Yunxia Feng, Hui Jiang, Weizhong Yang, Yu Wang, Neil M. Ferguson, and Zijian Feng

Pandemic influenza A (H1N1) 2009 virus spread rapidly around the world in 2009. We used multiple data sources from surveillance systems and specific investigations to characterize the transmission patterns of this virus in China during May–November 2009 and analyze the effectiveness of border entry screening and holiday-related school closures on transmission. In China, age distribution and transmission dynamic characteristics were similar to those in Northern Hemisphere temperate countries. The epidemic was focused in children, with an effective reproduction number of ≈1.2–1.3. The 8 days of national holidays in October reduced the effective reproduction number by 37% (95% credible interval 28%–45%) and increased underreporting by ≈20%–30%. Border entry screening detected at most 37% of international travel–related cases, with most (89%) persons identified as having fever at time of entry. These findings suggest that border entry screening was unlikely to have delayed spread in China by >4 days.

Pandemic influenza A (H1N1) 2009, hereafter referred to as A(H1N1)pdm09, spread rapidly, resulting in millions of cases and ≈18,000 deaths in ≈200 countries (*1*). On August 10, 2010, the World Health Organization (WHO) declared that the world had entered the postpandemic period (*2*). Much has been published about the epidemiology of the pandemic in Western countries (*3*–*9*), but far less has been published about the experience of a large and diverse country, such as the People's Republic of China. In addition, although many countries adopted so-called early containment strategies, data on their effectiveness are rare (*7*,*10*,*11*).

In response to the evolving global spread of A(H1N1) pdm09 virus infection, China established national surveillance on April 30, 2009. Initially, the country implemented an aggressive containment strategy based on the national pandemic preparedness plan, including isolation of all suspected case-patients in designated hospitals, contact tracing, medical observation of persons exposed to patients with confirmed cases, and border entry screening (online Technical Appendix, wwwnc.cdc.gov/EID/pdfs/11-0356-Techapp.pdf). On May 11, the first case of A(H1N1)pdm09 in mainland China was identified in a traveler returning from the United States (*12*). We report the transmission patterns of A(H1N1)pdm09 in China from that time through November 2009 and analyze the effectiveness of border entry screening and holiday-related school closures on transmission using multiple data sources from surveillance systems and specific investigations.

Author affiliations: Chinese Center for Disease Control and Prevention, Beijing, People's Republic of China (H. Yu, L. Zhou, L. Feng, N. Xiang, J. Zheng, M. Ye, Y. Huai, Q. Liao, Z. Peng, Y. Feng, H. Jiang, W. Yang, Y. Wang, Z. Feng); and Imperial College London, London, United Kingdom (S. Cauchemez, C.A. Donnelly, N.M. Ferguson)

DOI: http://dx.doi.org/10.3201/eid1805.110356

[1]These authors contributed equally to this article.

Methods

Sentinel Surveillance for Influenza-like Illness

National sentinel hospital-based surveillance for influenza-like illness (ILI) was launched in China in 2005. This type of surveillance is primarily dedicated to virologic surveillance with a goal of providing information for annual WHO influenza vaccine selection (online Technical Appendix). Each week, 193 sentinel hospitals in 30 provinces report the total number of outpatient visits and the number of those patients with ILI by age group to a centralized online system maintained by the Chinese Center for Disease Control and Prevention (China CDC). In addition, respiratory specimens are collected each day from the first or second ILI case-patient who visits each hospital's outpatient clinic. This collection results in virologic samples from 10–15 respiratory tract specimens per hospital each week. Specimens are sent to 1 of the 62 province- or prefecture-level disease control centers for testing. Laboratory results are reported weekly online to China CDC. These data are collected systematically throughout the year and are an unbiased sample of the timing of influenza activity.

Individual Case-based Surveillance

During the early containment phase of the 2009 pandemic (until mid-July 2009), an individual case–based surveillance system was implemented. A(H1N1)pdm09 virus infection was added to China's list of notifiable communicable diseases on April 30, 2009. Persons with suspected A(H1N1)pdm09 infection were identified through active surveillance with border entry screening and medical monitoring of close contacts exposed to confirmed case-patients or through passive reporting by clinicians when those patients sought health care. Any person entering China was required to undergo screening at the border (any point of entry into China from another country or from a neighboring region, such as Hong Kong Special Administrative Region), regardless of border type or travel mode. All patients with suspected A(H1N1) pdm09 virus infection, regardless of its clinical severity, were admitted to designated hospitals for containment (*13*,*14*). Upper respiratory specimens were collected and sent to the national sentinel ILI surveillance network of 62 laboratories for A(H1N1)pdm09 testing by real-time reverse transcription PCR (rRT-PCR) (online Technical Appendix). All suspected and laboratory-confirmed cases were reported online within 24 hours to China CDC by public health officers in county-, prefecture-, and province-level disease control centers and clinicians nationwide. Data posted on a standardized reporting card included sex, age, place, overseas travel history, and date of symptom onset.

Outbreak Surveillance

In accordance with recommendations from the Ministry of Health of China, local disease control centers were asked to investigate all institutional or community outbreaks (e.g., associated with particular schools or shared public transport vehicles) by using the case definition for acute respiratory illness (ARI). Data on all suspected cases, probable cases, and confirmed cases were reported online to China CDC.

Investigation of Cases Linked to International Travel

In addition, through July 31, a joint team from local disease control centers and China CDC investigated confirmed international travel–related cases (online Technical Appendix) to collect detailed epidemiologic information. A standardized questionnaire was used to collect data about international travel histories, date of symptom onset, and reported symptoms on arrival in China. Data on contacts were also obtained. In accordance with Ministry of Health recommendations, all close contacts of confirmed case-patients were quarantined at home or in designated hotels and monitored daily for fever and respiratory symptoms for 7 days after their last exposure to a confirmed case-patient.

We also learned whether the case was detected at the border. Data were not available on how these case-patients entered mainland China (e.g., by air, sea, or land).

Case Definitions

A case-patient with ARI had fever (temperature ≥37.3°C), and/or recent onset of ≥1 of the following: rhinorrhea, nasal congestion, sore throat, or cough. A case-patient with ILI had a body temperature ≥38°C with either cough or sore throat in the absence of an alternative diagnosis. A person with a suspected case of A(H1N1) pdm09 virus infection had ARI and 1 of the following: illness onset within 7 days after travel to an area with ≥1 confirmed A(H1N1)pdm09 cases or within 7 days after close contact with a confirmed case-patient. A person with a confirmed case had ARI and laboratory evidence of A(H1N1)pdm09 virus infection diagnosed by rRT-PCR of respiratory specimens. A person with a probable case had ARI that was epidemiologically linked to a patient with a confirmed case. On the basis of information about overseas travel and any identified links to other known case-patients, all reported confirmed cases were classified as international travel–related cases, individual domestic cases, and institutional or community outbreaks.

Change in Surveillance Strategy

By mid-August 2009, as A(H1N1)pdm09 activity expanded, the national surveillance strategy changed from individual case-based surveillance to identification of

hospitalized patients who required medical treatment for complications, identification of outbreaks, and ongoing routine sentinel ILI surveillance. Only patients who required hospital care were admitted; patients with milder infection were cared for at home.

Statistical Analysis

The serial interval of an infectious disease is defined as the time between onset of symptoms in an index patient and onset of symptoms in an infected contact. We analyzed data on transmission among the first 47 identified clusters we investigated, each with a single index case, to estimate the serial intervals associated with 60 infected contacts.

We estimated the incubation period distribution using data from the 22 persons with identified single-day exposures and the 35 persons with identified multiple-day exposure intervals (online Technical Appendix Table 2), excluding 3 persons with exposures implying incubation periods of >20 days (online Technical Appendix). We report the posterior median and 95% credible interval (CrI) of the mean and SD of the incubation period.

Doubling times in case numbers were estimated from the epidemic curve of weekly ILI incidence attributable to A(H1N1)pdm09 virus infection, obtained by multiplying raw ILI data by the weekly proportion of ILI case-patients who tested positive for A(H1N1)pdm09 virus. Those estimates, along with the evidence-based assumption that the generation time of influenza A(H1N1)pdm09 had a mean of 2.6 days and an SD of 1.3 days (*3*,*5*,*6*,*15*,*16*) (consistent with data analyzed on the serial interval), were used to estimate the effective reproduction number of A(H1N1)pdm09 virus infections in China. A simple epidemic model was fitted to the A(H1N1)pdm09 virus–attributable ILI case curve on the calendar weeks before and after the National Day Holiday (October 1–8) to estimate the effect of holidays on effective reproduction numbers and reporting rates. The model is based on the observation that numbers of cases increase at a rate that is a function of the reproduction number and the generation time of the disease (*17*). From the rate of growth of case numbers observed in the epidemic and the generation time of influenza A(H1N1) pdm09, the model can be used to derive the reproduction

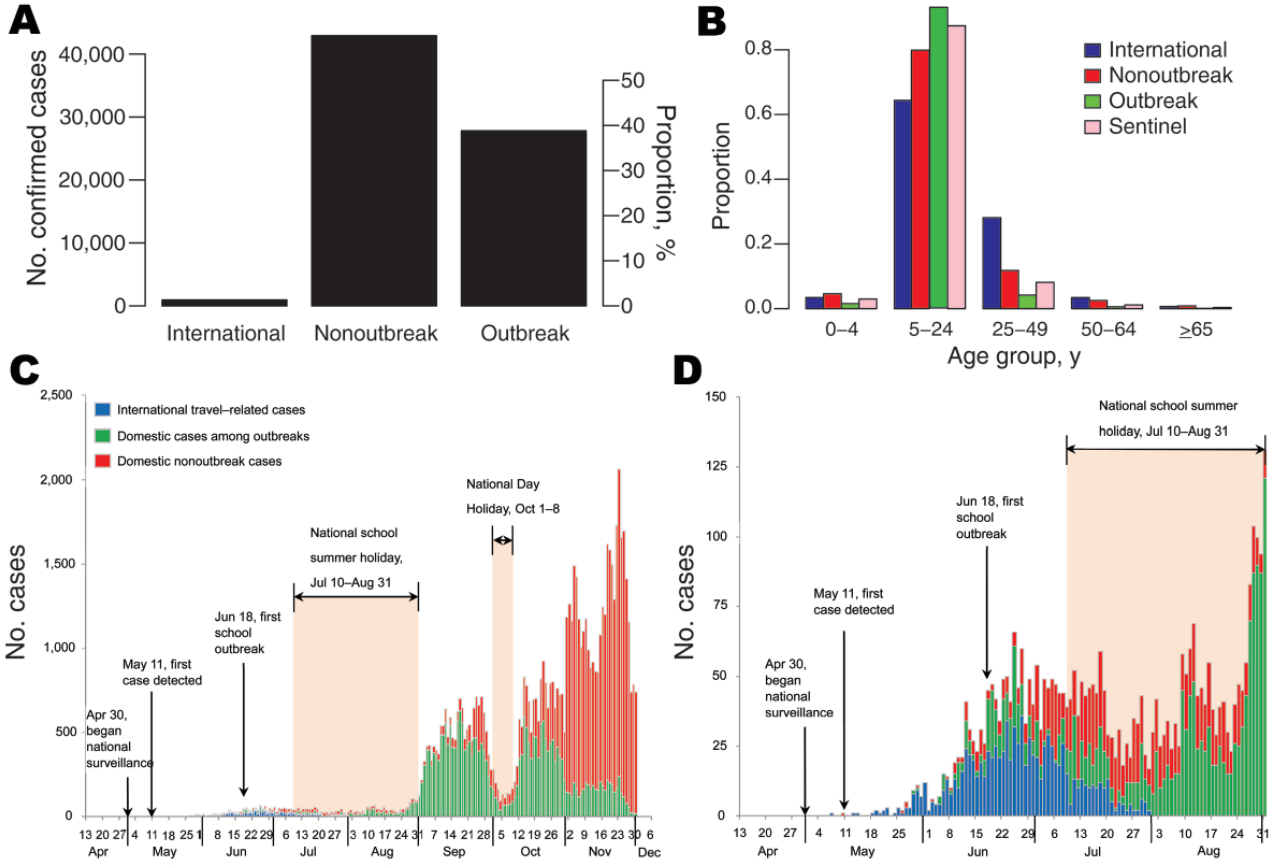


Figure 1. Confirmed cases of influenza A(H1N1)pdm09 virus infection, People's Republic of China, 2009. A) Number and proportion of confirmed A(H1N1)pdm09 cases by type (international travel–related cases, nonoutbreak cases, outbreak cases). B) Age distribution of patients with confirmed cases of A(H1N1)pdm09 infection gathered from different data sets. C, D) Number of confirmed A(H1N1)pdm09 cases by date of illness onset during May–August 2009 (C) and May–November 2009 (D) from case-based surveillance and outbreak investigations.

number of the disease for different intervals. In the past, this approach has been used to estimate the reproduction number of 1918 pandemic influenza in US cities (*18*).

International travel–related case-patients who had symptoms on arrival were classified as either "having fever" or "without fever but having respiratory symptoms" (online Technical Appendix). Frequency tables (with χ^2 tests) were constructed to examine the univariate associations between the probability of detection at the border and patients' characteristics. Univariable and multivariable logistic regression models were used to examine potential predictors of the probability of detection at the border (fever on arrival, time between onset and arrival, age group, and province) individually and simultaneously (i.e., using univariable and multivariable regression models, respectively) and to quantify their effects.

Results

Confirmed Cases

During May 7–November 30, 2009, a total of 71,665 persons with confirmed A(H1N1)pdm09 virus infection were reported to China CDC. Of those, 932 (1%) were related to international travel; 27,806 (39%) cases were detected during domestic outbreak investigations; and 42,917 (60%) were domestic nonoutbreak cases (Figure 1, panel A). The first case-patient was a traveler who returned from the United States with illness onset on May 7; the first domestic case-patient had symptom onset on May 10 (Figure 1, panels C, D). The origin of reported cases slowly shifted: most cases were international travel related until early June; in June, roughly half were international travel related and the other half were domestic; in July, most cases were domestic (Figure 1, panel C; online Technical Appendix Figure 2). The last known international travel–related case was reported on July 31, after which intensive border entry screening was gradually reduced. Irrespective of the type of case, persons 5–24 years of age were most affected, with the proportion of cases ranging from 64% in international travelers to 94% in outbreak cases (Figure 1, panel B). The proportion of persons 25–49 years was <12% in all categories, except international travel–related cases, for which it was 28% (likely because persons 25–49 years were overrepresented among international travelers).

The infection spread rapidly throughout China; 11 provinces (containing many of the most globally connected cities) reported confirmed cases in May, and all but 5 western provinces reported cases in July (Figure 2). By September, all provinces reported confirmed cases. Geographic variation occurred in the incidence of confirmed cases per 1 million persons throughout the epidemic, but how much this variation was caused by surveillance system variation (e.g., differences in access, use of health care, in laboratory capacity) is difficult to determine.

Sentinel ILI Surveillance

The percentage of visits for ILI from sentinel surveillance increased slowly from May 2009 through the end of August 2009, although the percentage was lower than that observed during the same months in 2007 and 2008 (Figure 3, panel A). In September 2009, ILI activity increased substantially and was higher than in the 2 previous seasons. ILI activity decreased sharply during the National Day Holiday, then rebounded at the end of the holiday period. Similar fluctuations were observed for other influenza viruses (Figure 3, panel B). The number and proportion of influenza-positive cases from sentinel ILI surveillance increased stably from May 2009 onward; A(H1N1)pdm09 became the predominant strain at the end of September and subsequently declined after early December.

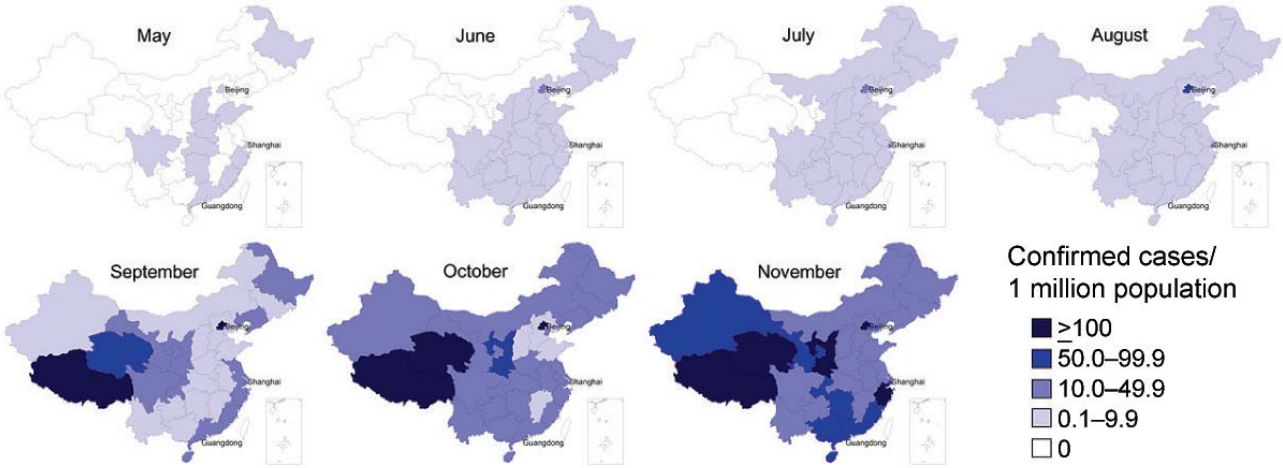


Figure 2. Incidence of confirmed cases of influenza A(H1N1)pdm09 virus infection per 1,000,000 inhabitants, by month and province, People's Republic of China, May–November 2009.

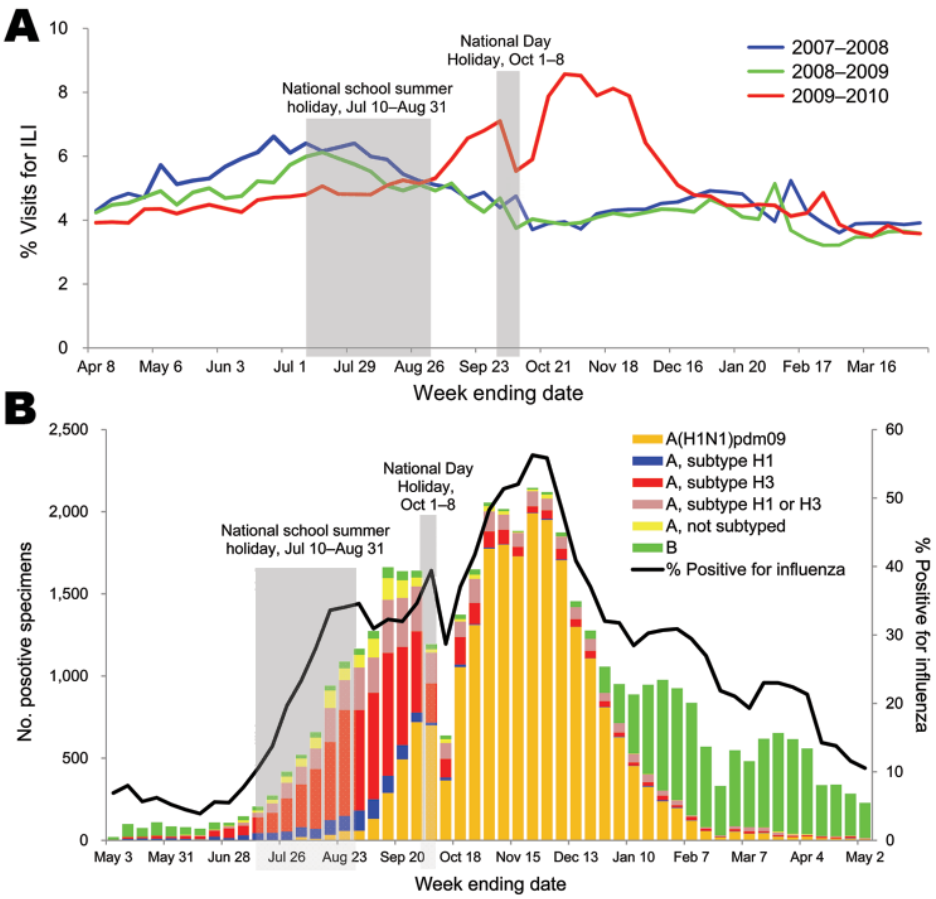


Figure 3. Sentinel surveillance for influenza-like illness (ILI) and virologic surveillance, People's Republic of China, 2007–2010, A) Weekly percentage of visits for ILI, sentinel ILI surveillance, People's Republic of China, 2007–08 through 2009–10. B) Number and percentage of specimens positive for influenza, by week of specimen collection during sentinel ILI surveillance in China, May–November 2009.

Serial Interval and Incubation Period

In the household setting, the average serial interval was 2.6 days (95% CI 2.2–3.0 days; Figure 4, panel A). Similar results were obtained in the analysis restricted to data from the 38 clusters in which the single index case-patient transmitted infection to a single contact. The incubation period had a mean of 2.2 days (95% CrI 1.9–2.5 days) and an SD of 1.0 days (95% CrI 0.8–1.2 days) (Figure 4, panel B).

Transmissibility and Effect of Holidays on Spread

We estimated that the effective reproduction number changed from 1.25 (95% CrI 1.22–1.28) before the National Day Holiday (August 31–September 30) to <1 during that holiday (0.79; 95% CrI 0.69–0.90) and back to 1.23 (95% CrI 1.15–1.32) after that holiday (October 7–October 25) (Figure 5, panel A; Table 1; online Technical Appendix Table 1). The National Day Holiday was therefore found to reduce the effective reproduction number by 37% (95% CrI 28%–45%). Our model also predicted that underreporting had increased by 19% (95% CrI 6%–31%) and 32% (95% CrI 11%–48%), respectively during the first and second calendar weeks of the National Day Holiday. However, the 8-week summer school holiday appeared to have had a limited effect on transmission as measured by A(H1N1)pdm09 virus–attributable ILI incidence, in contrast to what was observed in other countries, such as the United Kingdom (*19*). The doubling time during the summer school holiday (8.7 days during July 13–August 30) was similar to that observed in the month after schools reopened in September (7.1 days) (Figure 5, panel B). Using the rate of growth observed during July–August (Figure 5, panel B), we extrapolated the A(H1N1)pdm09 virus–attributable ILI case curve back in time and inferred that the first sentinel-detected ILI case caused by A(H1N1)pdm09 virus occurred in China in week 19 (May 11–17), near the date when the first imported case was detected (May 11).

Effectiveness of Border Entry Screening

International travel–related cases were detected either at the border or later by contact tracing and passive case finding within the country. Overall, 37% of international travel–related cases ever detected were detected at the border. The timing of onset of symptoms affected the probability of detection by symptom screening at the border. Half (468/932) of international travel–related case-patients ever detected had onset of symptoms ≥1 days after arrival (Figure 5, panel C).

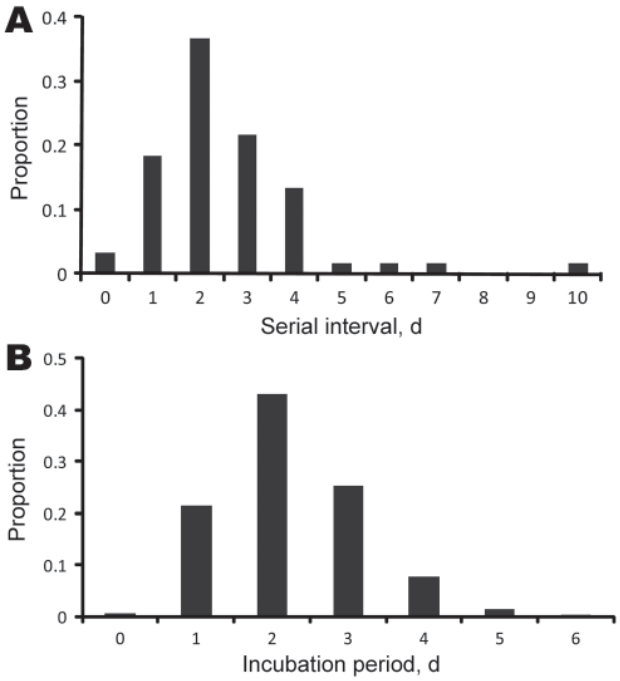


Figure 4. Natural history of influenza A(H1N1)pdm09 virus infection, People's Republic of China, 2009. A) Distribution of serial intervals among clusters of cases, each with a single index case. B) Incubation period distribution estimated from the 22 persons with identified single-day exposures and the 35 persons with identified multiple-day exposure intervals.

Among international travel–related case-patients who had symptoms on arrival, those with fever were significantly more likely to be detected at the border. The percentage of patients detected at the border was as follows: 76% for those with fever, 63% for those without fever but with respiratory symptoms (χ^2 4.41; df 1; p = 0.036; n = 464). Overall, 74% of persons ever detected with symptom onset on or before the day of arrival were identified at the border. Multiple logistic regression modeling showed a significant interaction (p = 0.023) between whether a case-patient had a fever on arrival and the time between symptom onset and arrival (stratified by those with onsets 0 or 1 day before arrival and those with onsets >1 day before arrival; Tables 2, 3). Thus, if a case-patient had a fever on arrival, then the time since onset was irrelevant. Similarly, the odds ratios (ORs) were similar for those with fever on arrival and onset 0 or 1 day before arrival (OR 1.80) relative to those with no fever and onset 0 or 1 day before arrival) and those with fever on arrival and onset >1 day before arrival (OR 1.91 relative to those with no fever and onset 0 or 1 day before arrival) (Table 3). However, among persons who did not have a fever on arrival, those who had been ill longer before arrival (>1 day) were more likely to be detected at the border (the percentage of detection = 83%, Table 1; OR 2.36, Table 3). After adjusting for these effects, neither age group nor province affected the probability of a case being detected at the border.

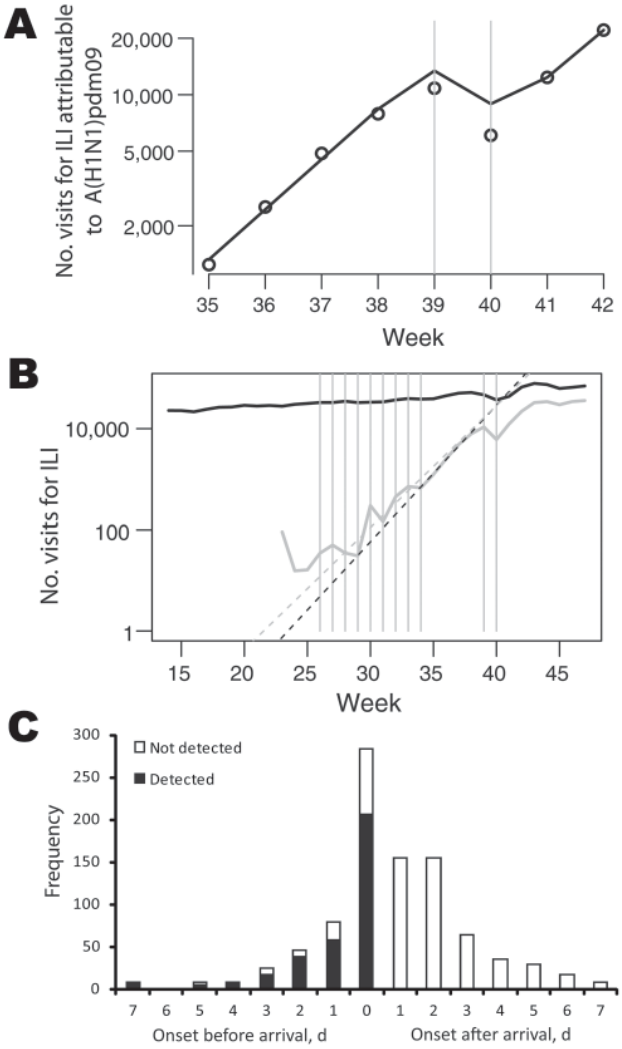


Figure 5. Effects of school holidays and border entry screening on influenza A(H1N1)pdm09 virus infections, People's Republic of China, 2009. A) Observed (black points) and predicted (solid line) number of visits for influenza-like illness (ILI) attributable to A(H1N1)pdm09 from week 35 (ending September 6) through week 42 (ending October 25). National Day Holiday occurred from Thursday, October 1 (week 39), through Thursday, October 8 (week 40). A simple epidemic model was fitted to data for calendar weeks before and after the National Day Holiday (gray bars) so that potential changes in reporting rates during holidays could be estimated. B) Number of visits for ILI. The black solid line shows raw numbers of visits for ILI; the gray solid line shows numbers corrected by the weekly proportion of ILI cases that are positive for A(H1N1)pdm09 virus. Gray dashed line shows growth rate in July-August. Black dashed line shows growth rate during the first 3 weeks of September. Gray bars indicate holiday periods. C) The distribution of intervals between symptom onset and arrival in China among confirmed international travel–related case-patients (N = 932).

Table 1. Reproduction numbers obtained by fitting a simple epidemic model to numbers of influenza-like illness cases attributable to pandemic influenza A (H1N1) 2009 virus, People's Republic of China, September–October 2009*

Interval	Mean (95% credible interval)
School term 1 (Sep 6–Oct 1)	1.25 (1.22–1.28)
Holidays (Oct 1–8)†	0.79 (0.69–0.90)
School term *2* (Oct 9–25)	1.23 (1.15–1.33)

*Fitted on data for the calendar weeks before and after the National Day Holiday.
†Period of National Day Holiday. Details can be found in online Technical Appendix Table 1 (wwwnc.cdc.gov/EID/pdfs/11-0356-Techapp.pdf).

Discussion

We described transmission patterns of A(H1N1) pdm09 virus infection in China during 2009 by using multiple epidemiologic data collected from surveillance and investigations. The age distribution and transmission dynamic parameters, including incubation period and serial interval, are consistent with those observed in other countries (*3*–*6*).

We can put an upper boundary only on the effectiveness of the border screening adopted early in the pandemic because data are available only on cases detected (either at the border or later through case-tracing), rather than missed cases. Given that travelers with mild illness or subclinical infection might not seek health care, a substantial proportion of international travel–related cases were likely never detected and therefore did not appear in our dataset. Hence, the proportion of imported cases that were detected at the border was, at most, 37%. Assuming the doubling time of the global epidemic in May was similar to that seen in China during July–August (8.7 days), and if the border screening reduced transmission from case-patients with imported cases by 37% (i.e., isolation of detected cases was 100% effective), the epidemic in China would have been delayed by 4 days (the additional time taken for cumulative imported cases to reach the level they would have reached in the absence of border controls). Thus, border controls likely delayed the epidemic by only a few days, even assuming few imported cases were missed altogether. This conclusion is supported by the observation that the trajectory of the epidemic in China appears relatively similar to that seen in the United Kingdom, another country to which infection had spread early in May but that did not employ border screening. Clearly, symptom-based border screening cannot detect infections among persons who are asymptomatic on arrival.

Our analysis suggests that the October national holiday might have reduced transmission by as much as 37% and reporting by ≈20%–30%. The National Day Holiday in China is similar in scope to the Christmas holiday in Western countries, with all kindergartens, schools, and universities and many businesses being closed. Most citizens leave their routine work, but festivals, mass gatherings, and travel occur during this period. However, the Summer School Holiday appears to have reduced transmission by a minimal amount (no more than 3% reduction in the effective reproduction number), in contrast to the large drop seen in other countries such as the United Kingdom. Why this discrepancy exists are unclear but might relate to the much more frequent use of collective childcare and summer camps and schools by Chinese parents during summer holidays than is typical in many European countries. In addition, seasonal factors that can limit transmission in temperate countries in summer might have had more limitedly affected the southern subtropical provinces of China.

The effective reproduction number for A(H1N1) pdm09 in China ranged from 1.2 to 1.3, which is consistent with that observed in other countries, although in the lower range. In comparison, the effective reproduction number was ≈1.4 in the United Kingdom in June–July 2009 (*19*). Because the proportion of the population <15 years of age is similar in both countries, demographic differences would not appear to explain these differences. However, spatial heterogeneity in the efficiency of spread and desynchrony between the epidemics in different regions of China might lead to the underestimation of transmissibility on a national scale. This remains a topic for future analysis. We relied on A(H1N1)pdm09 virus–attributable ILI incidence to estimate the epidemic growth rate because the proportion of ILI case-patients who tested positive for influenza increased substantially during the pandemic (Figure 3, panel B). As a consequence, the growth rate of the ILI incidence curve underestimates the epidemic growth rate (Figure 5, panel B). A similar approach was used by Baguelin et al. (*19*).

Our study has several limitations, which are inevitable, given that many of the data were collected as part of public health control rather than specifically to inform epidemiologic characterization of the pandemic. Case-based surveillance established by many countries in the early phase of the pandemic was critical to monitor early emergence and extent of geographic spread. However, in retrospect, those systems were not able to monitor the growth in case numbers over time because the ability to identify cases and conduct outbreak investigations could

Table 2. Percentage of case-patients detected by symptom status and interval between symptom onset and arrival among international travel–related case-patients who were symptomatic on arrival, People's Republic of China, 2009

Onset	Fever on arrival, %	No fever on arrival, %	Total, %
0 or 1 d before arrival	75, n = 329	49, n = 35	73, n = 364
>1 d before arrival	76, n = 76	83, n = 24	78, n = 100
Total	76, n = 405	63, n = 59	74, n = 464

Table 3. Potential predictors of the probability of detection at the border of international travel–related pandemic influenza A (H1N1) 2009 infection, People's Republic of China, 2009*

Model	OR (95% CrI)	p value
Univariable		
Fever on arrival	1.84 (1.04–3.27)	0.042
Onset of symptoms >1 d before arrival	1.05 (0.91–1.22)	0.288
Age group, y†		0.126
0–4	1	
5–24	1.67 (0.55–5.03)	
25–49	1.12 (0.36–3.50)	
50–64	0.58 (0.13–2.69)	
Province‡		0.400
44	1	
31	1.05 (0.49–2.23)	
35	0.66 (0.30–1.45)	
Multivariable§		
Fever on arrival	1.80 (1.26–2.57)	0.001
Onset of symptoms >1 d before arrival	2.36 (1.18–4.73)	0.016
Interaction between fever on arrival and onset of symptoms >1 d before arrival	0.45 (0.22–0.89)	0.023

*OR, odds ratio; CrI, credible interval.
†n = 463. Only 1 such person was >64 y of age, and this person was excluded from this analysis.
‡n = 302. Only 3 provinces had >40 persons so only they are included here.
§Likelihood ratio–based p value for the global hypothesis that all ORs equal 1 (3 df 0.008). The deviance (that is minus twice the log likelihood) for the multivariable model presented was 520.6, whereas the deviance for the model with only an intercept (i.e., no effects of fever or time from onset to arrival) was 532.5.

quickly be limited by saturated resources, for example, laboratory diagnostic capacity. Furthermore, the change from reporting individual cases regardless of clinical severity to reporting hospitalized cases likely affected the reporting rate of confirmed A(H1N1)pdm09 cases during mid-July and mid-August. In contrast, sentinel surveillance was not influenced by the change in case-based surveillance during the pandemic. However, for a country as large and diverse as China, some geographic variability is almost unavoidable in the quality of the surveillance system and capacity of health care system. This variability could make comparison of incidence levels by geographic zone somewhat difficult.

Improving and monitoring the homogeneity of the Chinese surveillance and health care system are challenging, yet vital, tasks to improve the monitoring of future pandemics. The effects of other interventions also need to be assessed, for example, strict case isolation, contact tracing, and medical observation, which might have helped delay the spread at early containment stage of the pandemic.

Thus, the overall picture of the epidemiology and transmission dynamics of A(H1N1)pdm09 that emerges from the surveillance data is comparable to that in many European countries and the United States. Border entry screening during the influenza pandemic delayed spread in China by a few days, at most, but the autumn school holidays reduced the effective reproduction number by ≈40%.

Acknowledgments

We thank local health departments and the Centers for Disease Control and Prevention in China for assistance in coordinating data collection, and the Ministry of Health, China for supporting this study.

H. Yu, S. Cauchemez, C.A. Donnelly, N.M. Ferguson, and Z. Feng conceived, designed and supervised the study, finalized the analysis, and interpreted the findings. L. Zhou, L. Feng, N. Xiang, J. Zheng, M. Ye, Y. Huai, Q. Liao, Z. Peng, Y. Feng, H. Jiang, and W. Yang assisted in data collection and analysis. H. Yu, S. Cauchemez, C.A Donnelly, and N.M. Ferguson drafted the manuscript. All other co-authors participated in data collection and management.

H.Y. and Z.F. received grants from the US National Institutes of Health (Comprehensive International Program for Research on AIDS grant U19 AI51915), and China–US Collaborative Program on Emerging and Re-emerging Infectious Diseases. S.C., C.A.D., and N.M.F. received funding support from the EU FP7 FluModCont project, the Bill and Melinda Gates Foundation, Research Councils UK, and the National Institutes of Health Modeling of Infectious Agents Study initiative for funding support, and the UK Medical Research Council for Centre support.

Dr Yu is deputy director of the Office for Disease Control and Emergency Response, China CDC, where he supervises China's national infectious disease surveillance systems and rapid response teams to provide technical support. He also leads the development of China's national strategy for control and prevention of influenza and emerging respiratory infectious diseases.

References

1. World Health Organization. Pandemic (H1N1) 2009—update 99 [cited 2012 Mar 8]. http://www.who.int/mediacentre/news/statements/2010/h1n1_vpc_20100810/en/index.html
2. World Health Organization. H1N1 in post-pandemic period. Director-General's statement at press conference. August 10, 2010 [cited 2012 Mar 8]. http://www.who.int/mediacentre/news/statements/2010/h1n1_vpc_20100810/en/index.html
3. Cauchemez S, Donnelly CA, Reed C, Ghani AC, Fraser C, Kent CK, et al. Household transmission of 2009 pandemic influenza A (H1N1) virus in the United States. N Engl J Med. 2009;361:2619–27. http://dx.doi.org/10.1056/NEJMoa0905498
4. Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team; Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S, Garten RJ, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med. 2009;360:2605–15. http://dx.doi.org/10.1056/NEJMoa0903810
5. Ghani AC, Baguelin M, Griffin J, Flasche S, Pebody R, van Hoek AJ, et al. The early transmission dynamics of H1N1pdm influenza in the United Kingdom. PLoS Curr. 2009;1:RRN1130. http://dx.doi.org/10.1371/currents.RRN1130
6. Lessler J, Reich NG, Cummings DA, New York City Department of Health and Mental Hygiene Swine Influenza Investigation Team, Nair HP, Jordan HT, et al. Outbreak of 2009 pandemic influenza A (H1N1) at a New York City school. N Engl J Med. 2009;361:2628–36. http://dx.doi.org/10.1056/NEJMoa0906089

7. Nicoll A, Ammon A, Amato A, Ciancio B, Zucs P, Devaux I, et al. Experience and lessons from surveillance and studies of the 2009 pandemic in Europe. Public Health. 2010;124:14–23. http://dx.doi.org/10.1016/j.puhe.2009.12.001
8. Presanis AM, De Angelis D, Hagy A, Reed C, Riley S, Cooper BS, et al. The severity of pandemic H1N1 influenza in the United States, from April to July 2009: a Bayesian analysis. PLoS Med. 2009;6:e1000207. http://dx.doi.org/10.1371/journal.pmed.1000207
9. Louie JK, Acosta M, Winter K, Jean C, Gavali S, Schechter R, et al. Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California. JAMA. 2009;302:1896–902. http://dx.doi.org/10.1001/jama.2009.1583
10. Wu JT, Cowling BJ, Lau EH, Ip DK, Ho LM, Tsang T, et al. School closure and mitigation of pandemic (H1N1) 2009, Hong Kong. Emerg Infect Dis. 2010;16:538–41. http://dx.doi.org/10.3201/eid1603.091216
11. Cowling BJ, Lau LL, Wu P, Wong HW, Fang VJ, Riley S, et al. Entry screening to delay local transmission of 2009 pandemic influenza A (H1N1). BMC Infect Dis. 2010;10:82. http://dx.doi.org/10.1186/1471-2334-10-82
12. Bin C, Xingwang L, Yuelong S, Nan J, Shijun C, Xiayuan X, 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;15:1418–22. http://dx.doi.org/10.3201/eid1509.090794
13. Ministry of Health. People's Republic of China. Clinical management of human infection with pandemic 2009 influenza A (H1N1) virus: initial guidance [in Chinese] [cited 2012 Mar 9]. http://www.moh.gov.cn/publicfiles/business/htmlfiles/mohyzs/s3585/200905/40478.htm
14. Yu H, Liao Q, Yuan Y, Zhou L, Xiang N, Huai Y, et al. Effectiveness of oseltamivir on disease progression and viral RNA shedding in patients with mild pandemic 2009 influenza A H1N1: opportunistic retrospective study of medical charts in China. BMJ. 2010;341:c4779. http://dx.doi.org/10.1136/bmj.c4779
15. Cauchemez S, Carrat F, Viboud C, Valleron AJ, Boelle PY. A Bayesian MCMC approach to study transmission of influenza: application to household longitudinal data. Stat Med. 2004;23:3469–87. http://dx.doi.org/10.1002/sim.1912
16. Ferguson NM, Cummings DA, Cauchemez S, Fraser C, Riley S, Meeyai A, et al. Strategies for containing an emerging influenza pandemic in Southeast Asia. Nature. 2005;437:209–14. http://dx.doi.org/10.1038/nature04017
17. Wallinga J, Lipsitch M. How generation intervals shape the relationship between growth rates and reproductive numbers. Proc Biol Sci. 2007;274:599–604. http://dx.doi.org/10.1098/rspb.2006.3754
18. Mills CE, Robins JM, Lipsitch M. Transmissibility of 1918 pandemic influenza. Nature. 2004;432:904–6. http://dx.doi.org/10.1038/nature03063
19. Baguelin M, Hoek AJ, Jit M, Flasche S, White PJ, Edmunds WJ. Vaccination against pandemic influenza A/H1N1v in England: a real-time economic evaluation. Vaccine. 2010;28:2370–84. http://dx.doi.org/10.1016/j.vaccine.2010.01.002

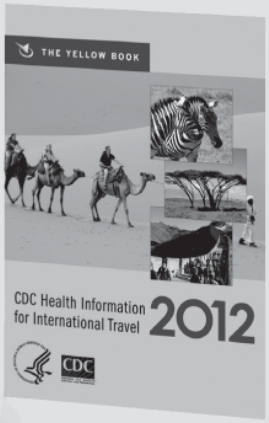
Address for correspondence: Neil M. Ferguson, MRC Centre for Outbreak Analysis & Modelling, Department of Infectious Disease Epidemiology, Imperial College London, London, UK; email: neil.ferguson@imperial.ac.uk

CDC Health Information for International Travel 2012

CDC

Health risks are dynamic and ever-changing, both at home and while traveling abroad. To stay abreast of the most up-to-date health recommendations, for decades health care professionals and travelers have relied on the Centers for Disease Control and Prevention's user-friendly Health Information for International Travel (commonly referred to as the The Yellow Book) as a trusted reference. Updated biennially by a team of experts, this book is the only publication for all official government recommendations for international travel.

The book's features include clear and easy-to-read disease risk maps, information on where to find health care during travel, specific health information and itineraries for popular tourist destinations, detailed country-specific information for yellow fever and malaria, advice for those traveling with infants and children, and a comprehensive catalog of diseases, their clinical pictures, and their epidemiologies. The Yellow Book addresses the pre-travel consult and provides post-travel clinical guidance on ways to approach common syndromes of returned travelers who are ill.



May 2011 640 pp.
9780199769018 Paperback $45.00

FEATURES

> Authoritative and complete information on precautions that the traveler should take for nearly all forseeable risks
> The definitive resource for health care professionals who see patients for pre-travel consultation
> The only publication for the US Government's most up-to-date recommendations for traveler safety

4 EASY WAYS TO ORDER!

Phone: 800-451-7556
Fax: 919-677-1303
Web: www.oup.com/us
Mail: Oxford University Press, Order Dept. 2001 Evans Road, Cary, NC 27513

OXFORD UNIVERSITY PRESS

Article DOI: http://dx.doi.org/10.3201/eid1805.110356

Transmission Dynamics, Border Entry Screening, and School Holidays during the 2009 Influenza A (H1N1) Pandemic, China

Contents

1 Containment interventions

1.1 Border entry screening

1.2 Case management

1.3 Medical observation of close contacts

2 Definitions

2.1 International-travel-related case

2.2 Close contact

3 Background information on national sentinel ILI surveillance

4 Laboratory testing

5 Derivation of exponential growth rates, doubling times and reproduction numbers

6 Fitting a piecewise exponential growth model to H1N1 attributable ILI visits

7 Impact of holidays on the epidemic curve of confirmed cases

8 References

1 Containment interventions

1.1 Border entry screening

From April 25 to mid of August, upon international arrival in China, all travelers via air, sea and land originated from a country with confirmed H1N1pdm infection were requested to complete a health declaration form at the entry points, and were screened for fever by hand wands or fixed-position infrared thermal scanner. Travellers who declared any one of following symptoms: fever, rhinorrhea, nasal congestion, sore throat, cough, headache, myalgia, dyspnea, or diarrhea in the form, or with fever detected by thermal scanner were evaluated by medical personnel and their body temperature was taken using mercuric thermometer. Any patient diagnosed with Acute Respiratory Illness (ARI) was isolated immediately at a local designated hospital for quarantine and tested for H1N1pdm virus infection by real-time reverse transcription polymerase chain reaction (rRT-PCR).

1.2 Case management

Early on, all suspected cases regardless of clinical severity were immediately admitted to designated hospitals and placed in a private room or a room with negative pressure, if available, for respiratory isolation. From mid-August 2009 onward, hospitalization was based on clinical judgment and mild cases were recommended to self isolate at home until 24h after clinical recovery.

1.3 Medical observation of close contacts

Up to July 8, close contacts of confirmed cases were identified as soon as possible and quarantined at home or in designated hotels, and monitored daily for fever and respiratory symptoms for 7 days after their last exposure to a confirmed case. The Ministry of Health of China did not recommend antiviral chemoprophylaxis for close contacts.

2 Definitions

2.1 International-travel-related case

For analysis purpose in this study, an international-travel-related case was defined as a case who had travelled to a country with confirmed H1N1pdm infection within 7 days before illness onset, while for those without such overseas travel history were defined as domestic cases.

2.2 Close contact

A close contact was defined as a person known to have been within 2 meters of a confirmed case-patient for any length of time during the case's infectious period, including household and social contacts, and health care workers who were assessed to have used suboptimal personal protective equipment. For airplane passengers and crew, a close contact was defined as any crew member who had provided face-to-face service to a confirmed case, or as any passenger seated in the same row or within three rows in front of or behind a confirmed case, adapted from WHO guidance (*1*). The infectious period for a confirmed case was defined to be one day prior to and through 7 days after illness onset or 24 h after resolution of symptoms, whichever was longer (*2*).

3 Background information on national sentinel ILI surveillance

The national sentinel hospital-based Influenza Like Illness (ILI) surveillance network was established in 2000, subsequently was expanded to 30 provinces and run stably using a standard ILI case definition (body temperature ≥38°C with either cough or sore throat in the absence of an alternative diagnosis) since October 2005. Each week, 193 sentinel hospitals of 30 provinces with exception of Tibet within the network report the total number of outpatient and/or

emergency department visits and the number of those patients with ILI by age group to a centralized on-line system maintained by China CDC. In addition, a subset of 10-15 respiratory specimens (nasopharyngeal swabs) were collected from ILI cases firstly arrived on average each week, on the day when they presented to the outpatient and/or emergency department, and placed in sterile viral transport medium for influenza virus testing following a standard protocol (*3*). The sample was inoculated into Madin-Darby canine kidney (MDCK) cells and/or specific pathogen free (SPF) chicken embryo for virus isolation. Hemagglutination inhibition (HI) and/or real-time reverse transcription polymerase chain reaction (rRT-PCR) assay were performed to identify types and subtypes of influenza virus as appropriate. These assays were performed in biosafety level (BSL) 2 facilities of 31 provincial and 32 prefecture level Centers for Disease Control and Prevention, and quality controlled by the National Influenza Center (NIC) of the China CDC. All reagents, primers and probes were provided by the NIC, China CDC. Such surveillance activities were implemented year-round in 99 hospitals of 15 Southern provinces in subtropical or tropical region (below 34° latitude) and 22 hospitals of three Northern provinces (Tianjin, Liaoning, and Gansu) in temperate regions, while running in winter season from October to next March for remaining 72 hospitals of 12 Northern provinces in temperate regions. In response to evolving pandemic H1N1, all 193 sentinel hospitals were asked to implement year-round since May 2009, and the network was expanded to all 411 provincial and prefecture level CDCs and 556 hospitals around the country since July 2009. We only included surveillance data from 193 sentinel hospitals and 62 laboratories for final analysis, given the data quality and expected suboptimal capacity among additional sentinel ILI surveillance network (additional 363 hospitals and 349 laboratories) established at speed as part of China's outbreak response.

4 Laboratory testing

Respiratory specimens (nasal, throat, and nasopharyngeal swabs) were collected from suspected H1N1pdm cases and placed in sterile viral transport medium for H1N1pdm virus testing following a standard protocol (*4*). RNA was extracted from specimens using the RNeasy Mini Kit (Qiagen, Valencia, CA) per the manufacturer's protocol and tested by rRT-PCR with H1N1pdm-specific primers and probes following the WHO protocol (*5*). These assays were performed in biosafety level (BSL) 2 facilities of National Sentinel Influenza Surveillance Network, and quality controlled by NIC of the China CDC.

5 Derivation of exponential growth rates, doubling times and reproduction numbers

Denote n_t the number of cases on day t. Under the assumption that the number of cases grows exponentially in time interval $[t_1, t_2]$,

$$n_t = n_{t_1} \exp\{r.(t - t_1)\} \qquad (1)$$

where r is the exponential growth rate. Equation (1) is equivalent to:

$$\log(n_t) = \log(n_{t_1}) + r.(t - t_1) \qquad (2)$$

In practice, the exponential growth rate r can be estimated on time interval $[t_1,t_2]$ via standard least-square fitting. It is equal to the coefficient of the linear regression of $\log(n_t)$ on $(t - t_1)$:

$$\mathrm{r} = \frac{\mathrm{cov}(\{\log(n_t)\}_{t\in[t_1,t_2]},[t_1,t_2]}{\mathrm{var}([t_1,t_2])} \qquad (3)$$

The doubling time d is such that $n_{t+d} = 2.n_t$

With equation (1): $n_t.\exp(r.d) = 2.n_t$

After simplification, the doubling time d is found to be:

$$\mathrm{d} = \frac{\log(2)}{r} \qquad (4)$$

For a Gamma-distributed generation time, the reproduction number is given by:

$$R = \left(1 + \frac{r}{b}\right)^a \qquad (5)$$

where a and b are the parameters of the Gamma distribution ($a = \mu^2/\sigma^2$ and $b = \mu/\sigma^2$ where μ and σ are the mean and standard deviation of the distribution, respectively) (*6*). Here, we make the evidence-based assumption that the generation time of 2009 H1N1pdm influenza has mean μ = 2.6 days and standard deviation σ = 1.3 days (*7–11*).

6 Fitting a piecewise exponential growth model to H1N1-attributable ILI visits

We fit a piecewise exponential growth model to H1N1-attributable ILI visits from week 35 (ending September 6th) to week 42 (ending October 25th) in order to assess the impact of National Day Holiday, that took place from Thursday October 1st (week 39) to Thursday October 8th (week 40), on growth rates, reproduction numbers as well as reporting rates.

Denote I_t the number of cases with symptoms onset at time t. We make the assumption that I_t grows exponential with an exponential growth rate $r(t)$ that is a piecewise function of time t:

$$I_t = I_0 \exp\{-\int_0^t r(u)\,du\}$$

where I_0 is the number of cases with onset at time 0 (defined as the start of week 35) and

$$r\ \ t\ \ = \begin{cases} r_{S1} & \text{if } t < \text{Oct 1st (school term)} \\ r_H & \text{if Oct 1st} \le \text{t} \le \text{Oct 8th (holidays)} \\ r_{S2} & \text{if Oct 8th} < t \text{ (school term)} \end{cases}$$

The number of cases with onset in time interval $[t_1,t_2]$ is:

$$U([t_1,t_2]) = \int_{t_1}^{t_2} I_t dt$$

$$U([t_1,t_2]) = \mathrm{I}_{t_1} \int_{t_1}^{t_2} \exp\{-\int_{t_1}^{t} r(u)\, du\} dt$$

Furthermore, we make the assumption that the observed number m_k of cases with onset in week k has a negative binomial distribution with mean U(week k) and size σ (i.e. variance is U(week k)+ U(week k)^2/σ).

Parameter vector $\theta = \{rS_1, r_H, rS_2, \sigma\}$ is estimated by fitting the model to H1N1-attributable ILI case curve for calendar weeks before and after the National Day Holiday, that is for weeks 35-38 and 41-42. In the baseline analysis, data for the 2 weeks on which the National Day Holiday took place were not used in the fitting procedure in order to estimate potential changes in reporting rates during those 2 weeks (Figure 5, panel A in the main text; Technical Appendix Table 1). In a sensitivity analysis, we also computed estimates obtained when data from the 2 calendar weeks when the National Day Holiday took place were used in the fitting procedure (Technical Appendix Figure 1; Technical Appendix Table 1).

Inference was done in a Bayesian setting, with flat priors specified for all parameters. Markov chain Monte Carlo sampling was used to explore the joint posterior distribution of the parameters, derive the posterior median and 95% Credible Intervals (*12*).

Equations (4) and (5) were used to derive estimates of doubling times and reproduction numbers from those of the exponential growth rates.

7 Impact of holidays on the epidemic curve of confirmed cases

The succession of holidays and school terms affected the incidence of confirmed cases reported through individual case-based surveillance (Figures 1c and SI3). There was a substantial reduction in the incidence of confirmed cases during the National Day Holiday. In addition, a sharp increase in case numbers was observed when schools reopened, with a very short doubling time of 2.3 days in the time interval August 31st-September 4th and of 2.4 days in the time interval October 9th-11th (Technical Appendix Figure 3). However, it is likely that part of those fluctuations were due to a change in the intensity of surveillance/reporting since once schools had reopened, growth rates quickly reduced to lower values (doubling time of 32.3 days between September 4th-27th and of 37.5 days between October 12th-26th).

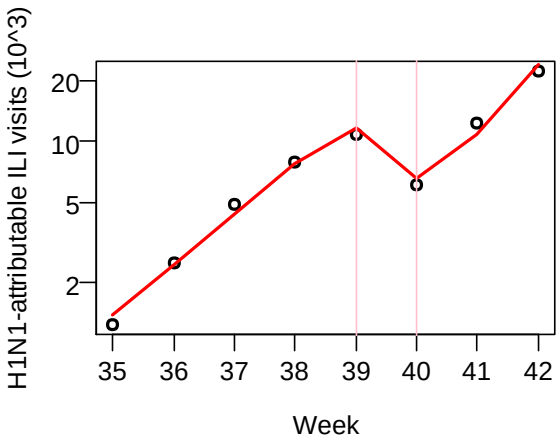
Technical Appendix Table 1: Posterior median (95% Credible Intervals) of the exponential growth rates and reproduction numbers obtained by fitting a piecewise exponential growth model to H1N1-attributable ILI case numbers from week 35 (ending September 6th) to week 42 (ending October 25th). The National Day Holiday, took place from Thursday October 1st (week 39) to Thursday October 8th (week 40).

	Baseline fit – calendar weeks when holidays took place are not used in fitting procedure	Sensitivity analysis – calendar weeks when holidays took place are used in fitting procedure
Growth rate		
- School term *S1* (up to Oct 1st) r_{S1}	0.088 (0.078, 0.098)	0.083 (0.070,0.094)
- Holidays *H* (Oct 1st-8th) r_H	-0.089 (-0.041, -0.138)	-0.123 (-0.166,-0.076)
- School term *S2* (after Oct 8th) r_{S2}	0.083 (0.053,0.113)	0.113 (0.086,0.141)
Reproduction number		
- School term *S1* (up to Oct 1st) R_{S1}	1.25 (1.22,1.28)	1.23 (1.19, 1.27)
- Holidays *H* (Oct 1st-8th) R_H	0.79 (0.69,0.90)	0.72 (0.63, 0.82)
- School term *S2* (after Oct 8th) R_{S2}	1.23 (1.15, 1.33)	1.33 (1.24, 1.42)
Initial number of cases I_0	114 (97, 136)	121 (97,158)

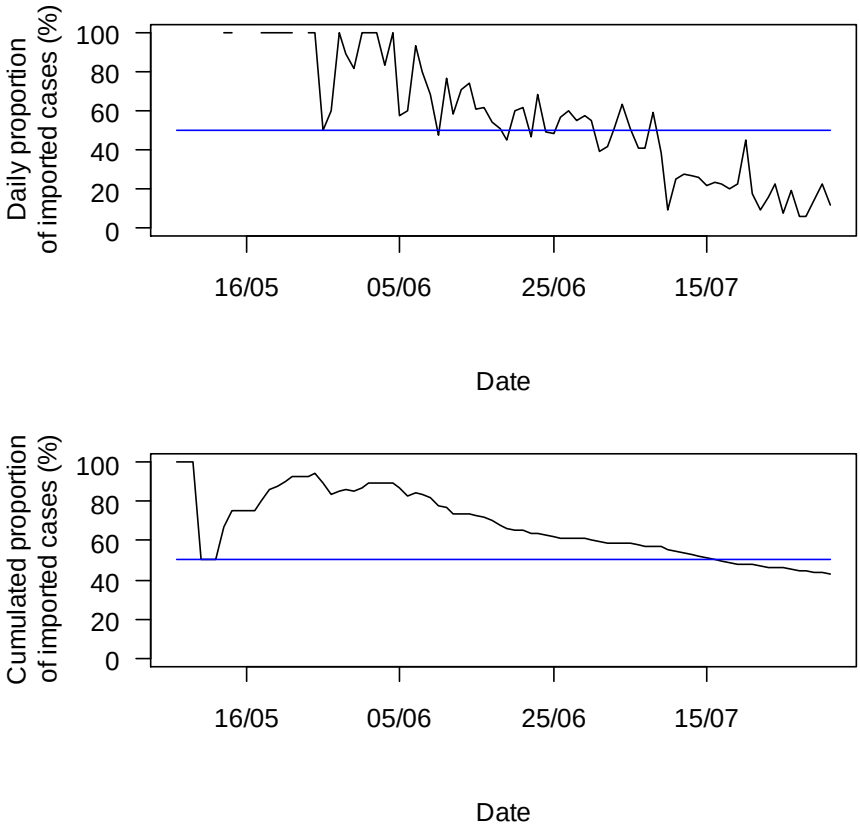
Technical Appendix Table 2: Overview of the data on 2009 H1N1 incubation periods based on periods of exposure to index cases. Each row represents the number (n) of individuals with a particular incubation period (red) or a particular range of possible incubation periods (blue).

n	Incubation periods (in days)						
	0	1	2	3	4	5	6
7							
2							
1							
1							
5							
4							
4							
3							
10							
6							
5							
1							
3							
1							
3							
1							

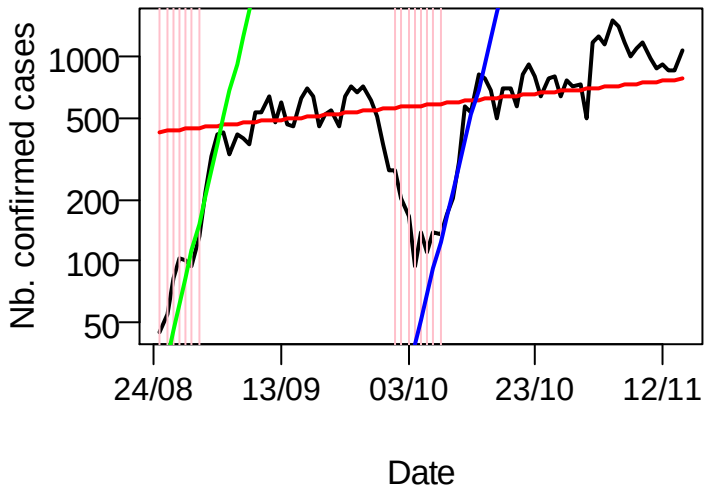
Technical Appendix Figure 1: Observed (black points) and predicted (red line) number of H1N1-attributable ILI visits from week 35 (ending September 6th) to week 42 (ending October 25th). Same as Figure 5a in the paper but when data from the calendar weeks when holidays take place are used in the fit.



Technical Appendix Figure 2: Daily and cumulated proportion of international-travel-related cases in the early phase of the pandemic.



Technical Appendix Figure 3: Daily number of confirmed H1N1pdm cases (log-scale) derived from case-based surveillance from August 25th to November 15th. Pink bars indicate holiday periods. The red line shows the expected number of cases extrapolated from the school-term time period September 4th-September 27th. The green and blue lines show the sharp growth in case numbers observed when schools reopen on September 1st (green) and on October 9th (blue).



8 References

1. WHO (2010) WHO technical advice for case management of Influenza A (H1N1) in air transport.

2. CDC. (2009) Interim Guidance on Infection Control Measures for 2009 H1N1 Influenza in Healthcare Settings, Including Protection of Healthcare Personnel.

3. Chinese-CDC Influenza sentinel surveillance protocol (2005-2010). August 19, 2005 ed.

4. CDC Interim Guidance on Specimen Collection, Processing, and Testing for Patients with Suspected Swine-Origin Influenza A (H1N1) Virus Infection.

5. WHO CDC protocol of realtime RTPCR for swine influenza A (H1N1).

6. Fraser C, Donnelly CA, Cauchemez S, Hanage WP, Van Kerkhove MD, Hollingsworth TD, et al. Pandemic potential of a strain of influenza A (H1N1): early findings. Science. 2009;324:1557–61. PubMed http://dx.doi.org/10.1126/science.1176062

7. Cauchemez S, Carrat F, Viboud C, Valleron AJ, Boelle PY. A Bayesian MCMC approach to study transmission of influenza: application to household longitudinal data. Stat Med. 2004;23:3469–87. PubMed http://dx.doi.org/10.1002/sim.1912

8. Cauchemez S, Donnelly CA, Reed C, Ghani AC, Fraser C, Kent CK, et al. Household transmission of 2009 pandemic influenza A (H1N1) virus in the United States. N Engl J Med. 2009;361:2619–27. PubMed http://dx.doi.org/10.1056/NEJMoa0905498

9. Ferguson NM, Cummings DA, Cauchemez S, Fraser C, Riley S, et al. Strategies for containing an emerging influenza pandemic in Southeast Asia. Nature. 2005;437:209–14. PubMed http://dx.doi.org/10.1038/nature04017

10. Ghani A, Baguelin M, Griffin J, Flasche S, van Hoek AJ, Cauchemez S, et al. (2009) The early transmission dynamics of H1N1pdm influenza in the United Kingdom. PLoS Curr Influenza. 2009; RRN1130.

11. Lessler J, Reich NG, Cummings DA, Nair HP, Jordan HT, et al. Outbreak of 2009 pandemic influenza A (H1N1) at a New York City school. N Engl J Med. 2009;361:2628–36. PubMed http://dx.doi.org/10.1056/NEJMoa0906089

12. Gilks WR, Richardson S, Spiegelhalter DJ. Markov chain Monte Carlo in practice. London: Chapman and Hall; 1996.