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Transmission potential of the novel avian influenza A(H7N9) infection in mainland China

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HIGHLIGHTS

- Assess transmission potential of A(H7N9) infection in mainland China.
- Estimate the reproduction number for human-to-human transmission.
- A new outbreak may be possible due to virus mutation and adaption or periodic outbreaks in poultry.
- Careful surveillance and persistent intervention strategies in poultry are suggested.

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ABSTRACT

We propose and analyze a mathematical model to mimic its transmission dynamics to assess the transmission potential of the novel avian influenza A(H7N9) virus. By fitting the model to data of the confirmed human cases we estimate the reproduction number for human-to-human transmission as 0.467 (95% CI 0.387–0.651). Simulation results indicate that approximate twofold of the current human-to-human transmission rate or periodic outbreaks of avian influenza in poultry may induce an outbreak in human. Through the recent limited transmission potential of the novel avian influenza A(H7N9) virus, a new outbreak may be possible due to virus mutation and adaption or periodic outbreaks in poultry, and hence careful surveillance and persistent intervention strategies in poultry have to be required.

1. Introduction

A novel influenza A(H7N9) virus associated with human deaths has emerged in eastern China since February 2013 (WHO, 2013). The global public health community has been on alert since H7N9 virus isolated from patients possesses some genetic signatures associated with effective replication and transmission, and with high virulence in mammals. While there were only a handful of H7N9 cases during the summer months after a surge in April, two human case of the deadly H7N9 strain of bird flu have been confirmed in October, which implies, as flu experts warn, that the threat posed by the virus has not passed.

Almost all confirmed cases have been sporadic, with no epidemiologic link to other human cases (Li et al., 2013; CDC, 2013). However, at least three family clusters have been reported where limited human-to-human transmission might have occurred (Li et al., 2013; Chen et al., 2013). Sporadic infections may continue to occur in humans, given that the source of the virus appears to be market poultry, though the link is not definitive. As the northern hemisphere temperature getting cooler, it is not clear if human H7N9 infections could spike again, a pattern commonly seen with seasonal flu strains and other avian influenza viruses like H5N1 that circulate in poultry.

The lack of information about the virus and its mode of transmission makes it difficult to predict whether A(H7N9) might be a next pandemic (Horby, 2013), so various interventions including closure of live poultry market or culling of birds have been implemented. For example, authorities in Shanghai on April 5th, 2013 closed a live poultry trading zone in an agricultural products market and began slaughtering all birds there. Despite the huge social and economic disruption, the effect of implemented intervention strategies remains unclear and falls within the scope of this study. Here, we formulate a mathematical model to include both poultry and human and to describe the bird-to-human and human-to-human transmissions. The model is fitted to data of the confirmed human cases, and the calibrated model is

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then used to estimate the reproduction number for human-to-human transmission, as well as the bird-to-human and human-to-human transmission rates.

2. Methods

The data: Case data was obtained from the China Ministry of Health (CMH) (China CDC, 2013). Individual case information includes the date of illness onset, age, gender, geographic location, current clinical status, the date of diagnosis, the presence of contact with animals. The CMH reported cases daily right after confirmation of human infection with H7N9 influenza virus, but then (since April 25th, 2013) changed to report once every week. Since there are various delays between illness onset and laboratory confirmation we employed the information of the history of contacts with live poultry among cases and obtained the distribution of laboratory confirmed cases by data of illness onset, as shown in Fig. 1(A). Fig. 1(B) gives the number of infected individuals. The data were analyzed anonymously.

Mathematical model: Although the presence of human-to-human transmission has not been firmly established, there have been two family clusters reported (Li et al., 2013) where limited human-to-human might have occurred. We then postulate that the transmission of the novel avian influenza A(H7N9) virus for humans is via either the interaction from poultry to the humans or among humans, as shown in Fig. 2. The underlying structure of the model comprises of classes of humans and poultry that are susceptible poultry (S_p) and infected poultry (I_p). The individual human passing through the latent period (E_h) will become infectious(I_h), either asymptomatically (Cowling et al., 2013) or symptomatically, until recovery (R_h) or death (D_h) due to avian influenza A(H7N9) infection. Note that we do not consider the asymptotical class in the model since we do not have reliable parameters for the relative infectiousness of asymptomatically infected individuals. The model takes the following form:

$$\begin{cases} \dfrac{dS_p(t)}{dt} = -\omega\dfrac{S_pI_p}{N_p}, \\ \dfrac{dI_p(t)}{dt} = \omega\dfrac{S_pI_p}{N_p} - mI_p, \\ \dfrac{dS_h(t)}{dt} = -\beta_p(t)S_h\dfrac{I_p}{N_p} - \beta_hS_h\dfrac{I_h}{N_h}, \\ \dfrac{dE_h(t)}{dt} = \beta_p(t)S_h\dfrac{I_p}{N_p} + \beta_hS_h\dfrac{I_h}{N_h} - \delta E_h, \\ \dfrac{dI_h(t)}{dt} = \delta E_h - (\alpha+\gamma)I_h, \\ \dfrac{dD_h(t)}{dt} = \alpha I_h, \\ \dfrac{dR_h(t)}{dt} = \gamma I_h, \end{cases} \tag{1}$$

where N_h and N_p are the total numbers of human and poultry population, respectively. We model the implementation of intervention strategies (initiated at time T_1) by the following piecewise

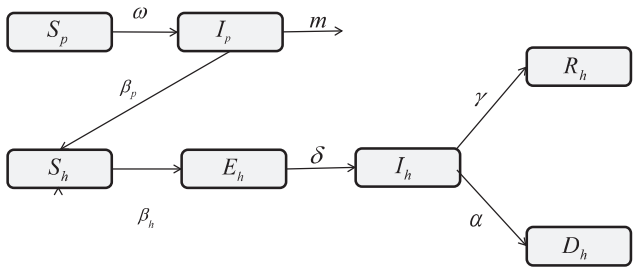

Fig. 2. Flow diagram for the novel avian influenza A(H7N9) spread in mainland China.

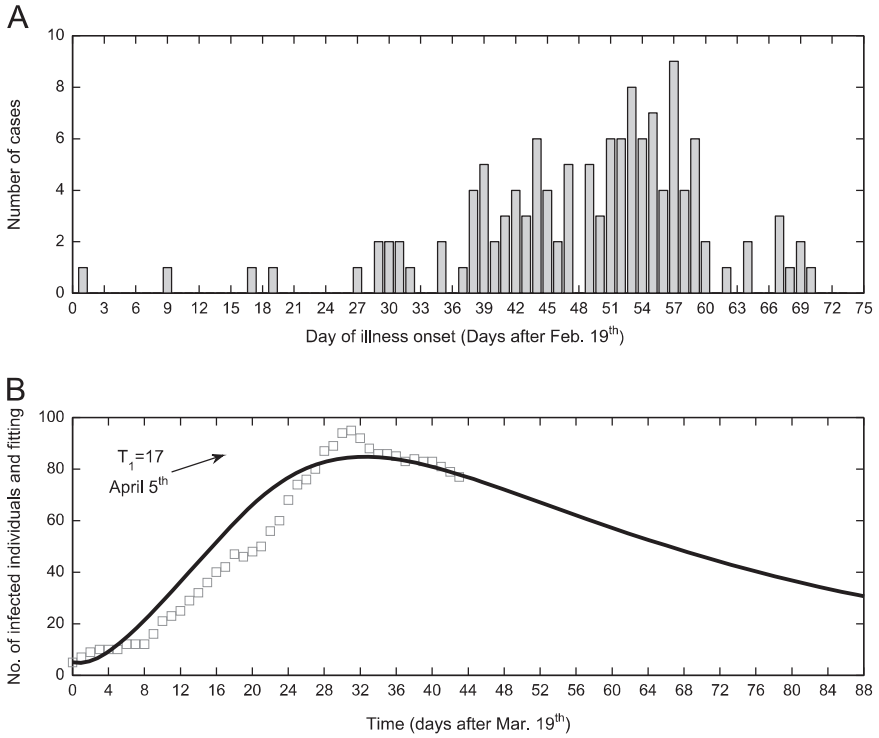

Fig. 1. (A) Number of confirmed cases of human infection with avian influenza A(H7N9) virus ($N=129$) by the date of onset of illness from February 19th to May 3rd, 2010 and (B) goodness of fit and prediction of recent H7N9 trends.

function $\beta_p(t)$ (here on April 5th, 2013):

$$\beta_p(t)=\begin{cases}\beta_{p0}, & t\le T_1,\\ \beta_{p0}e^{-k(t-T_1)}, & t>T_1,\end{cases} \tag{2}$$

where β_{p0} is the baseline transmission rate from poultry to humans and k measures the combined effect on transmission of different interventions. The definitions of parameters are given in Table 1.

Parameter estimation: Using the Kaplan–Meier (KM) method to data available, we obtained the estimation for the mean time from the date of illness onset to death as 13 days, leading to $\alpha=1/13$ (median=13, 95% credibility interval (CI): 11–17, shown in Fig. 3 (A)). Similarly, we obtained the recovery rate $\gamma=1/11$ (median=11, 95% CI: 10–15, Fig. 3(B)). As of April 26, 2013, the China Ministry of Agriculture reported that 68,060 bird and environmental specimens have been tested, 46 (0.07%) were confirmed H7N9-positive by culture (MoA, 2013). We thus assume that $I_p/N_p=0.07\%$. This will be denoted by η in our simulations. To estimate the parameters and their standard deviations without estimating the initial susceptible population sizes, and to reduce the number of parameters needed to be estimated to the minimum, we note that in the early outbreak S_h/N_h approximately equals to 1. This leads to the following reduced model:

$$\begin{cases}\dfrac{dS_h(t)}{dt}=-\eta\beta_p(t)S_h-\beta_hI_h,\\ \dfrac{dE_h(t)}{dt}=\eta\beta_p(t)S_h+\beta_hI_h-\delta E_h,\\ \dfrac{dI_h(t)}{dt}=\delta E_h-(\alpha+\gamma)I_h.\end{cases} \tag{3}$$

By using an adaptive Metropolis–Hastings (M–H) algorithm we carried out the Markov-chain Monte-Carlo (MCMC) procedure, and after a burn-in period of 500,000 iterations the next 1,000,000 samplers give estimates. We then used the Geweke convergence diagnostic method to assess the convergence of chains (Haario et al., 2006; Geweke, 1992). We fit the model (3) to data of confirmed cases on the bases of exponential growth during the early stage of the outbreak (between March 19th and April 17th, 2013) to estimate mean values including the poultry-to-human transmission rate (β_{p0}), the human-to-human transmission rate (β_h) and other parameters.

3. Results

The basic reproductive number (Diekmann and Heesterbeek, 2000) for human-to-human transmission is given by

$$R_0=\frac{\beta_h}{\gamma+\alpha}.$$

We estimated the mean reproductive number (R_0) of human-to-human transmission as 0.467 (95% CI: 0.387–0.651). The values of other parameters are listed in Table 1. We also plotted the best-fit solution in Fig. 1(B).

To examine the effect of interventions (including live animal market closure and/or culling poultry) on the peak timing and the outbreak magnitude we increased the parameter k from 20% to 200% of the baseline value. The results shown in Fig. 4(A) indicate that interventions, if implemented decisively, can greatly reduce the magnitude of the outbreak. Fig. 4(B) shows that the earlier the intervention strategies are implemented (i.e., the smaller T_1) the

Table 1
Definitions of the parameters used in the model (1) with (2).

Parameter	Definition	Parameter estimate mean value (95% CI)	References
ω	Transmission rate among poultry	–	–
m	Disease-related death and culling for poultry	–	–
β_{p0}	Transmission rate from poultry to humans	0.207 (0.0117–0.297)	MCMC
β_h	Transmission rate among humans	0.078 (0.074–0.082)	MCMC
δ	Rate of progression to latent	0.051 (0.049–0.053)	MCMC
k	Intervention intensity	0.102 (0.098–0.106)	MCMC
α	Disease-related death for humans	0.077 (0.059–0.091)	KM method
γ	Recovery rate of infectious human	0.091 (0.067–0.100)	KM method
S_{h0}	Initial size of susceptible humans	1.40×10^5 (79,604–200,395)	MCMC
E_{h0}	Initial size of latent humans	1.725 (0–5.182)	MCMC

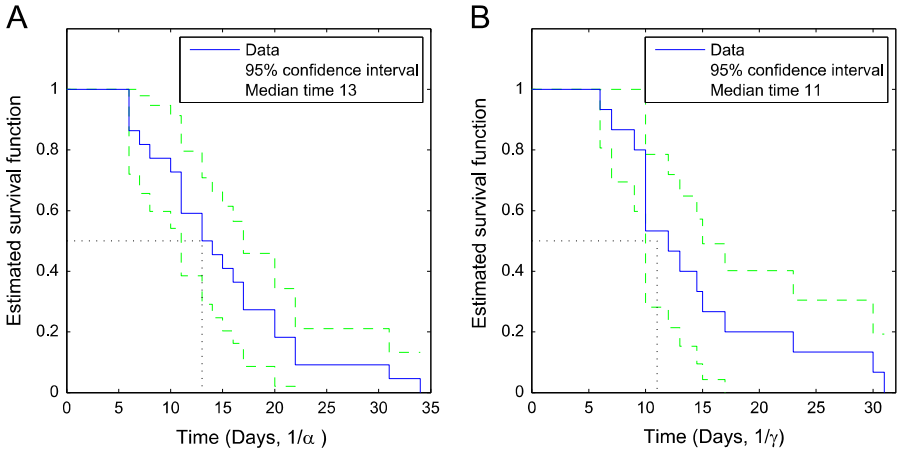

Fig. 3. KM Survival Estimate and Confidence intervals (SPlus). (A) Estimation for disease-related death and (B) estimation for recovery.

smaller the outbreak is. In particular, had the interventions been implemented on March 30, one day after the novel avian influenza A(H7N9) virus was confirmed, the maximum case number would be around 60, which is significantly lower than the observed magnitude of the outbreak. These imply that early implementation of interventions would lead to much smaller outbreak and hence are very important in curbing early epidemic outbreak.

An immediate consequence of adaption of avian influenza A (H7N9) virus to human is the increase of transmission rate or susceptible populations. To assess the impact of varying adaption

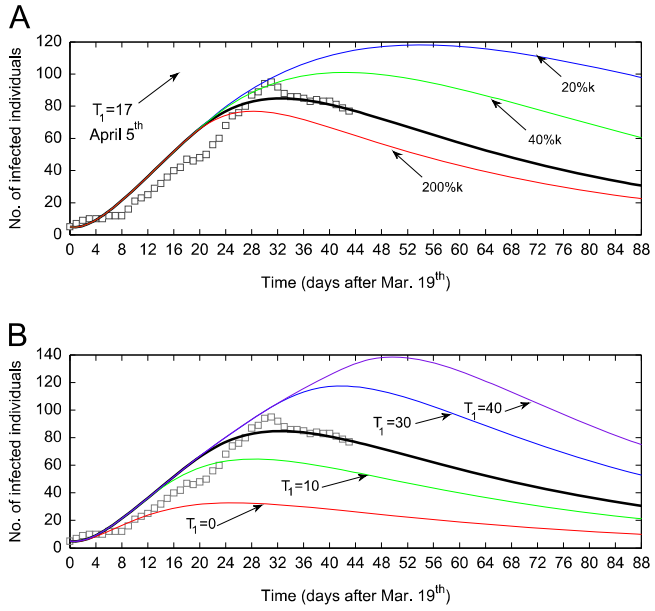

Fig. 4. The best-fit solution with implementation of interventions. Effects of (A) intensities of the interventions (various k) and (B) timings of implemented interventions (various T_1) on the peak timing and magnitude of outbreak. All other parameters are given in Table 1.

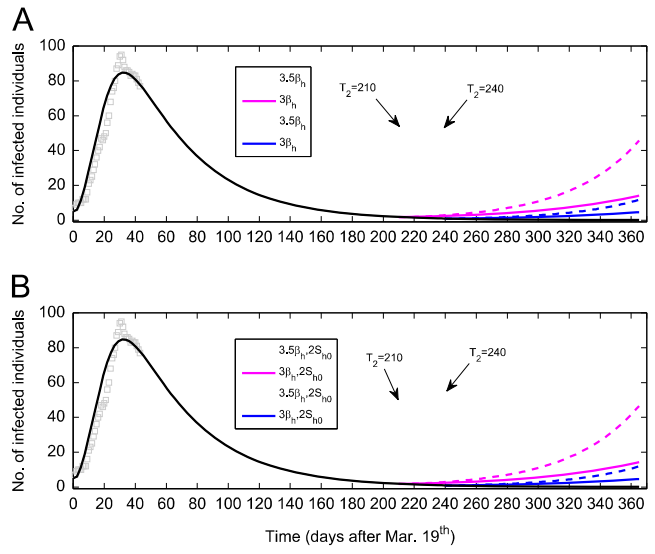

Fig. 5. Prediction of the next outbreak with various (A) human-to-human transmission rates and (B) susceptible sizes. The purple (blue) curves correspond to the timing $T_2 = 140$ (150) days after March 19th, 2013, when virus is mutated to be easy to transmit among humans. All other parameters are given in Table 1. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

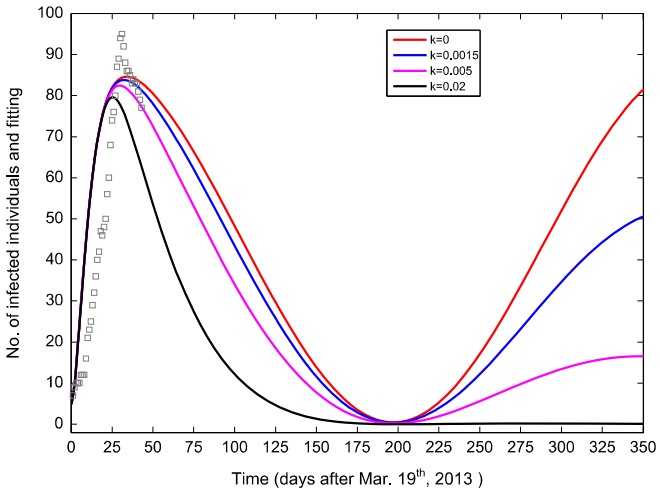

Fig. 6. Prediction of the next outbreak with periodic prevalence of infection in poultry and various intensify of interventions. Parameters are $\eta = 0.0007$, $\alpha = 1/13, \gamma = 1/11, \beta_{p0} = 0.12, \beta_h = 0.015, \delta = 0.2, k = 0.0015, S(0) = 8.2713 \times 10^4$, $E(0) = 4, I(0) = 5$.

of avian influenza A(H7N9) virus on the future trend of H7N9 infection in mainland China, we simulated models (1) and (2) with $I_p(t)/N_p(t) = \eta$ and kept the poultry-to-human transmission unchanged. We considered the scenarios that increase in transmission rate or susceptible population size that are taken place at some time T_2 (e.g. $T_2 = 210$, 240 days after March 19, 2013, which are around middle of October, November, 2013). Fig. 5(A) shows that a greater human-to-human transmission rate ($3\beta_h$ or $3.5\beta_h$) changes the downward trend of the epidemic. In fact, $2.152\beta_h$ will induce a new outbreak as it will increase the human-to-human reproduction above unity, conditional upon no poultry-to-human transmission. Comparing Fig. 5(B) with (A) shows that more susceptible population will result in a slight greater magnitude of next outbreak.

Periodic outbreaks of pathogenic avian influenza occur in poultry around the world, we then fit our models (1) and (2) to the data that confirmed human cases by letting the periodic prevalence of infection in poultry $I_p(t)/N_p(t) = \eta(1 + \cos(2\pi t/365))$ with $\eta = 0.07\%$. It follows from Fig. 6 that the periodic infection of poultry will induce the second outbreak in human population. However, if the intervention strategies keep strict (e.g., relatively high level of parameter k in the piece function (2)) then the downward trend of the epidemic may not be changed (black curve shown in Fig. 6). In particular, the more the intervention strategies are strengthened in the poultry the lower magnitude of the second outbreak in human population is.

4. Discussion

It is critical for public-health management to accurately estimate the basic reproduction number for human-to-human transmission of the novel influenza A (H7N9) virus, as this provides a measure of the intensity of interventions required to achieve effective control of the epidemic. Due to the lack of data on poultry and susceptible population sizes, we then initially assumed that prevalence of A(H7N9) infection in poultry remains relatively unchanged (i.e. 0.07%) according to the surveillant data (MoA, 2013) to estimate parameter values. Our estimated human-to-human reproduction number from the confirmed cases is 0.467 (95% CI 0.387–0.651), which is well below unity and in agreement with the observed limited human-to -human transmission (Li et al., 2013). Our mean estimate of the basic reproduction

number is a bit higher than the estimated 0.28 (95% CI 0.11–0.45) by Nishiura et al. (2013) and the estimated 0.1 (95% CI 0.01–0.49) by Chowell et al. (2013), however their 95% credible intervals are intersectant with ours.

Our numerical simulations suggest that poultry culling or market closure could mitigate the infection, and the earlier or the stronger the interventions are implemented the smaller magnitude of the outbreak is. Our simulations (Fig. 5) show that the occurrence of the next outbreak is more likely associated with the adaption of avian influenza A(H7N9) virus to human or more close human-to-human contacts. In the past, we have noticed that this second outbreak was due to the relaxation of interventions, for example, in A/H1N1 pandemic infection (Tang et al., 2010) and in the 1918 influenza pandemic in U.S. (Hatchett et al., 2007). Our numerical simulations suggest that if the human-to-human transmission rate of avian influenza A(H7N9) virus increases by 215% the second outbreak becomes possible.

On the basis of periodic outbreak of influenza in poultry we simulated our model by assuming periodic prevalence of infection in poultry. It is seen that the second outbreak in human may be possible (shown in Fig. 6), which is associated with the occurrence of the autumn wave of A/H1N1 in U.S. (Towers and Feng, 2009). However, persistent and strict intervention strategies in poultry may prevent the second outbreak. These observations indicate the potential risk of a new outbreak as avian influenza A(H7N9) virus mutates to be easily transmitted or periodic outbreak in poultry, and this new outbreak will require fast and strong implementation of intervention strategies. This is particular so in mainland China as the potential outbreak will then coincide with the Spring Festival in the end of January 2014, when close human-to-human contacts and/or reopening of live poultry market are expected.

By explicitly modeling the dynamics of the poultry our model (1) describes both human-to-human transmission and poultry-to-human transmission, which is more accurate and dynamic than the model developed by Chowell et al. (2013) in which a constant daily rate of new infections arising from exposure to the reservoir is included. Due to the information on prevalence in poultry (MoA, 2013) we can reasonably simplify the proposed model and estimate parameter values. Our model-based method based on MCMC provides an alternative approach to estimate the basic reproduction number, compared to the estimation methods used by Nishiura et al. (2013) and Chowell et al. (2013). In particular, our model-based method estimates not only the basic reproduction number R_0 but also the transmission coefficients including both human-to-human and poultry-to-human transmission rates, and other parameters such as the intervention intensity (k) and initial size of susceptible humans. Further, we simulate the future trend of H7N9 infection and predicate that a new outbreak may be possible due to virus mutation and adaption or periodic outbreaks in poultry. This novel result is associated with the latest news that there were 110 confirmed cases of human infection with influenza A(H7N9) virus from January 1st to January 28th, 2014 (News, January 31st, 2014).

Note that there is evidence of infected individuals without showing illness (WHO, 2013), therefore, the estimates without considering asymptomatic infection (Cowling et al., 2013) may underestimate the disease spread. Despite these caveats, our simulation results indicate the limited transmission potential of the novel avian influenza A(H7N9) virus, but an increase by two fold (2.152) of the current human-to-human transmission rate may induce a new outbreak, so surveillance has to be carefully designed to monitor the virus mutation and adaption.

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References

CDC. CDC Health Advisory: Human Infections with Novel Influenza A (H7N9) Viruses, US Department of Health and Human Services, CDC, Health Alert Network, Atlanta, GA, 2013. Available at ⟨http://emergency.cdc.gov/han/han00344.asp⟩.

Chen, Y., Liang, W.F., Yang, S.G., et al., 2013. Human infections with the emerging avian influenza A H7N9 virus from wet market poultry: clinical analysis and characterisation of viral genome. Lancet. 381 (9881) 1916–1925,. http://dx.doi.org/10.1016/S0140-6736(13)60903-4.

Chinese Center for Disease Control and Prevention (China CDC): Statistics of H7N9 Confirmed Cases Beijing, China CDC, China, 2013.

Chowell, G., Simonsen, L., Towers, S., Miller, M.A., Viboud, C., 2013. Transmission potential of influenza A/H7N9, February–May 2013, China. BMC Med. 11, 214.

Cowling, B.J., Freeman, G., Wong, J.Y., Wu, P., et al., 2013. Preliminary inferences on the age-specific seriousness of human disease caused by avian influenza A (H7N9) infections in China, March–April 2013, Euro Surveill. 18(19). pii=20475.

Diekmann, O., Heesterbeek, J.A.P., 2000. Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation. John Wiley & Son, Ltd., Chichester

Geweke, J., 1992. Evaluating the accuracy of sampling-based approaches to the calculation of posterior moments. In: Bernardo, J.M., Berger, J., Dawid, A.P., Smith, A.F.M. (Eds.), Bayesian Statistics, vol. 4. Oxford University Press, Oxford, pp. 169–193.

Haario, H., Laine, M., Mira, A., Saksman, E., 2006. Dram: efficient adaptive MCMC. Stat. Comput. 16, 339–354.

Hatchett, R.J., Mecher, C.E., Lipsitch, M., 2007. Public health interventions and epidemic intensity during the 1918 influenza pandemic. Proc. Natl. Acad. Sci. USA 104, 7582–7587.

Horby, P., April 25, 2013. H7N9 is a virus worth worrying about. Nature 496 (7446), 399. http://dx.doi.org/10.1038/496399a.

Li, Q., Zhou, L., Zhou, M., et al., April 24, 2013. Preliminary report: epidemiology of the avian influenza A (H7N9) outbreak in China. N. Engl. J. Med. http//:dx.doi.org.10.1056/NEJMoa1304617.

Ministry of Agriculture of the Peoples Republic of China. No H7N9 Virus Found In Poultry Farm Samples, Ministry of Agriculture, Beijing, China, 2013. Available at http://english.agri.gov.cn/news/ dqnf/201304/t20130427-19537.htm.

Nishiura, H., Mizumoto, K., Ejima, K., 2013. How to interpret the transmissibility of novel influenza A(H7N9): an analysis of initial epidemiological data of human cases from China. Theor. Biol. Med. Model. , http://dx.doi.org/10.1186/1742-4682-10-30

The 110 Confirmed Cases of Human Infection with H7N9, January 1st–28th, 2014, Mainland China. ⟨http://js.people.com.cn/html/2014/01/31/285833.html⟩(In Chinese).

Tang, S.Y., Xiao, Y.N., Yang, Y.P., et al., 2010. Community-based measures for mitigating the 2009 H1N1 pandemic in China. PLoS ONE 5, 1-1 (e10911).

Towers, S., Feng, Z., 2009. Pandemic H1N1 influenza: predicting the course of a pandemic and assessing the efficacy of the planned vaccination programme in the United States. Euro Surveill. 14 (41) (pii=19358).

World Health Organization. Global Alert and Response (GAR): Human Infection with Influenza A(H7N9) Virus in China, World Health Organization, Geneva, Switzerland, 2013. Available at ⟨http://www.who.int/csr/don/2013-04-01/en/index.html⟩.