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Supplementary appendix

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Technical Appendix

Estimation of the number of A(H7N9) symptomatic infections who sought medical care at ILI sentinels

Define the following:

$X_{t,k}$ is the no. of A(H7N9) onsets detected by virologic surveillance in city k on day t

$x_{t,k}$ is the observed no. of A(H7N9) onsets detected by virologic surveillance in city k on day t

$A_{t,k}$ is the no. of A(H7N9) who sought care at ILI sentinels in city k on day t

$y_{t,k}$ is the no. of specimens tested by virologic surveillance in city k on day t

$z_{t,k}$ is the no. of ILI cases registered by ILI surveillance in city k on day t

$p_{t,k} = y_{t,k}/ z_{t,k}$ is the proportion of cases in ILI surveillance that were selected for virologic surveillance in city k on day t

We assumed that RT-PCT was 100% sensitive for detecting A(H7N9) infections. We assumed a constant daily force of onset λ'_k in city k and each A(H7N9) symptomatic infection seek medical care at ILI sentinel with probability q_k'. We chose the date of local live poultry market closure as the end of the time horizon because the number of new cases dropped to 0 within a week after that. Under such assumptions, the number of A(H7N9) onsets that visited ILI sentinels in city k on different days were i.i.d. Poisson random variables with mean $\lambda_k = \lambda_k' q_k'$. The likelihood was

$$L_k(\lambda_k) = \prod_{t<\text{market closure}} P(X_{t,k} = x_{t,k} \mid y_{t,k}, z_{t,k}) \text{ where}$$

$$P(X_{t,k} = x_{t,k} \mid y_{t,k}, z_{t,k}) = \sum_{a=x_{t,k}}^{z_{t,k}} \underbrace{Poisson(a,\lambda_k)}_{\substack{a \text{ onsets visited ILI sentinels} \\ \text{in city } k \text{ on day } t}} \cdot \underbrace{Hypergeometric(x_{t,k}, y_{t,k}, a, z_{t,k})}_{\substack{\text{When } y_{t,k} \text{ of } z_{t,k} \text{ ILI cases were selected for virologic} \\ \text{surveillance, } x_{t,k} \text{ of these } a \text{ onsets were detected}}}$$

This likelihood is well approximated by

$$\tilde{L}_k(\lambda_k) = \prod_{t<\text{market closure}} \frac{e^{-\lambda_k p_{t,k}} \left(\lambda_k p_{t,k}\right)^{x_{t,k}}}{x_{t,k}!}$$

which simply assumed that the number of onsets that were detected by virologic surveillance were i.i.d. Poisson random variables with mean $\lambda_k p_{t,k}$ (i.e. disregarding the constraints $y_{t,k}$ and $z_{t,k}$ imposed on $A_{t,k}$ and $X_{t,k}$). To take into account the increased medical care seeking behavior of ILI cases after local announcement of the first laboratory-confirmed A(H7N9) cases, we modified the likelihood by scaling the mean number of A(H7N9) visits at ILI sentinels on day t with the number of ILI cases registered by ILI surveillance $z_{t,k}$ as follows:

$$\tilde{L}_k(\lambda_k) = \prod_{t<\text{market closure}} \frac{e^{-\lambda_k b_{t,k} p_{t,k}} \left(\lambda_k b_{t,k} p_{t,k}\right)^{x_{t,k}}}{x_{t,k}!}$$

where $b_{t,k} = z_{t,k}/z_{1,k}$. The mean daily number of infections λ_k was estimated using Markov Chain Monte Carlo methods. We assumed non-informative priors for all parameters and implemented Monte Carlo Markov Chain (MCMC) using the Metropolis algorithm to obtain posterior distributions of the parameters. A random step size was chosen for each parameter at every iteration and the variance of the step size for each parameter was automatically adjusted such that the acceptance proportion was between 30% and 70% for each parameter. The MCMC was run for 100,000 iterations for each parameter and the posterior distributions were compiled from the final 70% of the iterations. The total expected number of A(H7N9) infections that attended ILI sentinels was approximately

$$M_{sentinels,k} \sum_{t<\text{market closure}} x_{t,k} + \lambda_k \sum_{t<\text{market closure}} b_{t,k} \ .$$

We considered two methods for estimating the total number of symptomatic A(H7N9) infections (M_k) from the above estimates of the number of A(H7N9) infections who sought care at ILI sentinels ($M_{sentinels,k}$):

Method 1: Assuming that the proportion of A(H7N9) symptomatic infections that sought care at ILI sentinels was similar to that for A(H1N1) pdm09

Between 28 June 2009 and 31 January 2010, ILI and virologic surveillance in China estimated that around 0.77 million A(H1N1) pdm09 infection visited ILI sentinels (the number of A(H1N1) pdm09 infections that visited ILI sentinels in any given week was estimated as the product of ILI counts and percentage of virologic specimens that were positive for A(H1N1) pdm09). Nationwide serosurvey in China estimated that the number of A(H1N1) pdm09 infections between June 2009 and January 2010 was 207.7 million of whom 50% were symptomatic [1]. These data together suggested that around 0.75% of A(H1N1) pdm09 symptomatic infections sought medical care at ILI sentinels. The ILI surveillance system has not changed substantially and only covers a small fraction of the hospitals in affected regions of China. Specifically, the current ILI sentinel network comprises 554 of 20291 hospitals in China, and crude scaling by hospital counts suggests that 0.75% × 20291/554 = 27% of A(H1N1)pdm09 symptomatic infections sought medical care , which is a plausible estimate. The proportion of symptomatic A(H7N9) virus infections that sought medical care was likely to have been higher than assumed here because (i) laboratory-confirmed A(H7N9) cases seemed to have faster and more severe disease progression than A(H1N1)pdm09 and (ii) residents of the highly developed cities of Shanghai and Nanjing were more likely to seek medical care than the general population of China. As such, our estimates of the number of symptomatic A(H7N9) virus infections in this method could be interpreted as upper bounds, although the true number of A(H7N9) cases could be even higher if there has been substantial underdetection of cases in some areas.

Method 2: Assuming that all A(H7N9) symptomatic infections sought care at ILI sentinels and the probability of seeking care at ILI sentinels was the same as the ratio of outpatient visits at ILI sentinels to that at all hospitals

When calculating this ratio, we considered only outpatient visits in the internal medicine, pediatrics and emergency departments because A(H7N9) symptomatic cases were most likely to have sought medical care in these departments. Online statistics from the Ministry of Health in China (http://www.moh.gov.cn/htmlfiles/zwgkzt/ptjnj/year2011/index2011.html) indicated that the daily average number of outpatient visits in these departments among all hospitals in Shanghai in 2010 was 112,340 which accounted for approximately 40% of all outpatient visits. Online Nanjing Health Statistics (http://www.njh.gov.cn/html/wstj/2013/05/131122040107.shtml) indicated that the daily average number of outpatient visits in all departments among all hospitals in Nanjing was 94,125 in 2012. Because outpatient visits stratified by departments were not available from this database, we assumed that the proportion of outpatient visits in the internal medicine, pediatrics and emergency departments was similar to that in Shanghai, i.e. 40%. The China CDC ILI surveillance database indicated that the daily average number of outpatient visits in the internal medicine, pediatrics and emergency departments in the ILI sentinels in Shanghai and Nanjing were 23,870 and 4,070, respectively, between 1 January and 16 May 2013.

Note that because it was likely that some A(H7N9) symptomatic infections had not sought medical care, our estimates of the number of symptomatic A(H7N9) virus infections in this method could be interpreted as lower bounds.

The Appendix Table shows the results of the above statistical inference using the data from Shanghai and Nanjing, two cities that detected A(H7N9) infections from their routine virologic surveillance and accounted for around 1/3 of all lab-confirmed cases in China.

The Appendix Figure shows incidence of laboratory-confirmed A(H7N9) cases in Shanghai and Nanjing, and rates of influenza-like illness consultations and numbers of ILI specimens tested in the two cities.

References

1. Xu C, Bai T, Iuliano AD, et al. The seroprevalence of pandemic influenza H1N1 (2009) virus in China. *PloS one.* 2011;6(4):e17919.

Appendix Table. Estimates of the number of symptomatic influenza A(H7N9) virus infections in Shanghai and Nanjing.

	Shanghai	**Nanjing**
No. of A(H7N9) infections detected by sentinel virological surveillance	2	1
Estimated mean no. of infections per day, λ (posterior median and 95% credible interval)	0.26 (0.06-0.72)	0.67 (0.1-2.2)
Estimated no. of A(H7N9) infections with ILI that sought care at ILI sentinel sites (posterior median and 95% credible interval)	23 (7-58)	40 (7-129)
Average daily no. of outpatient visits* in ILI sentinels ($O_{Sentinels}$)	23,900	4,070
Average daily no. of outpatient visits* in all hospitals (O_{all})	112,000 (from year 2010)	37,500 (from year 2012)
Estimated no. of symptomatic A(H7N9) infections assuming:		
Method 1: The proportion of A(H7N9) symptomatic infections who sought medical care at ILI sentinels was similar to that for A(H1N1)pdm09 (0.75%)	3,020 (900-7,800)	5,310 (880-17,300)
Method 2: All A(H7N9) symptomatic infections sought medical care at hospitals, $O_{Sentinels}/O_{all}$ of which sought care at ILI sentinels	107 (33-273)	367 (61-1,200)

*Only outpatient visits in the internal medicine, pediatrics and emergency departments were included because A(H7N9) symptomatic cases were most likely to have sought medical care in these departments.

Appendix Figure. Numbers of laboratory-confirmed A(H7N9) cases in (A) Shanghai and (B) Nanjing, detected via the ILI sentinel surveillance network or detected by other means. The second plot in each panel shows the daily number of ILI consultations reported by sentinel clinics and the daily number of specimens collected from ILI cases for laboratory testing in each city.