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Campus quarantine (*Fengxiao*) for curbing emergent infectious diseases: Lessons from mitigating A/H1N1 in Xi'an, China

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ABSTRACT

During the 2009 A/H1N1 influenza pandemic, very strict interventions including campus quarantine (*Fengxiao*) (restrictions on the movements of university personnel) were taken in mainland China to slow down the initial spread of the disease from the university network to a wider community. The decision for implementation and/or relaxation of *Fengxiao* depends on the assessment of the level of infection within the university network compared with that in the wider community and on the degree of interruption of normal academic activities and the associated social/economic costs. However, the most important consideration influencing the decision is whether the initiation and termination of *Fengxiao* can alter the pattern of disease spread in the entire community for effective prevention and control of the emerging disease. Here we formulate and analyze a dynamic model to evaluate the effectiveness of *Fengxiao* as a social distance measure for curbing the outbreak in major cities of China. Using data from the initial laboratory-confirmed cases admitted to the 8th Hospital of Xi'an (the capital city of the Shaanxi Province), we estimated the reproduction number for the period under consideration in the range 1.273–1.784 and concluded that the population's mobility, combined with the suspension of the *Fengxiao* strategy, was a key factor contributing to a subsequent epidemic wave. *Fengxiao* in China is a reversal of the usual strategy of *school closures* adopted in many other countries, but the lessons learnt from it may be useful for disease management in other countries where restrictions on the movements across a facility boundary and close monitoring of the infection within the facility are feasible in the long term.

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1. Introduction

The 2009 A/H1N1 influenza pandemic exhibited some unique features in mainland China (CMH, 2009; SPBH, 2009; Tang et al., 2010). Since initial cases were all imported by Chinese students returning home after completing their spring academic semesters in North America, strict screening at entry ports to detect imported cases was enforced. This was supplemented by intensive contact tracing, quarantine and isolation. These efforts appeared to be quite efficient in delaying large scale outbreaks until the first week of September when schools and universities started their autumn semesters after the summer break.

As indicated in Figs. 1 and 2, the most cases in early September were from universities and colleges. A special non-pharmaceutical intervention (NPI) strategy known as campus quarantine (*Fengxiao*),

involving restriction on the movement of university personnel while closely monitoring the level of infection within the campus (Tang et al., 2010), was implemented in many provinces after the early September outbreak (*Fengxiao*, 2009a,b). Substantial increases in the overall number of reported cases were not observed until after the October holiday when there were very significant population movements and the restrictive *Fengxiao* was weakened. Hence the national and the provincial epidemic curves in 2009 displayed bimodality with a small first wave and a large second wave as shown in Fig. 1(A) and (C). In contrast to the two epidemic waves (spring and autumn waves) reported in many areas of the world, there was no significant weather change during the aforementioned period from early September to the middle of October. Therefore, the linkage between the bimodality of the epidemic curve and varying rates of mobility, exogenous seasonal processes and/or endogenous changes in the population, as discussed in Chowell et al. (2006), requires further examination. In particular, an interesting and important question is whether relaxation of *Fengxiao* contributed to the occurrence of the second wave or not.

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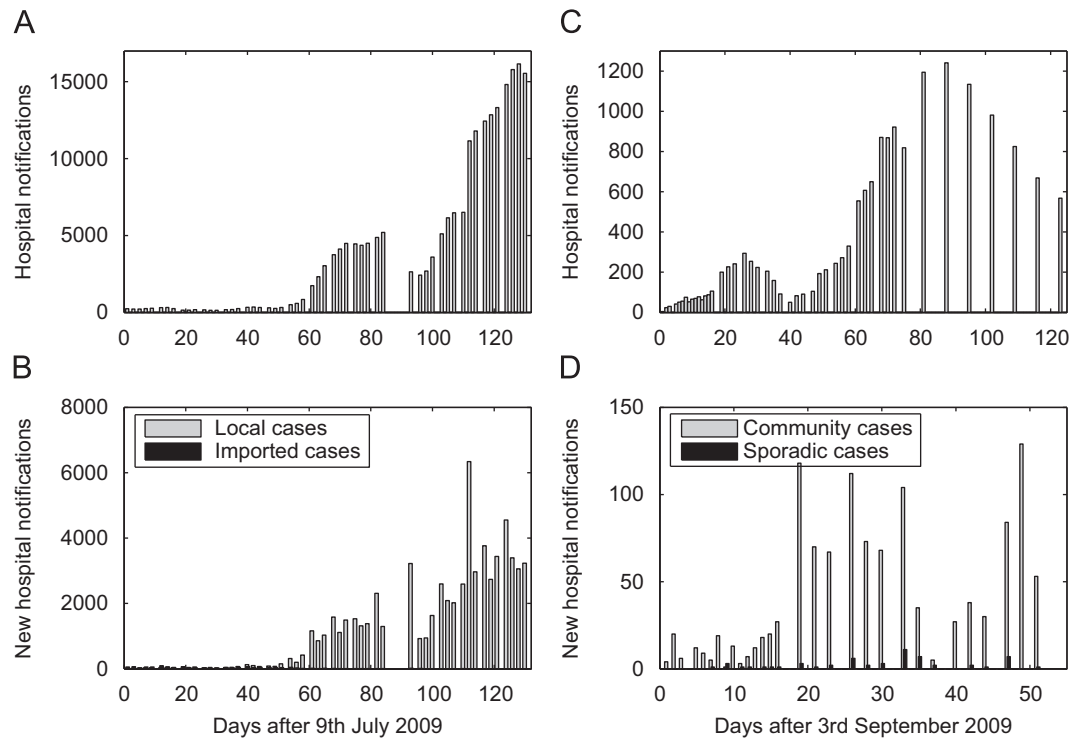


Fig. 1. The reported cases of A/H1N1 influenza for mainland China and Shaanxi Province. (A) Non-regularly reported number of hospital notifications in mainland China from 9th July to 15th November. (B) Non-regularly reported local and imported cases in mainland China from 9th July to 15th November. (C) Non-regularly reported number of hospital notifications in Shaanxi Province from 3rd September to 20th December. (D) Non-regularly reported community and sporadic cases from 3rd September to 23rd October for Shaanxi Province.

Fengxiao, a special proactive measure fiercely implemented in September of 2009 by many universities and colleges in China (SPBH, 2009; Fengxiao, 2009a; Tang et al., 2010), restricted students, faculty, and staff members to their campuses and prohibited visits to the campuses of non-university personnel, but allowed the maintenance of essential services and nearly normal university activities. This was further enhanced by close monitoring of the level of infection, rapid isolation of infected individuals and the quarantining of those believed to have been exposed to the pathogen, within the campuses. Such a measure was feasible in mainland China since nearly all college students reside on campus and college faculty and other staff members are housed in special zones on or near the campuses.

The timings of implementation and suspension of *Fengxiao* play essential roles in determining its efficacy. This role was examined in Tang et al. (2010) by formulating a compartmental model within the network of universities/colleges, and it was shown that appropriate implementation of *Fengxiao* can substantially delay the timing of the outbreak's peak within localized universities/colleges. However, the model framework developed in Tang et al. (2010) was restricted by the data available at the time. Also, it ignored the disease dynamics in the general population so that the effect on the global outcome of *Fengxiao* imposed in the network of universities/colleges remained unknown. Quantifying this effect, the main focus of this study, is now possible due to the availability of new data from the major infection control hospital, the 8th Hospital, in Xi'an the capital city of the Province Shaanxi. In this paper we describe the use of both model-based and likelihood-based methods to estimate the basic reproduction number and other parameters of the disease's dynamics and spread.

Tang et al. (2010) estimated the basic reproduction number on the basis of data reported by the public information system of the

Province of Shaanxi, which inevitably included reporting delays (RP, 2009). Here we used data from the 8th Hospital of Xi'an, where the majority of the confirmed cases in the Province of Shaanxi in early September 2009 was isolated, to obtain the estimation of the basic reproduction number accurately. We initially developed a compartmental model within the universities/colleges population, based on the stratification of the population (Anderson and May, 1991) according to both the disease progression and the specific intervention measures adopted (Fig. 3). We then extended the model to a meta-population model including the general population (Fig. 3), with individuals in the affected university/college community allowed to move across the campuses, in order to explore the effect of *Fengxiao* on the disease's spread within the entire community. With this meta-population model, we analyzed the impact of the duration and intensity of *Fengxiao* on the final outcome in the population as a whole. We used the data on laboratory confirmed cases in the 8th Hospital to parameterize the model and, further, we combined the data reported by the public information system of the Province of Shaanxi to explore the value of *Fengxiao* for the control of emergent infectious diseases in general.

2. Models and methods

2.1. Data source

We obtained data on laboratory-confirmed cases of pandemic A/H1N1 influenza admitted to the 8th Hospital of Xi'an (Fig. 2), and data from the Province's Public Health Information System (Fig. 1(C), (D)) and the China Ministry of Health (Fig. 1(A), (B)) (CMH, 2009; SPBH, 2009). The data included information on the

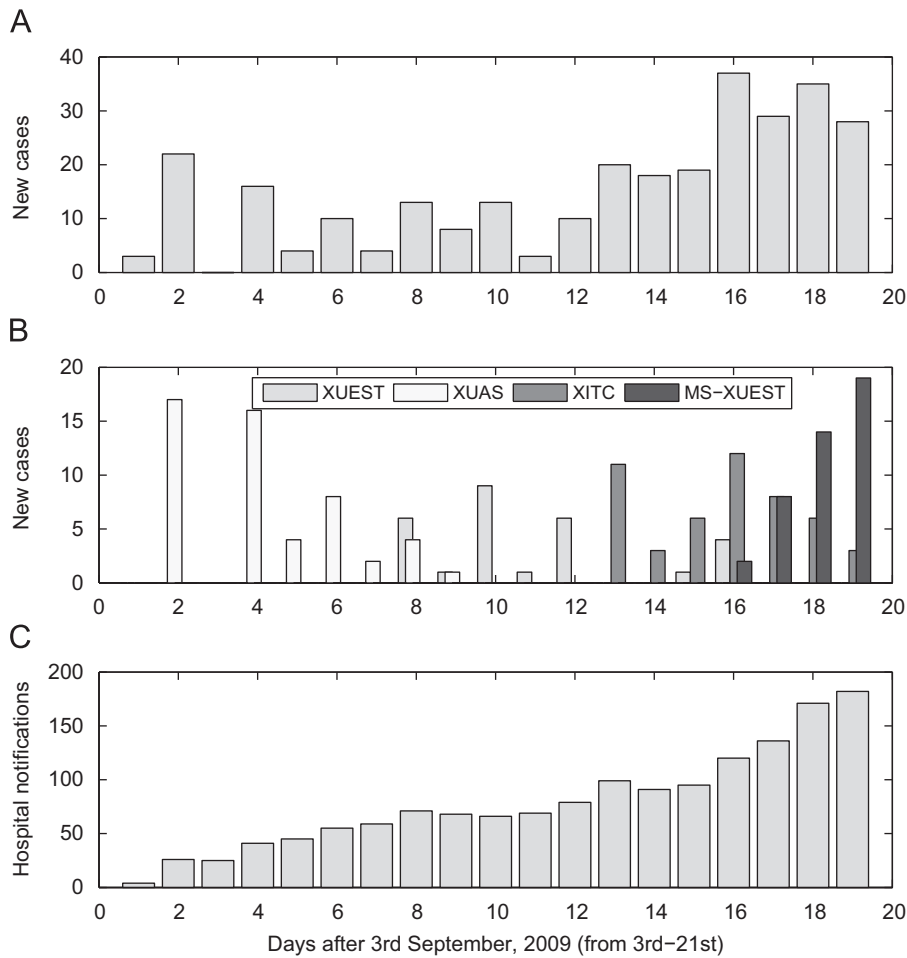


Fig. 2. The numbers of cases of A/H1N1 influenza in the 8th hospital of Xi'an. (A) Newly reported cases in the 8th Hospital of Xi'an from 3rd to 21st September 2009. (B) New cases in the 8th hospital for three severe outbreak universities (Xi'an University of Arts and Science (XUAS), Xi'an University of Electronic Science and Technology (XUEST), Xi'an Institute of Technology and Commerce (XITC)) and one middle school attached to Xi'an University of Electronic Science and Technology (MS-XUEST). (C) Daily number of hospital notifications for the 8th Hospital of Xi'an from 3rd to 21st September 2009.

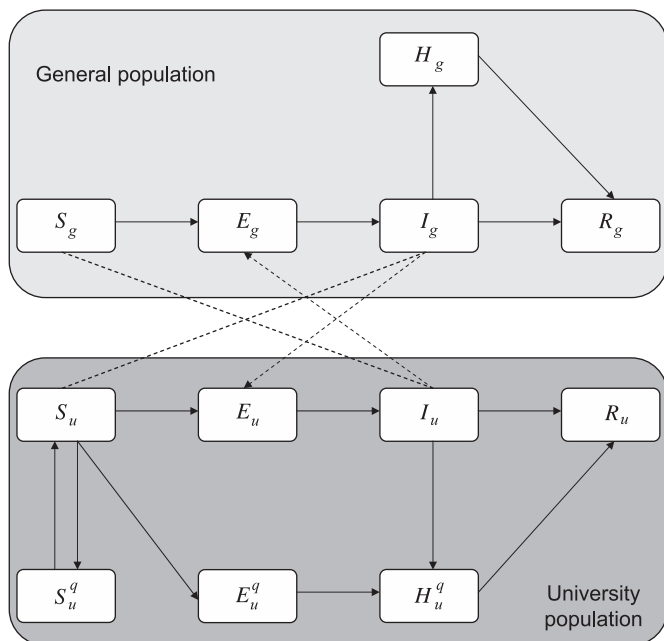


Fig. 3. Flow diagram for the pandemic A/H1N1 spread in Shaanxi Province that incorporates disease progression and key intervention measures (Fengxiao).

daily number of hospital notifications, and the number of newly reported hospital notifications (local/imported cases in mainland China or community/sporadic cases in Shaanxi Province) identified within the previous two days or previous week. It was on 9th July when the China Ministry of Health re-started the reporting of local and imported cases separately every two days. No data were available at weekends or holidays.

On the 3rd September, local cases were found and reported in the Xi'an University of Arts and Science, and laboratory-confirmed cases began to be reported elsewhere in Shaanxi Province (Fig. 1(C), (D)), which was reproduced from Tang et al. (2010)). Note that community cases for the Shaanxi Province consistently dominated the sporadic cases (Fig. 1(D)). After the 23rd October, the numbers of cases amongst the university community and sporadic cases from elsewhere were no longer reported separately. During the exponential growth phase (from the 3rd to the 21st September), Shaanxi Province reported 307 laboratory-confirmed cases, and almost all confirmed cases (293) were isolated and treated in the 8th Hospital (Fig. 2). At the early stage, the most severe outbreaks occurred at three universities and one attached to high school (172 cases reported in the 8th Hospital, Fig. 2(B)). It is interesting to note that A/H1N1 influenza took off in these four universities/school sequentially, with an interval about 4–6 days, and the outbreak periods of any pair of two successive universities overlapped (Fig. 2(B)). The daily number of

hospital notifications for the 8th Hospital of Xi'an from the 3rd to the 21st of September 2009 is given in Fig. 2(C).

2.2. The models

During the initial stage of the H1N1 outbreak in Shaanxi Province, the reported cases were mainly university/college/school students. Most universities implemented the *Fengxiao* strategy aimed at controlling the spread of infections. *Fengxiao* appears to have reduced the transmission from the campuses into the general population or from the general population to the campuses. Complete isolation was of course impossible, but it is interesting to investigate how the strength of *Fengxiao* or mobility between university and the wider community affect the global outcome of the A/H1N1 pandemic infection. We initially formulate a model for the closed university population and then extend it to address the effect of the dynamics of the general population on the global outcome.

We formulate a baseline model for the university population that reflects some key epidemiological properties of the pandemic A/H1N1 influenza and the implemented public health interventions (quarantine and hygiene precautions). We assume that a susceptible individual exposed to the virus may or may not become infected, depending on the protection measures adopted by that individual. Once infected, the individual moves to the latent compartment E_u (Cauchemez et al., 2009a). The individual passing through this latent period will become infectious (with different infectiousness), either asymptotically (A_u) or symptomatically (I_u), until recovery or death (R_u). Note that we do not consider the A_u class in the model since we do not have reliable parameters for the relative infectiousness of asymptotically infected individuals. Some of the infectious individuals will be hospitalized (H_u). When contact tracing and quarantine are implemented, a proportion, q_u , of individuals exposed to the virus is quarantined before they become infectious. These individuals move to the compartment E_u^q or S_u^q , depending on whether they are indeed infected or not (Keeling and Rohnei, 2008). Those in the E_u^q class will be hospitalized once they develop symptoms. Our model also incorporates precautionary measures: when effective precautionary measures are taken, a proportion, ϕ_u , of the individuals exposed to the virus is protected from the infection. It is also assumed that those who were quarantined and/or isolated/hospitalized did not contribute to the spread. See Fig. 3 for a schematic illustration of the baseline model, and Table 1 for parameter definitions.

Denote $P_{Su} = \beta_u c_u (1 - \phi_u) + c_u q_u (1 - \beta_u)$, $P_{Eu} = \beta_u c_u (1 - q_u) (1 - \phi_u)$, $Q_{Su} = (1 - \beta_u) c_u q_u$, $Q_{Eu} = \beta_u c_u q_u (1 - \phi_u)$, then the model

equations are

$$\begin{cases} \frac{dS_u}{dt} = \frac{P_{Su} S_u I_u}{N_u} + \lambda S_u^q, \\ \frac{dE_u}{dt} = \frac{P_{Eu} S_u I_u}{N_u} - \delta_1 E_u, \\ \frac{dI_u}{dt} = \delta_1 E_u - (\delta_2 + \gamma_1) I_u, \\ \frac{dS_u^q}{dt} = \frac{Q_{Su} S_u I_u}{N_u} - \lambda S_u^q, \\ \frac{dE_u^q}{dt} = \frac{Q_{Eu} S_u I_u}{N_u} - \delta_1 E_u^q, \\ \frac{dH_u^q}{dt} = \delta_2 I_u + \delta_1 E_u^q - \gamma_2 H_u^q, \\ \frac{dR_u}{dt} = \gamma_1 I_u + \gamma_2 H_u^q, \end{cases} \tag{2.1}$$

where $N_u = S_u + E_u + I_u + S_u^q + E_u^q + H_u^q + R_u$ is the total population, which is assumed to be constant. We calculate the basic reproduction number by using the next generation matrix (Diekmann and Heesterbeek, 2000; Van den Driessche and Watmough, 2002). We call this the *control* reproduction number since interventions were implemented during the period of consideration. This control reproduction number R_c^u , the spectral radius of the next generation matrix, is given by

$$R_c^u = \frac{\beta_u c_u (1 - q_u) (1 - \phi_u)}{\delta_2 + \gamma_1} = \frac{P_{Eu}}{\delta_2 + \gamma_1}. \tag{2.2}$$

To include the general population, individuals from the university/college are allowed to leave their campus to mingle with the general population and then return within a specified time. Without loss of generality, we may assume that on average the proportion of the university/college population who would be exposed to the virus while away from their campus is h (the off-campus rate). Then it follows from the diagram (shown in Fig. 3) that we have the model equations for both the university and general populations and their interactions (see Appendix A model (A.2)). This model allows us to analyze the effects of the duration and strength of *Fengxiao* on the timing of the peak of the second wave, and evaluate the effectiveness of spatially relevant interventions on the outbreaks of A/H1N1.

2.3. Estimation of the reproduction number

The detailed records from the 8th Hospital of Xi'an city revealed how long it took patients to become negative and how long the patients stayed in the hospital. The mean duration from

Table 1
Parameter definitions and values for the (A.2).

Parameter	Definition	First wave (source, std)	Second wave (source, std)
β	Probability of transmission per contact	0.3936 (LS, 0.02)	0.3936 (LS, 0.01)
c_u	Contact rate for the university population (days ⁻¹)	10 (LS, 0.2)	10 (LS, 0.1)
c_g	Contact rate for the general population (days ⁻¹)	0	4 (LS, 0.02)
q_u	Quarantine rate for the university population (days ⁻¹)	0.0862 (LS, 0.02)	0.0862 (LS, 0.02)
q_g	Quarantine rate for the general population (days ⁻¹)	0	0.08 (LS, 0.02)
ϕ_u	Proportion of exposed persons in the university population who took effective precautions ([0, 1])	0.1 (fixed, 0.02)	0.05 (LS, 0.02)
ϕ_g	Proportion of exposed persons in the general population who took effective precautions ([0, 1])	0	0.05 (LS, 0.02)
λ	Rate at which the quarantined uninfected contacts were released into the wider community	1/7 (CDC, 0.02)	0.3 (LS, 0.01)
δ_1	Rate of progression to latent (days ⁻¹)	1/3.45 (Tuite et al., 2009, 0.02)	0.55 (LS, 0.01)
δ_2	Diagnosis rate (days ⁻¹)	0.689 (LS, 0.02)	0.689 (LS, 0.01)
γ_1	Recovery rate for the symptomatic class (days ⁻¹)	1/6.56 (data, 0.02)	0.48 (LS, 0.01)
γ_2	Recovery rate for the hospitalized class (days ⁻¹)	1/7.48 (data, 0.02)	0.085 (LS, 0.01)
h	Strength of <i>Fengxiao</i> strategy	0	1/5 (LS, 0.02)

positive to negative was 6.56 days ($\gamma_1 = 1/6.56$) with a variance of 1.65 days, and the mean duration of stays in the hospital was 7.48 days ($\gamma_2 = 1/7.48$) with a variance of 1.66 days, see Fig. 4. The latent period (i.e., time from E_u class to I_u class) was fixed at 3.45 days ($\delta_1 = 1/3.45$) (Tuite et al., 2009).

Method 1: Model-based estimate of R_c . In order to estimate the mean R_c^u and its standard deviation directly and to reduce the number of parameters and initial populations to be estimated, we note that in the early outbreak, the initial introduction of pandemic A/H1N1 influenza into the Xi'an population gives S/N approximately equal to 1. Then the full model (2.1) becomes the reduced model (A.1). We initially used a much simplified version of our baseline model, model (A.1), that involves only R_c^u , the quarantine rate q_u and the diagnosis rate. This is suitable for fitting to the initial exponential growth of the outbreak. Subsequently, we recall the model (2.1) to estimate the size of the

population which would be exposed to the virus during the entire course of a particular outbreak.

We used an adaptive Metropolis–Hastings (M–H) algorithm (Haario et al., 2006) to carry out the Markov chain Monte Carlo (MCMC) procedure. We then estimated mean values of R_c^u and other parameters and their standard deviations on the basis of the models (e.g., models (2.1) and (A.1)), and the exponential growth in hospital notifications between the 3rd and the 21st September for Xi'an city. The algorithm was run for 500,000 iterations with a burn-in of 500,000 iterations, and the Geweke convergence diagnostic method was employed to assess convergence of chains (Geweke, 1992). See Appendix B for details.

Method 2: Likelihood-based estimate of R_c^u . We employed the likelihood-based method or generation interval-informed method of White and Pagano (2008), using the following likelihood:

$$L(R_c, p | \mathcal{N}) = \prod_{t=1}^T \frac{\exp(-\phi_t) \phi_t^{N_t}}{\Gamma(N_t + 1)}, \tag{2.3}$$

where $\phi_t = R_c \sum_{j=1}^k p_j N_{t-j}$ and k is the maximum value of the serial interval (chosen as $k=6$ here) and $\Gamma(x)$ is the gamma function. $\mathcal{N} = \{N_0, N_1, \dots, N_T\}$ where N_j denotes the total number of cases on day j and T is the last day of observations. p_j is the probability function for the generation interval on day j . We assumed that the generation interval follows a gamma distribution with mean μ (given in Table 2) and variance $\sigma = 1.6$. Since the generation interval of the 2009 pandemic A/H1N1 influenza has yet to be fully clarified, we investigated the sensitivity of R_c^u to different μ ranging from 2.5 to 4 days. Estimates for the generation interval in a different setting have recently been provided by Cowling et al. (2009) and Fraser et al. (2009).

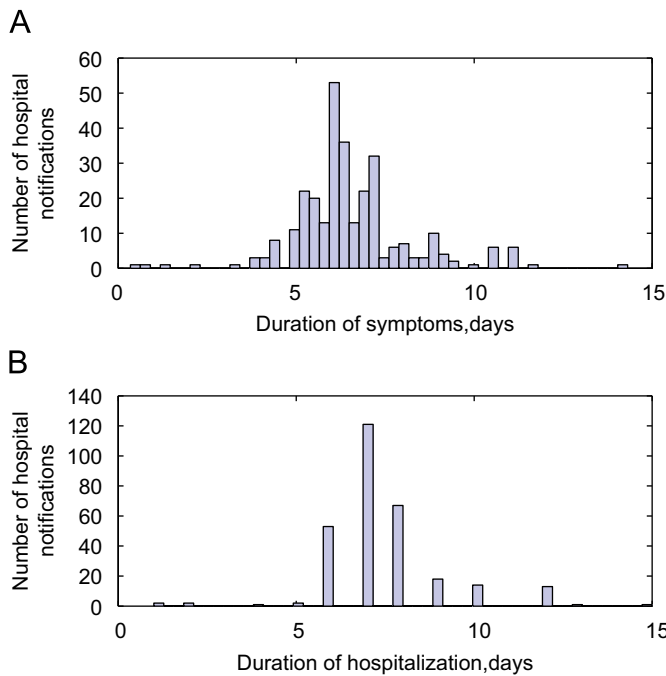


Fig. 4. The durations of symptoms and hospitalization (time from onset to resolution of symptoms and length of stays in hospital) in 296 laboratory-confirmed cases of pandemic A/H1N1 influenza for those whose data were available.

Table 2

Parameter estimates for the 2009 A/H1N1 influenza outbreak based on data from the 8th Hospital of Xi'an city.

Parameter	Sep. 3–18		Sep. 3–19		Sep. 3–20		Sep. 3–21	
	Mean	Std	Mean	Std	Mean	Std	Mean	Std
$R_c^u(M)$	1.431	0.087	1.548	0.071	1.717	0.070	1.688	0.057
q_u	0.261	0.194	0.264	0.200	0.250	0.194	0.261	0.199
δ_2	1.901	0.586	1.867	0.579	1.844	0.576	1.842	0.576
$S_u(0)$	140,550	42,650	140,090	42,790	135,780	45,400	138,210	43,779
$E_u(0)$	9	6	8	4	6	4	6	4
$I_u(0)$	6	5	4	3	3	2	3	2
$S_u^q(0)$	3808	3863	4559	4383	15,901	10,950	7208	6561
$E_u^q(0)$	48	13	58	9	70	7	68	6
$R_c^u(L, 2.5)$	1.363	0.097	1.335	0.089	1.322	0.081	1.273	0.075
$R_c^u(L, 3)$	1.481	0.105	1.455	0.097	1.437	0.089	1.375	0.081
$R_c^u(L, 3.5)$	1.617	0.115	1.598	0.106	1.577	0.097	1.501	0.088
$R_c^u(L, 4)$	1.784	0.127	1.772	0.118	1.751	0.108	1.663	0.098

$R_c(M)$ denotes the model-based estimation of the reproduction number and $R_c(L, d)$ represents the likelihood-based estimations of the reproduction number with the mean generation interval d days. Here $(\delta_1, \gamma_1, \gamma_2, \lambda, \phi) = (1/3.45, 1/6.56, 1/7.48, 1/7, 0.1)$.

2.4. Uncertainty and sensitivity analyses

We explored the parameter space by performing an uncertainty analysis using a Latin hypercube sampling (LHS) method, which is an extension of Latin square sampling. Sensitivity analysis was performed by evaluating partial rank correlation coefficients (PRCCs) (Blower and Dowlatbadi, 1994; Marino et al., 2008; McKay et al., 1979) for various input parameters against output variables (e.g., infectious individuals and hospital notifications) over time, and then the key parameters (such as off-campus rate, quarantine and hygiene precaution rates) involved in generating the two-wave pattern of the A/H1N1 outbreak in Shaanxi Province were determined. We performed uncertainty and sensitivity analyses for all parameters in the model (A.2)

using LHS with 1000 samples. Parameter ranges are given in Table 1, and a normal distribution function was used for all parameters.

3. Results

3.1. Model-based and likelihood-based estimates

Based on the data on laboratory-confirmed cases of pandemic A/H1N1 influenza in the 8th Hospital of Xi'an city, and using our models (2.1) and (A.1) we initially estimated the mean control reproductive number R_c^u as 1.688 (95% Confidence Interval (CI) 1.576–1.8), the mean quarantine rate q_u as 0.261 and mean diagnosis rate δ_2 as 1.842 for the period between the 3rd and the 21st September. The number of individuals who were exposed to the virus was also estimated to be 138,210 with large variation, and the initial values for other compartments are listed in Table 2. Note that $S_u(0)$, the number of individuals who would be exposed to the virus during the entire course of a particular outbreak, is much smaller than the population size of Xi'an city (7.41 million). This is because the early stages of the outbreak were restricted to within three universities and one school (Fengxiao, 2009b), and moreover, it reflects the effectiveness of the quarantine and isolation followed by contact tracing and Fengxiao (Tang et al., 2010). To show the sensitivity of the reproduction number R_c to the periods under consideration or to mean generation intervals,

we considered the periods between the 3rd September and the 18th, the 19th, the 20th and the 21st September, respectively, and mean generation times from 2.5 to 4 days for Xi'an city. Our results are presented in Table 2. The reproduction number based on model-based estimations varied from 1.431 to 1.717, and the data fitting for four interesting intervals are shown in Fig. 5.

Likelihood-based estimation of R_c^u on the bases of exponential growth during the early stages of the outbreak for Xi'an city gives a mean value of 1.663 (95% CI 1.273–2.053) for the period from the 3rd to the 21st September with a generation time of four days. The reproduction number based on likelihood-based estimation ranged from 1.273 to 1.784 and it follows from Table 2 that R_c is sensitive to changes in mean generation intervals rather than variation in periods under consideration. Note that the 95% confidence interval of the estimated reproduction number for the likelihood-based estimation overlaps with the model-based estimates (Table 2).

3.2. Effectiveness of Fengxiao

To assess the impact of the duration of the implementation of the Fengxiao strategy and increasing the impact of the off-campus transition rate on controlling the spread between the university campus and the wider community, we used the aforementioned patch model (A.2) involving a university patch and a general population patch. For the least-squares fitting procedure, we employed the Levenberg–Marquardt method with line-search,

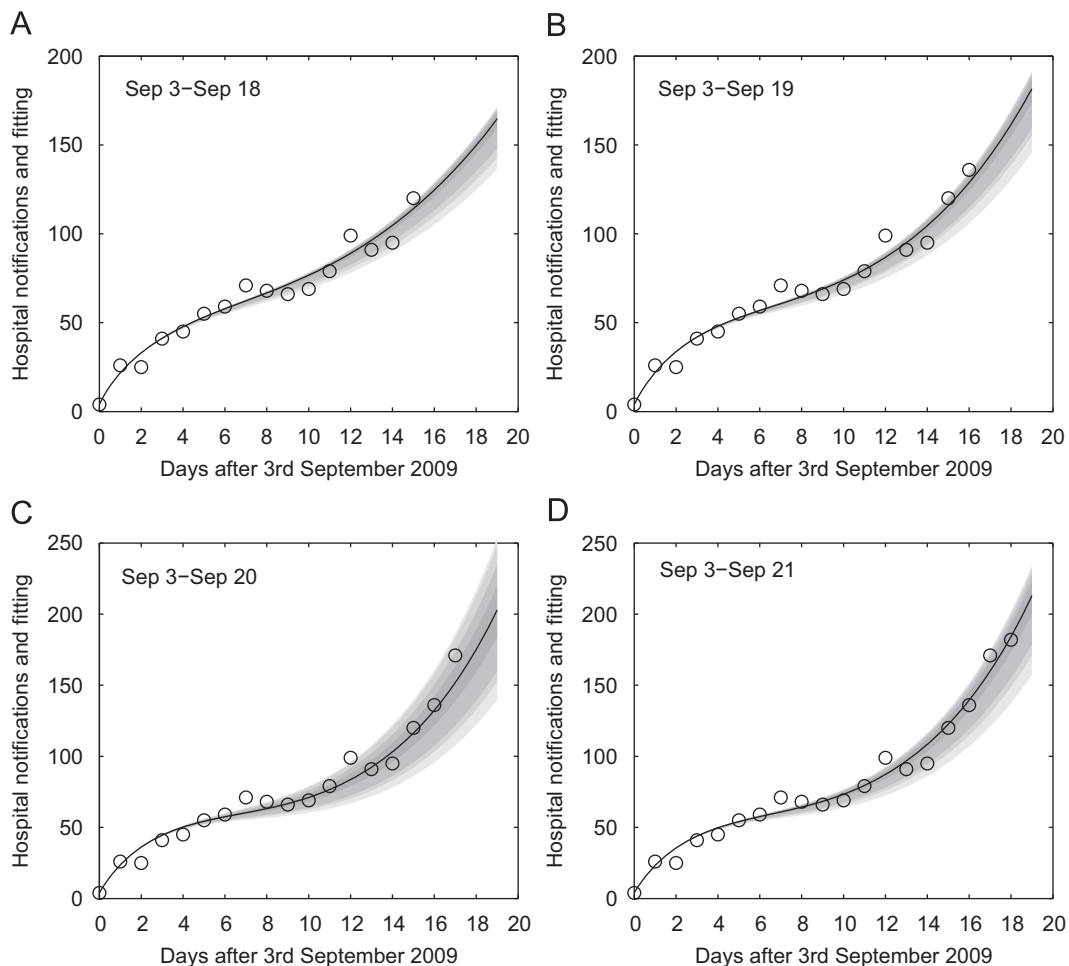


Fig. 5. Data fitting for four interesting intervals: (A) 3rd to 18th September; (B) 3rd to 19th September; (C) 3rd to 20th September; (D) 3rd to 21st September. Circles represent the hospital notifications in the 8th Hospital. The areas from the darkest to the lightest correspond to the 50%, 90%, 95% and 99% posterior limits of the model uncertainty.

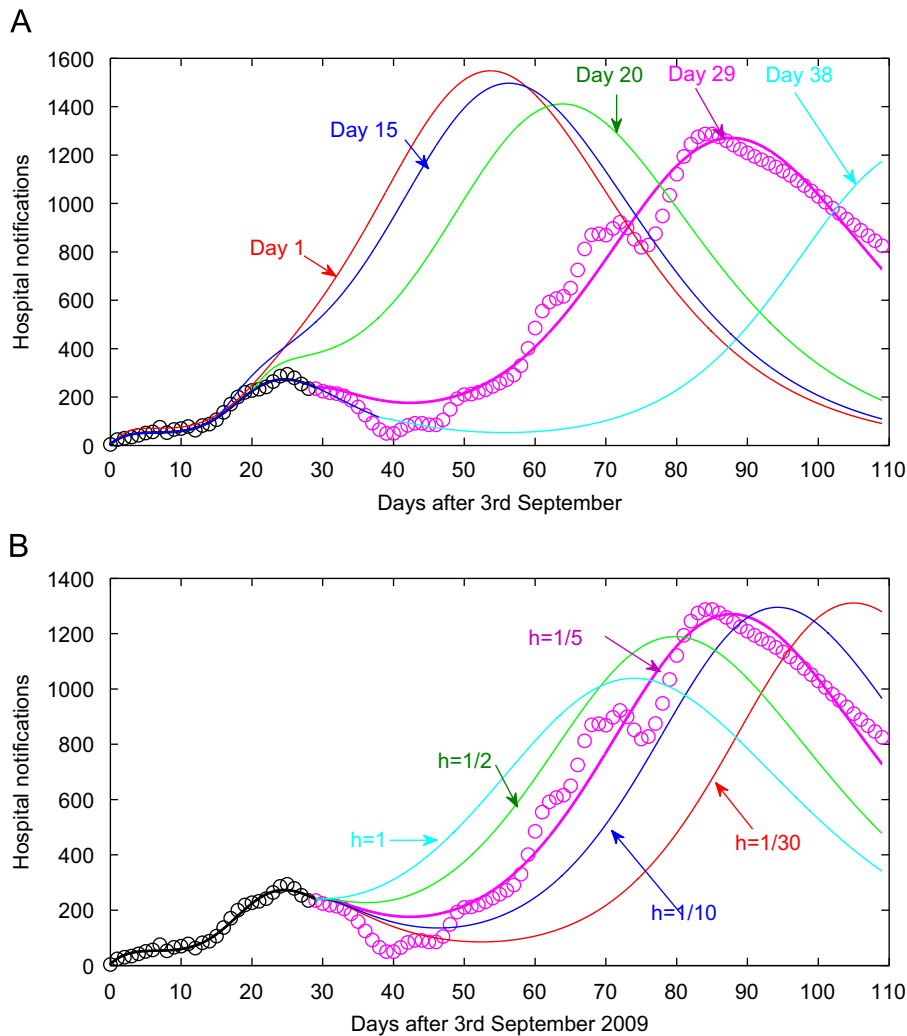


Fig. 6. The best-fit solution with implementation of the *Fengxiao* strategy. (A) The effects of duration of the *Fengxiao* strategy on the peak time and outbreaks, where day n means that the complete *Fengxiao* measures were suspended on day n from which the off-campus transition rate was nonzero (here $1/5$). (B) The effects of mobility of university individuals to the general population on the peak times and outbreaks. We fitted model (2.1) for the first wave from 3rd September to 1st October and fitted model (A.2) for the second wave from 1st October to 20th December. All other parameters are given in Table 2.

implemented in Matlab 7.6 in the built-in routine *fmincon* which is part of the optimization toolbox. Due to the two-wave pattern shown in Fig. 1(C) and the national holiday starting from the 1st of October, we obtained the best-fit solutions by fitting the model (2.1) for the first wave (from 3rd September to the 1st October) and the model (A.2) for the second wave (from the 1st October to the 20th December) to the number of hospital notifications for Shaanxi Province as a whole. The resulting parameter estimates are listed in Table 1, and the best model fit to the daily number of hospital notifications is shown in Fig. 6 (bold curves, black part: from 3rd September to 1st October, pink part: after 1st October).

To examine the effect of the duration of *Fengxiao* on the timing of the peak and the extent of the outbreak of A/H1N1 in both the university and the general populations we consider different durations of implementation of *Fengxiao*, which is realized by changing the off-campus transition rate h from 0 to nonzero (say, $1/5$) from day n ($n = 1, 15, 20, 29$). In particular, if we choose $n=1$ it means that the *Fengxiao* strategy has never been implemented. The results shown in Fig. 6(A) indicate that *Fengxiao*, if implemented for a long time, can greatly delay the epidemic peak and reduce the magnitude of the outbreak. In particular, if *Fengxiao* is not invoked, i.e., the off-campus rate $h=1/5$ from the first day

(day 1 or the 3rd September), only a single wave with a relatively large and long-lasting outbreak was generated. If the *Fengxiao* measures were maintained until day 38, the peak time was significantly delayed. It follows from Fig. 6(A) that the two waves merged together if the durations of implementation of *Fengxiao* were relatively short. We increased the off-campus transition rate (h) on day 29 (the 1st October) to investigate the effect of variation of mobility between the university campus and the general population on the global outcome of the A/H1N1 infection. Fig. 6(B) shows that low off-campus transition rates can greatly delay the timings of the peaks and slightly enlarge the magnitude of the outbreaks.

As in Figs. 6 and 7(A) give the separating plots of hospital notifications for two patches. It indicates that the shorter the duration of the implementation of *Fengxiao*, the earlier and more severe is the outbreak in the general population. It follows from Fig. 7(A) that although *Fengxiao* causes a more severe outbreak within the university patch, it is greatly beneficial to the general population in terms of delaying the timing of the peak and reducing the magnitude of the outbreak. In Fig. 7(B) we consider the effect of strengthening the local control strategies (such as increasing quarantine rate q_u , diagnostic rate δ_2 for the campus patch and hygiene precaution rate ϕ_g for the general population

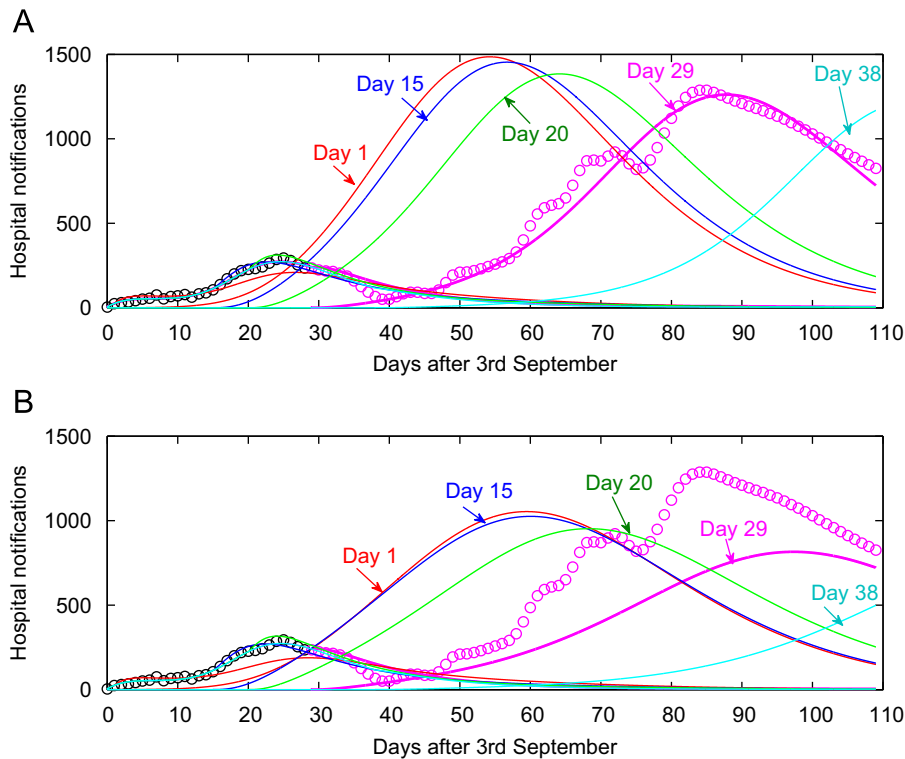


Fig. 7. The best-fit solution with implementation of the *Fengxiao* strategy. (A) The effects of duration of the *Fengxiao* strategy on the peak time and outbreaks for two waves are shown separately, where day n means that the *Fengxiao* measures were suspended on day n from which the off-campus transition rate was nonzero (here $1/5$). (B) The effects of local control measures such as quarantine rate q_u , diagnostic rate δ_2 and hygiene precaution rate ϕ_g on the peak times and outbreaks. We increased q_u , δ_2 and ϕ_g by 10% simultaneously once the *Fengxiao* measures were suspended. We fitted model (2.1) for the first wave from 3rd September to 1st October and fitted model (A.2) for the second wave from 1st October to 20th December. All other parameters are given in Table 2.

simultaneously) on the global outcome of the infection when the *Fengxiao* strategy was suspended. Comparing Fig. 7(A) with (B) shows that strengthening local control strategies significantly reduces the magnitudes of outbreaks.

3.3. Uncertainty and sensitivity analysis

In the absence of available data on the distribution functions, we chose a normal distribution for all input parameters with mean values and standard deviations for the first and second waves shown in Table 1, and tested for significant PRCCs for all parameters of the model (A.2). PRCC indexes can be calculated for multiple time points and plotted versus time. This allows us to assess whether significance of one parameter occur over an entire time interval during the progression of the model dynamics. Fig. 8 shows an example of PRCCs plotted over the first and second waves for all parameters with respect to the number of infected individuals and hospital notifications for the university patch or with general populations combined. We considered absolute values of PRCC greater than 0.4 as indicating an important correlation between input parameters and output variables, values between 0.2 and 0.4 as moderate correlations, and values between 0 and 0.2 are not significantly different from zero which are indicated by gray areas in Fig. 8.

Fig. 8(A) and (B) shows the model outputs (model (A.2), $I_u(t), H_u(t)$) for the first wave corresponding to the LHS matrix and scheme defined by varying all input parameters. In Fig. 8(C) we see that the effects of parameters q_u, δ_2 and ϕ_u change with respect to infectious individuals over time. As the quarantine rate q_u (blue curves) and hygiene precaution rate ϕ_u (red curves) change, they are negatively correlated with small PRCCs immediately after infection (early time points), and then significantly correlated with large PRCCs until the peak. Finally,

they become positively correlated in the decline trend of the first wave. As the diagnosis rate δ_2 changes (green curve) it is negatively correlated with strong PRCCs until the time of the first peak, and then becomes positively correlated. However, the effects of each of the three NPI parameters on the hospital notifications ($H_u(t)$) are slightly different (Fig. 8(D)). The PRCC values for them are not significantly different from zero at the early time, and then become negatively correlated (strong PRCCs) during the exponential growth phase of the hospital notifications. Fig. 8(E) and (F) shows the effects of all epidemiological parameters on the infectious individuals and hospital notifications over the first wave.

The positive sign of their PRCCs indicates that if the NPI parameters q_u, δ_2 and ϕ_u are increased, the number of infectious individuals and/or hospital notifications increase (and vice versa). The negative sign suggests that, if increased, the number of infectious individuals and/or hospital notifications decrease (and vice versa). Therefore, strengthening NPIs are responsible for lowering the numbers of infectious cases and hospital notifications during the exponential growth phase.

For the second wave (see Fig. 8(G)–(L)), the most significant NPI parameters are δ_2, ϕ and h (see Fig. 8(I), (J)), and the quarantine rates q_u (blue curve) and q_g (magenta curve) become less important sources of infection, probably due to the disease having spread into the general population during the second wave. It follows from Fig. 8(I) and (J) that changing the strength of the *Fengxiao* strategy (i.e., varying parameter h —cyan curve) shows it to be positively correlated (very strong PRCC, almost perfect positive correlation) immediately after suspension of *Fengxiao*, but it then becomes negatively correlated as the infection progresses to the second peak. While δ_2 (green curve) and ϕ (red curve) vary they are negatively correlated (very strong PRCCs, almost perfect negative correlation), then become positively

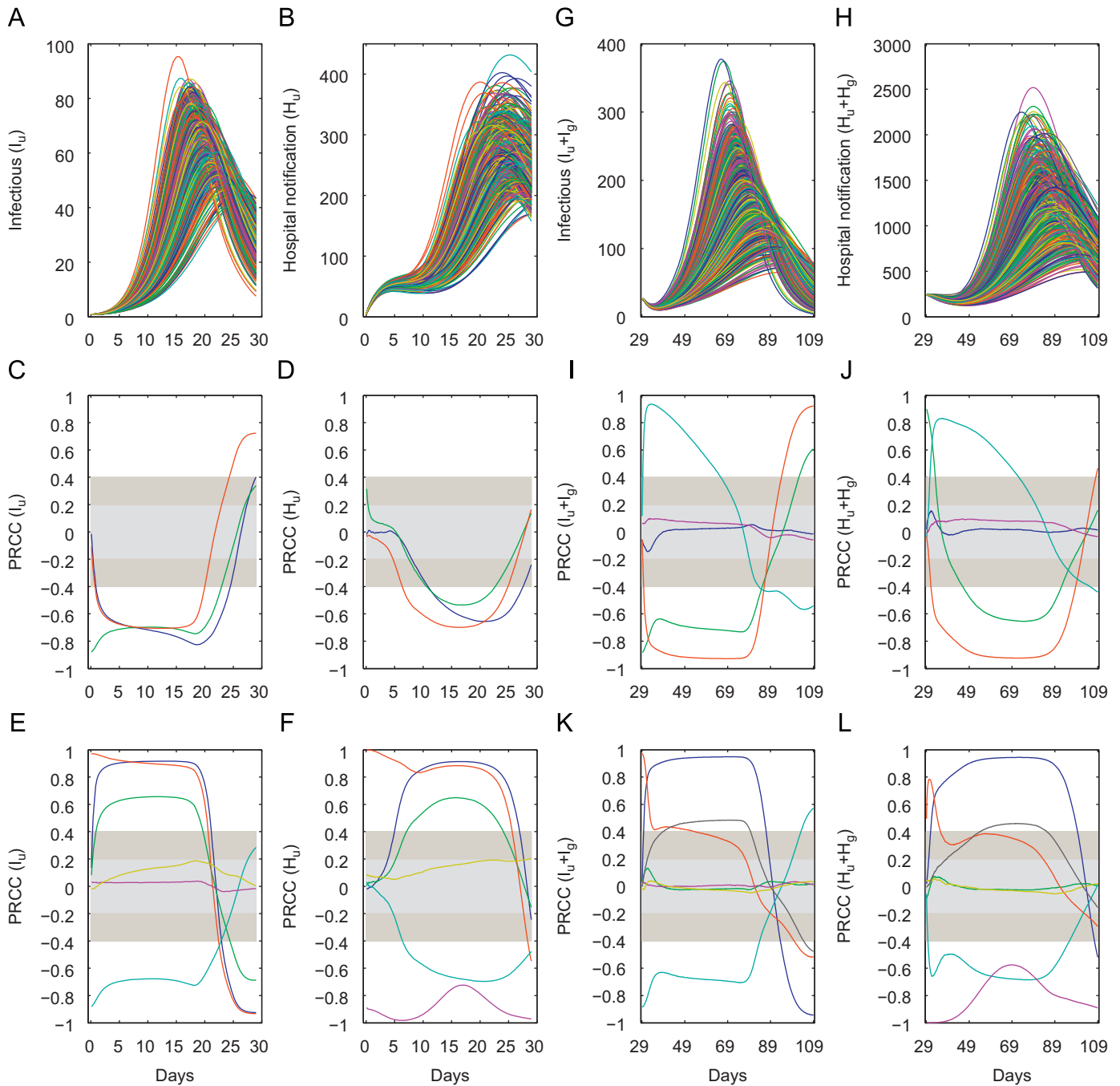


Fig. 8. Sensitivity analysis. Plots of output (1000 runs) of the model (2.1) for the first wave (A), (B) and of the model (A.2) for the second waves (G), (H). PRCCs of the model (2.1) for the first wave for NPI parameters q_u , δ_2 and ϕ_u (C), (D); and for epidemic parameters β , c_u , δ_1 , γ_1 , γ_2 , λ (E), (F); PRCCs of the model (A.2) for the second wave for NPI parameters q_u , δ_2 , $\phi_u = \phi_g = \phi_h, q_g$ (I), (J); for epidemic parameters β , c_u , δ_1 , γ_1 , γ_2 , λ , c_g (K), (L). The PRCCs were calculated with respect to the number of infected individuals and hospital notifications within the university community and the general population. Color orders in each subplot are blue, green, red, cyan, magenta, yellow, black. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

correlated as the infection progresses to the time of the second peak. The PRCC values over the second wave for all epidemic parameters with respect to the total number of infectious cases and hospital notifications are shown in Fig. 8(K) and (L).

4. Discussion

We developed a compartmental model, based on the stratification of the population according to the disease progression (susceptible, latent, infectious/treated and recovered) and the

specific intervention measures adopted (quarantined, isolated/hospitalized). The model described intensive contact tracing followed by quarantining of suspected individuals who had high risks of having been exposed to the virus, which was implemented in the autumn of 2009 in mainland China. This modelling framework is more realistic (Keeling and Rohnai, 2008) than that developed in our previous work (Tang et al., 2010) where the strategy of quarantine, although modelled, did not actually follow the contact tracing. Further, compared to the our previous work (Tang et al., 2010), a novelty of the work reported here is the inclusion of the dynamics of the general population. These allow

qualitatively different dynamical patterns. It is in differences in these and other parameters that we seek to address the impact of the strength of the *Fengxiao* strategy on the global outcome of the A/H1N1 infection.

We used the data on laboratory-confirmed cases in the 8th Hospital of Xi'an to parameterize the model and to estimate the reproduction number. Since these data have no reporting delays compared with data for early September from Shaanxi Province's Public Health Information System, the estimated reproduction number obtained here is expected to be more accurate. We further estimated the number of individuals who were exposed to the virus, an important characterization of the effectiveness of the intervention measures, especially for the first wave.

On the basis of the number of cases notified by the 8th Hospital in Xi'an city the mean reproduction number was estimated as 1.688 (95% CI 1.576–1.8) based on the model (A.1) and as 1.663 (95% CI 1.273–2.053) from likelihood-based estimation. The estimates of the reproduction number were found to be consistent with each other (in the range $R_c \approx 1.273$ –1.784 with overlapping CIs) when using the initial epidemic phase including 19 days from the 3rd to the 21st September. Note that the mean reproduction number obtained here based on the model (2.1) is quite similar to that from the data for Shaanxi Province obtained by Tang et al. (2010) but with a narrower confidence interval. These little differences in estimates of the reproduction number could well be associated with differences in methodology (see Table 2). These estimates were not as high as expected since very strict control strategies were implemented throughout the whole nation during the early A/H1N1 influenza spread in 2009.

Further, many factors such as differences in population densities, realization of control measures and mobility of the population among regions led to a wide range of reproduction numbers. Our estimated reproduction number from the hospital notifications are in broad agreement with those obtained in studies on data from Mexico (1.2–1.6) (Fraser et al., 2009), Canada (1.25–1.38) (Tuite et al., 2009), the United States of America (1.7–1.8 after adjustment for increasing ascertainment of cases) (White et al., 2009) and from New Zealand (1.96, 95% CI 1.80–2.15) (Nishiura et al., 2009) during the Southern Hemisphere winter.

It is important to remark that *Fengxiao* in mainland China, with people being confined to their workplace areas where they also live, contrasts markedly with the school closure measures in other countries, when people remain at home and are banned from their educational premises. The main results obtained here imply that *Fengxiao*, if it is implemented for a long time, is beneficial as it both delays outbreak peaks and reduces their magnitudes. Our findings are relevant to the conclusion by Cauchemez et al. that school closure might lead to reductions in the peak incidence of cases if children are sufficiently isolated or if the policy is well implemented (Cauchemez et al., 2009b; Gojovic et al., 2009; Wallinga et al., 2010). Note that it may cause more severe outbreaks due to the aggregate outbreaks within the universities/college sector while, nevertheless, preventing the disease spreading to the general population. Sensitivity analysis indicates that *Fengxiao* cannot reduce the number of infectious individuals (or hospital notifications) in the general population unless it is implemented early, especially before the peak in the general population sector (see Fig. 8(I), (J)). This interesting result is associated with our previous results (Tang et al., 2010) that *Fengxiao*, if it is implemented early, is beneficial as a public health policy in China, as it delays outbreak peaks and thus provides a critical response time needed for vaccine production and facility preparation. Moreover, the sensitivity analysis suggests the latest time for implementing *Fengxiao* after which it becomes ineffective.

It follows from Fig. 6(A) that the shorter the duration of *Fengxiao*, the less the likelihood of the second wave occurring (i.e., only a big first wave occurs), and if the *Fengxiao* strategy is persistently implemented, the simulation result implies that the second wave will not occur and only a small first wave can be observed in this scenario. If *Fengxiao* is only implemented for a limited period and massive population mobility occurs (increasing off-campus transition rate h) it is more likely to be associated with a large number of A/H1N1 cases (Khan et al., 2009) and hence occurrence of the second wave (see Fig. 6). This result may partly explain why the epidemic in China exhibited the second outbreak after the National Day holidays. So, although the bimodality of an epidemic may in general be due to a variety of factors such as varying rates of mobility, exogenous seasonal processes and/or endogenous changes in the population, the suspension of *Fengxiao* and consequent population mobility are revealed as the main factors that induced the second wave of the 2009 A/H1N1 pandemic infection in the Province of Shaanxi or in mainland China as a whole.

Complete isolation was of course impossible, but our results indicate that *Fengxiao* did indeed reduce A/H1N1 transmission from the campuses into the wider community, and substantially delayed the timing of the peak of the infection in the general population. Therefore, the main health benefit of proactive *Fengxiao* comes from slowing down the spread of virus into a wider community, thus flattening the peak of infections in the general population, although a slightly more severe outbreak within the university community results. Just like school closure, this benefit becomes especially important when the number of people requiring medical care at the peak of the pandemic threatens to saturate or overwhelm the health care capacity. By slowing the speed of spread, *Fengxiao* can also buy some time as countries intensify preparedness measures or build up supplies of vaccines, antiviral drugs, and other interventions.

The implications of our simulation results should be interpreted with care. Our findings suggest that persistent *Fengxiao* is credited with keeping the epidemics down to low levels, but how “long” it needs to be implemented has to be balanced with normal living requirements, which remains an issue for discussion. Hence, decisions on the timings of the triggering of *Fengxiao* and its suspension are crucial (Day et al., 2006; Cauchemez et al., 2009b; Hatchett et al., 2007). Despite the above caveats, our simulation results strongly suggest that *Fengxiao* is required to slow down the spread of virus into a wider community and thus flatten the peak of infections in the general population. It is therefore recommended as a suitable policy should a new emergent infectious disease arise.

The feasibility of *Fengxiao* derives largely from the unique features of the social network and academic activities in Chinese campuses, however, the effectiveness of *Fengxiao* suggests that similar measures should be considered in managing disease outbreaks in similar facilities of other countries.

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Appendix A. The detailed model equations

Using S/N approximately equal to 1, the full model (2.1) becomes the following reduced model:

$$\begin{cases} \frac{dE_u}{dt} = R_c^u(\delta_2 + \gamma_1)I_u - \delta_1 E_u, \\ \frac{dI_u}{dt} = \delta_1 E_u - (\delta_2 + \gamma_1)I_u, \\ \frac{dE_u^q}{dt} = \frac{q(\delta_2 + \gamma_1)}{1-q} R_c^u I_u - \delta_1 E_u^q, \\ \frac{dH_u^q}{dt} = \delta_2 I_u + \delta_1 E_u^q - \gamma_2 H_u^q. \end{cases} \quad (A.1)$$

The definitions of variables and parameters are the same as those for the full model (2.1).

Given the flow diagram Fig. 3 that we have the following model:

$$\begin{cases} \frac{dS_u}{dt} = \frac{P_{Su}S_uI_u}{N_u} - \frac{P_{Sg}S_uI_g}{N_g} + \lambda S_u^q, \\ \frac{dE_u}{dt} = \frac{P_{Eu}S_uI_u}{N_u} + \frac{P_{Eg}S_uI_g}{N_g} - \delta_1 E_u, \\ \frac{dI_u}{dt} = \delta_1 E_u - (\delta_2 + \gamma_1)I_u, \\ \frac{dS_u^q}{dt} = \frac{Q_{Su}S_uI_u}{N_u} + \frac{Q_{Sg}S_uI_g}{N_g} - \lambda S_u^q, \\ \frac{dE_u^q}{dt} = \frac{Q_{Eu}S_uI_u}{N_u} + \frac{Q_{Eg}S_uI_g}{N_g} - \delta_1 E_u^q, \\ \frac{dH_u^q}{dt} = \delta_2 I_u + \delta_1 E_u^q - \gamma_2 H_u^q, \\ \frac{dR_u}{dt} = \gamma_1 I_u + \gamma_2 H_u^q, \\ \frac{dS_g}{dt} = \frac{\beta_0 S_g(I_g + hI_u)}{N_g}, \\ \frac{dE_g}{dt} = \frac{\beta_0 S_g(I_g + hI_u)}{N_g} - \delta_1 E_g, \\ \frac{dI_g}{dt} = \delta_1 E_g - (\delta_2 + \gamma_1)I_g, \\ \frac{dH_g}{dt} = \delta_2 I_g - \gamma_2 H_g, \\ \frac{dR_g}{dt} = \gamma_1 I_g + \gamma_2 H_g, \end{cases} \quad (A.2)$$

where $N_u(t)$ denotes the total number of university/college individuals at time t which can be determined by $N_u = (1-h)S_u + (1-h)E_u + (1-h)I_u + S_u^q + E_u^q + H_u^q + (1-h)R_u$, $N_g(t)$ represents the total number of people in the general population at time t which can be calculated as

$$N_g = S_g + E_g + I_g + H_g + R_g + hS_u + hE_u + hI_u + hR_u,$$

$$P_{Su} = (1-h)^2[\beta c_u(1-\phi_u) + c_u q_u(1-\beta)], \quad P_{Eu} = (1-h)^2 \beta c_u(1-q_u)(1-\phi_u),$$

$$Q_{Su} = (1-h)^2(1-\beta)c_u q_u, \quad Q_{Eu} = (1-h)^2 \beta c_u q_u(1-\phi_u),$$

$$P_{Sg} = (1-h)[\beta c_g(1-\phi_g) + c_g q_g(1-\beta)], \quad P_{Eg} = (1-h)\beta c_g(1-q_g)(1-\phi),$$

$$Q_{Sg} = (1-h)(1-\beta)c_g q_g, \quad Q_{Eg} = (1-h)\beta c_g q_g(1-\phi_g),$$

and

$$\beta_0 = \beta c_g(1-\phi_g).$$

Appendix B. Parameter estimation

Note that due to the irregular reporting of the data caused by reporting delays at weekends and changes in reporting policy, we

generated the numbers of daily hospitalized cases by using the cubic spline interpolation method on what data there were, implemented as a Matlab program, to fit the two-wave pattern and then evaluate the effectiveness of NPIs.

The variance of the measured component, $H_u(t)$, was given by an inverse gamma distribution with hyper-parameters (0.01, 4), where 0.01 is the initial error variance, which are updated by an inverse gamma distribution (see <http://www.helsinki.fi/~mjlaine/mcmc/>), and the small MCMC package provided at that website was used to estimate the parameters. When estimating unknown parameters and initial values based on the data for the 8th Hospital of Xi'an city and in the model (A.1) and the model (2.1), the following prior information was given: $R_c^u \in (1, 5), q \in (0, 1), \delta_2 \in (1, 3), S_u(0) \in (10^4, 2 \times 10^5), E_u(0) \in (0, 100), I_u(0) \in (0, 100), S_u^q(0) \in (500, 10^5), E_u^q(0) \in (0, 100)$. The proposal density was chosen to be a multivariate normal distribution. These prior values were used to ensure good convergence of the MCMC chain.

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