Transmission Potential of Influenza A(H7N9) Virus, China, 2013–2014

Adam J. Kucharski,1 Harriet L. Mills,1 Christl A. Donnelly, Steven Riley

To determine transmission potential of influenza A(H7N9) virus, we used symptom onset data to compare 2 waves of infection in China during 2013–2014. We found evidence of increased transmission potential in the second wave and showed that live bird market closure was significantly less effective in Guangdong than in other regions.

From February 19, 2013, through April 22, 2014, a total of 429 cases of influenza A(H7N9) virus infection in humans in China were reported and occurred in 2 outbreak waves. During the first wave in spring 2013, live bird markets were closed in several parts of China (1,2); these market closures substantially reduced the risk for infection in affected regions (3). During a second wave in autumn 2013 (4), markets were again closed in some provinces (5–7). Analysis of the largest clusters of subtype H7N9 virus infection in 2013 suggested that the basic reproduction number ($R_0$), the average number of secondary cases generated by a typical infectious host in a fully susceptible population) was higher in some clusters than in others (8,9), although the absence of sustained transmission implied that $R_0$ was less than the critical value of 1. To determine the transmission potential of influenza A(H7N9) virus in the first and second waves in 2013, we compared symptom onset data. We also measured the extent to which market closures in 2014 reduced spillover hazard (i.e., risk for animal-to-human infection).

The Study
We focused on the locations of the 6 largest outbreaks: Shanghai, Zhejiang, and Jiangsu (first wave) and Guangdong, Zhejiang, and Jiangsu (second wave). To infer market hazard and human-to-human transmission potential, we used a statistical model of infection spillover (9). We assumed that cases could be generated in 1 of 2 ways: on each day, the expected number of reported cases was equal to the sum of animal exposure and secondary cases generated by earlier infectious hosts (online Technical Appendix, http://wwwnc.cdc.gov/EID/article/21/5/14-1137-Techapp1.pdf).

Use of such a framework enables estimation of the degree of human-to-human transmission from symptom onset data and of exposure hazard from markets; the accuracy of these estimates is greatly improved when the timing of a sudden change in hazard, such as a market closure, is known (9). We therefore constrained the timing of the drop in exposure hazard to reported market closure dates (online Technical Appendix Table 1). We also estimated $R_0$ for each of the 6 outbreaks. For patients with known exposure, cluster reports suggest that the serial interval (time delay between symptom onset in primary and secondary case-patients) could be 7–8 days (online Technical Appendix Table 2). We therefore assumed a serial interval of 7 days for our main analysis and tested a range of values from 3 to 9 days during sensitivity analysis. We adjusted for potential delays between symptom onset and case report on the basis of the distribution of delays to date (online Technical Appendix Figure 1).

During the first wave, cases were initially concentrated around Shanghai; reports centered on the city and neighboring Zhejiang and Jiangsu (Figure 1, panel A). A wave-like relationship between location and onset timing was apparent; distance between the location of the first case-patient in Shanghai and subsequent case-patients increased over time (Figure 1, panel B). The pattern of cases at the start of the second wave suggests that infection did not spread outward from a single source; in October 2013, initial cases occurred in Guangdong and Zhejiang.

We used our statistical model to estimate the relative contributions of animal-to-human and human-to-human transmission. In Zhejiang, Shanghai, and Guangdong, market hazard clearly increased and decreased at the start and end of the outbreak, respectively (Figure 2). We also estimated $R_0$ for different regions over the 2 outbreak waves (Table). Although our estimates for Jiangsu did not change significantly between the 2 waves, for Zhejiang, $R_0$ was significantly higher for the second wave than for the first wave in spring 2013 ($p = 0.045$). We estimated $R_0$ to be 0.06 (95% credible interval [CrI] 0.00–0.25) in the first wave and 0.35 (95% CrI 0.15–0.65) in the second.

Using our estimates for $R_0$ and market hazard, we estimated the number of cases in each outbreak that resulted from human-to-human rather than animal-to-human transmission. We found evidence of a small but significant amount of transmission between humans in the first and second waves (Table). Our findings agree with reports of possible human clusters in the first wave (1,10–12) and corroborate media reports of possible human clusters in Zhejiang and Guangdong.

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during 2013–2014. We identified 5 clusters during the first wave (February–April 2013) and 8 clusters during the second wave (November 2013–May 2014); the clusters in both waves had median size of 2 cases per cluster (online Technical Appendix Table 2). These conclusions were robust under different assumptions about the duration of serial interval (online Technical Appendix Figures 2, 3).

During the second wave, market closures in Zhejiang began on January 22, 2014, and ended on January 26, 2014 (Table). The reduction in spillover hazard after these closures was significant. We estimated that closures for a serial interval of 7 days reduced hazard by 97% (95% CrI 92%–99%). During 2013, estimated effectiveness was similar in Zhejiang (99%; 95% CrI 97%–100%) and Shanghai (99%; 95% CrI 95%–100%). These estimates are in agreement with those from other analyses for the first wave (3). The 95% CrI was broader for Jiangsu, however, where estimated effectiveness was 97% (95% CrI 80%–100%). In Guangdong, Guangzhou markets closed on February 16, 2014, and reopened on February 28; markets in other cities in Guangdong closed around the same time for 2 weeks. Our results suggest that these closures reduced hazard by 73% (95% CrI 53%–89%). This reduction was significantly smaller than that for Shanghai and Zhejiang (p<0.01). Our result was robust at different serial intervals of infection (online Technical Appendix Figure 4).

Despite the effectiveness of closures during the first wave, interventions in most regions were delayed until after the Chinese New Year (January 31, 2014). Some regions are investigating alternative market practices: Guangzhou has implemented a trial of a permanent ban on live poultry sales in certain markets, potentially to extend over the entire city by 2024 (5). Our results support recommendations made after the first wave of outbreaks in 2013 (3), which suggest that prompt closure of markets could lead to substantially fewer infections. However, our finding that the relative effectiveness of the shorter closure in Guangdong was lower suggests that such interventions are needed for a sufficiently long time to prevent recurrence.

Our study has limitations. First, case data were insufficient for us to jointly infer serial interval and transmissibility. We therefore tested our results against a wide range of plausible assumptions about the serial interval of infection (online Technical Appendix). We also assumed that the market hazard increased and decreased in a simple stepwise manner (Figure 2). Local market density could also influence the size of spillover hazard and, hence, effectiveness of interventions (13). If the market hazard could be better characterized (e.g., by longitudinal serologic surveillance [14]), the accuracy of our estimates would probably be improved (9). When estimating $R_0$, we did not incorporate individual-level variability in transmission and potential superspreading events. However, the framework that we used can still produce reliable estimates of $R_0$ when a population contains superspreaders (9).
Conclusions
We found no evidence of reduced human-to-human transmission between the 2 waves. For a serial interval of 7 days, we estimated that $R_0$ increased in Zhejiang. Furthermore, the effectiveness of live bird market closures varied between regions; short-term closures were substantially less effective than interventions in other regions. These results emphasize the value of prompt and sustainable control measures during outbreaks of influenza A(H7N9) virus infection.

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<table>
<thead>
<tr>
<th>Region, outbreak wave</th>
<th>Total no. cases</th>
<th>$R_0$ (95% CrI)</th>
<th>Human-to-human transmission, no. cases (95% CrI)</th>
<th>Hazard reduction, % (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shanghai, first</td>
<td>29</td>
<td>0.32 (0.06–0.60)</td>
<td>11.0 (2.3–14.8)</td>
<td>99 (95–100)</td>
</tr>
<tr>
<td>Jiangsu</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>23</td>
<td>0.24 (0.03–0.69)</td>
<td>6.7 (2.0–12.2)</td>
<td>97 (80–100)</td>
</tr>
<tr>
<td>Second</td>
<td>26</td>
<td>0.13 (0.01–0.41)</td>
<td>2.9 (0.1–8.7)</td>
<td>NC</td>
</tr>
<tr>
<td>Zhejiang</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First</td>
<td>46</td>
<td>0.06 (0.00–0.25)</td>
<td>3.8 (0.8–12.4)</td>
<td>99 (97–100)</td>
</tr>
<tr>
<td>Second</td>
<td>92</td>
<td>0.35 (0.15–0.65)</td>
<td>32.5 (17.3–48.9)</td>
<td>97 (92–99)</td>
</tr>
<tr>
<td>Guangdong, second</td>
<td>103</td>
<td>0.16 (0.01–0.54)</td>
<td>16.7 (1.0–48.8)</td>
<td>73 (53–89)</td>
</tr>
</tbody>
</table>

*A serial interval of 7 days was assumed. For sensitivity analysis, see online Technical Appendix (http://wwwnc.cdc.gov/EID/article/21/5/14-1137-Techapp1.pdf). CrI, credible interval; NC, not calculated; $R_0$, reproduction number (average number of secondary cases generated by a typical infectious host in a fully susceptible population).
Fogarty International Center with the Science and Technology Directorate, Department of Homeland Security.

Dr. Kucharski is a research fellow in infectious disease epidemiology at the London School of Hygiene and Tropical Medicine. His research focuses on the dynamics of emerging infections and how population structure and social behavior shape disease transmission at the animal–human interface. Dr. Mills is a postdoctoral research associate in the Medical Research Council Centre for Outbreak Analysis and Modelling, Department of Infectious Disease Epidemiology, Imperial College London. Her research includes examination of human mobility patterns and their influence on disease transmission and the analysis of emerging epidemics.

References

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A History of the Emerging Infectious Diseases Journal

Dr. James Hughes and Dr. D. Peter Drotman discuss the history of the Emerging Infectious Diseases journal

http://www2c.cdc.gov/podcasts/player.asp?f=8635993
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Technical Appendix

Data

Using WHO reports and news reports, we collated a line list of reported influenza A/H7N9 cases between 19th February 2013 and 22nd April 2014. In this period there were 429 cases in total, split into two outbreak waves: 144 cases in the spring 2013 wave, which started on 19th February 2013, and 285 cases in the 2013/2014 wave, which began on 7th October 2013 (Figure 1A).

Transmission model

In the model, human cases could be generated in one of two ways [1]. First, they could come from exposure to live bird markets (LBMs). We defined \( h_A(t) \) to be the expected number of new human cases with onset on day \( t \) due to market exposure. We assumed this to be a step function with \( S \) steps and \( S - 1 \) change points. Cases could also come from human-to-human transmission. In our model, infected individuals had an infectiousness profile described by a Poisson distribution with mean \( \lambda \), the serial interval of the disease. The number of new infections generated by each infectious individual was dependent on \( R_0 \); because there were few total infections relative to the population size, we assumed that depletion of the susceptible pool did not affect the dynamics [2]. We defined \( h_H(t) \) to be the expected number of new human cases with onset on day \( t \) due to previous human cases,

\[
h_H(t) = \sum_{i=1}^{I_t} R_0 \frac{d_i}{(t - d_i)!} e^{-R_0} \]

where \( d_i \) was the time infected, hence \( t - d_i \) was the time since individual \( i \) was infected, and \( I_t \) was the total number of infected individuals at time \( t \).

We assumed that the number of new human cases on a given day, \( N_t \), followed a
Poisson distribution with mean $h_A(t) + h_H(t)$. Hence the expected number of cases on day $t$ was given by:

$$
m_t = \begin{cases} 
    h_A(t, \theta) & \text{if } t = 0; \\
    \min(k, t) \frac{R_0 N_{t+i} e^{-m_t} t!}{i!} + h_A(t, \theta) & \text{if } t > 0 
\end{cases}
$$

(2)

where $k$ is the maximum value the generation time distribution can take.

We used a likelihood-based approach to estimate epidemiological parameters. For a time series of observed human onsets $\{N_t\}_{t=1}^T$, the likelihood of our parameter set is [3]:

$$
L(\theta | N) = \prod_{t=0}^{T-1} \frac{N_t!}{N_{t+1}!} \frac{t!}{N_t!} e^{-m_t} N_t N_{t+1}
$$

(3)

The expected number of cases, $\mu_t$, depends both on the shape of the spillover hazard function, $h_A(t, \theta)$, and human-to-human transmission parameters, $R_0$ and $\lambda$. For five of the outbreaks, we assumed that the temporal change in market hazard followed a step-wise hazard function with three steps. The hazard function had five parameters: 3 parameters controlling the relative amplitude of spillover infections, and 2 controlling the timing of the increase and decrease in hazard. We constrained the timing of the drop based on reported market closure dates (Table S1). In the first wave, we assumed that market hazard decreased on a date within 7 days either side of 6th April 2013; in Shanghai, we assumed closure occurred on on 10th April 2013 ($\pm 7$ days) in Jiangsu and on 16th April 2013 ($\pm 7$ days) in Zhejiang. During the second wave, we assumed that hazard dropped on 26th January 2014 ($\pm 7$ days) in Zhejiang and on 16th February 2014 ($\pm 7$ days) in Guangdong. As we could not find reports of market closures in Jiangsu in 2014, we used a two-step hazard function for this outbreak, with only an increase in hazard. As well as market hazard, we estimated the basic reproduction number, $R_0$, for each of the six outbreaks.

For individual sets of parameter estimates, we used a fixed serial interval, $\lambda$. For patients with known exposure, the incubation period of H7N9 infection had a median of 6 days [4] and cluster reports suggest serial interval could be around 7-8 days (Table S2). In our main analysis, we therefore assumed a serial interval of 7 days. However, there is evidence that serial interval for seasonal influenza can be as low as 3-4 days [5]. During sensitivity analysis, we tested a
range of values from 3 to 9 days. We also adjusted for potential delays between symptom onset and case report based on the observed distribution of reporting delays (Figure S1). We assumed that the delay between onset and report followed a normal distribution: based on H7N9 cases reported up to 22nd April 2014, the reporting delay has a mean of 9.0 days and standard deviation of 3.3 days.

Model inference was performed using the full likelihood and Markov Chain Monte Carlo (MCMC) over the space of possible parameter values. We assumed that each parameter was positive, with a flat prior distribution.

The size distribution of human clusters can also be used to estimate the reproduction number of an infection [6]. However, estimation of $R_0$ from the total outbreak size distribution is implicitly conditional on the infection having so far failed to cause a large epidemic. This condition means it is not possible identify whether $R_0$ is greater or less than one, and hence whether it has pandemic potential [7]. Moreover, cluster size analysis does not account for change in exposure hazard over time, which can affect the accuracy of transmissibility estimates [8]. The method we here is robust to both of these issues: we did not make the implicit assumption that $R_0 < 1$, and we incorporated information on the temporal change in market hazard when estimating transmission potential.

**Calibration of animal-to-human component of model**

Before estimating $R_0$, we calibrated the market exposure component of the model without the presence of human-to-human transmission. LBMs were closed in Guangdong and Zhejiang in spring 2014. Previous work has shown that a 3 step hazard function performed best according the Bayesian Information Criterion (BIC) for the first wave [1]. We also found most support for 3 step function in 2014 (Table S3). Because we found no reports of closures in Jiangsu in 2014, we assumed a 2 step hazard function for this region.
February 2014 (± 7 days); in Jiangsu on 23rd March 2013 (± 7 days); and Zhejiang on 31st March 2013 (± 7 days). Dates as reported in public news sources, including Shanghai Daily, Xinhuanet, Guangzhou Daily, Anhui News, China Daily.

Cluster ID 1
- Shanghai
  - Father of ID310: Son of ID44 (parents had bought chickens from parents of ID44)
  - Daughter of ID284
  - Father of ID289
  - Daughter of ID286
  - Daughter of ID288
  - Father of ID289

Cluster ID 2
- Shandong
  - Father of ID127
  - Son of ID106
  - Daughter of ID120
  - Mother of ID310: Traveller, developed fever in Guangdong, Son of ID300. Unclear whether he also travelled.

Cluster ID 3
- Guangdong
  - Father of ID120
  - Mother of ID310
  - Son in law of ID129

Cluster ID 4
- Zhejiang
  - Father in law of ID144
  - Son in law of ID129

Cluster ID 5
- Shandong
  - Father of ID144
  - Son in law of ID129

Cluster ID 6
- Guangdong
  - Father of ID289
  - Father of ID284

Cluster ID 7
- Zhejiang
  - Father of ID289
  - Father of ID284

Cluster ID 8
- Hunan
  - Father of ID286
  - Daughter of ID288

Cluster ID 9
- Guangxi
  - Mother of ID310: Traveller, developed fever in Guangdong, Son of ID300. Unclear whether he also travelled.

Cluster ID 10
- Guangdong
  - Father of ID289
  - Father of ID284

Cluster ID 11
- Guangdong
  - Father in law of ID144

Cluster ID 12
- Zhejiang
  - Father in law of ID144

Cluster ID 13
- Shandong
  - Father of ID447

*Data from news sources (CIDRAP, Recombinomics, Xinhua Net, South China Morning Post) and journal papers [9, 10]. Case ID refer to the lineist IDs.
Technical Appendix Table 3. Comparison of different market hazard functions in the absence of human-to-human transmission

<table>
<thead>
<tr>
<th>Outbreak</th>
<th>Model</th>
<th>Likelihood</th>
<th>Parameters</th>
<th>BIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guangdong (2nd wave)</td>
<td>3 step</td>
<td>-150.0</td>
<td>5</td>
<td>326.7</td>
</tr>
<tr>
<td></td>
<td>4 step</td>
<td>-146.1</td>
<td>7</td>
<td>329.5</td>
</tr>
<tr>
<td></td>
<td>5 step</td>
<td>-141.9</td>
<td>9</td>
<td>331.8</td>
</tr>
<tr>
<td></td>
<td>6 step</td>
<td>-139.6</td>
<td>11</td>
<td>337.7</td>
</tr>
<tr>
<td></td>
<td>7 step</td>
<td>-140.2</td>
<td>13</td>
<td>349.6</td>
</tr>
<tr>
<td>Zhejiang (2nd wave)</td>
<td>3 step</td>
<td>-101.6</td>
<td>5</td>
<td>229.8</td>
</tr>
<tr>
<td></td>
<td>4 step</td>
<td>-98.0</td>
<td>7</td>
<td>233.3</td>
</tr>
<tr>
<td></td>
<td>5 step</td>
<td>-97.8</td>
<td>9</td>
<td>243.5</td>
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<tr>
<td></td>
<td>6 step</td>
<td>-95.4</td>
<td>11</td>
<td>249.3</td>
</tr>
<tr>
<td></td>
<td>7 step</td>
<td>-96.3</td>
<td>13</td>
<td>261.7</td>
</tr>
</tbody>
</table>

Technical Appendix Table 4. Estimated change in $R_0$ between 2014 and 2013 for influenza A/H7N9 outbreaks in Jiangsu and Zhejiang provinces

<table>
<thead>
<tr>
<th>Outbreak</th>
<th>Serial interval</th>
<th>$R_{0, 2014} - R_{0, 2013}$ (95%CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jiangsu</td>
<td>3</td>
<td>-0.14(-0.73-0.48)</td>
<td>0.606</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>-0.08(-0.56-0.50)</td>
<td>0.721</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>-0.10(-0.61-0.23)</td>
<td>0.581</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>-0.01(-0.45-0.48)</td>
<td>0.957</td>
</tr>
<tr>
<td>Zhejiang</td>
<td>3</td>
<td>0.25(-0.50-0.72)</td>
<td>0.448</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.27(-0.16-0.62)</td>
<td>0.181</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>0.28(-0.01-0.61)</td>
<td>0.045</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>0.20(-0.04-0.44)</td>
<td>0.020</td>
</tr>
</tbody>
</table>

*Two-sided p-values are given for null hypothesis that $R_0$ is the same in both outbreak waves.

Technical Appendix Table 5. Estimated difference in market hazard reduction between Guangdong and other geographic regions

<table>
<thead>
<tr>
<th>Region</th>
<th>Outbreak wave</th>
<th>Serial interval</th>
<th>Difference in hazard reduction</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shanghai</td>
<td>1st</td>
<td>3</td>
<td>0.28(0.10-0.59)</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>0.26(0.09-0.49)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>0.26(0.09-0.46)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9</td>
<td>0.25(0.09-0.45)</td>
<td>0.002</td>
</tr>
<tr>
<td>Jiangsu</td>
<td>1st</td>
<td>3</td>
<td>0.25(-0.02-0.56)</td>
<td>0.059</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>0.23(-0.02-0.46)</td>
<td>0.061</td>
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<tr>
<td></td>
<td></td>
<td>7</td>
<td>0.24(0.01-0.45)</td>
<td>0.044</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9</td>
<td>0.23(-0.01-0.43)</td>
<td>0.053</td>
</tr>
<tr>
<td>Zhejiang</td>
<td>1st</td>
<td>3</td>
<td>0.29(0.12-0.59)</td>
<td>0.001</td>
</tr>
<tr>
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<td>5</td>
<td>0.27(0.10-0.49)</td>
<td>0.002</td>
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<td>7</td>
<td>0.26(0.09-0.46)</td>
<td>0.002</td>
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<tr>
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<td></td>
<td>9</td>
<td>0.26(0.09-0.45)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>2nd</td>
<td>3</td>
<td>0.27(0.09-0.58)</td>
<td>0.007</td>
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<tr>
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<td>5</td>
<td>0.25(0.08-0.47)</td>
<td>0.005</td>
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<tr>
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<td></td>
<td>7</td>
<td>0.24(0.07-0.45)</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9</td>
<td>0.23(0.07-0.43)</td>
<td>0.006</td>
</tr>
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</table>

*Two-sided p-values are given for null hypothesis that there is no difference in hazard between Guangdong and specified region.
Technical Appendix Figure 1. Distribution of delay between case onset and report. We fitted a normal distribution (blue line) to influenza A/H7N9 cases reported between 19th February 2013 and 17th April 2014 (grey bars).
Technical Appendix Figure 2. Estimates of basic reproduction number in different regions as serial interval, $\lambda$, varies. Blue point, median of posterior estimate; blue line, 95% credible interval.
**Technical Appendix Figure 3.** Estimated human-to-human cases in different regions as serial interval, $\lambda$, varies. Dashed line, total reported cases; green point, estimated non-index cases; green line, 95% credible interval. (A) Shanghai (1st outbreak wave), (B) Jiangsu (1st wave), (C) Jiangsu (2nd wave), (D) Guangdong (2nd wave), (E) Zhejiang (1st wave), (F) Zhejiang (2nd wave).
Technical Appendix Figure 4. Estimates of reduction in market hazard in different regions as serial interval, $\lambda$, varies.