BRIEF ORIGINAL CONTRIBUTION

Estimation of the incubation period distribution of human infections with avian influenza A (H7N9) virus

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Running head: Incubation period of influenza A(H7N9) infection

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

ML, LF, HJ, JZ, YC, YQ, QL and HY collected data. VV and BJC analyzed the data. VV wrote the first draft. All authors interpreted the results, edited the manuscript and approved the final version.

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Abstract

A novel avian influenza A(H7N9) virus emerged in China in early 2013 and caused severe disease in humans, with infections occurring most frequently after recent exposure to live poultry. The incubation period distribution is of interest to epidemiologists and public health officials, but estimation of the distribution is complicated by interval censoring of exposures. Imputation of the midpoint of intervals was used in some early studies, resulting in estimates of mean incubation approximately 5 days. In this study, we estimated the incubation period distribution of human infections with influenza A(H7N9) using exposure data available for 229 laboratory-confirmed patients from mainland China. A non-parametric model (Turnbull) and several parametric models (Weibull, gamma, lognormal, log-logistic, exponential) were fitted to the data accounting for the interval censoring in some exposures. The Akaike Information Criterion was used to compare parametric models. The mean incubation period was 3.4 days (95% confidence interval: 3.0-3.7 days) and the variance was 2.9 days for the best-fitting parametric model (Weibull) and very similar for the non-parametric Turnbull estimate. Under the Weibull model the 95th percentile was 6.4 days (95% confidence interval: 5.9-7.0 days). The midpoint approximation for interval-censored exposures led to overestimation of the mean incubation period. Public health observation of potentially exposed persons for 7 days after exposure would be appropriate.

Key words: influenza A, H7N9, incubation, human

Abbreviations:

H7N9	influenza A(H7N9)
AIC	Akaike's Information Criterion

Introduction

The incubation period of a viral infectious disease is defined as the delay from viral infection to the onset of illness (1). In early 2013 a novel avian influenza A(H7N9) (H7N9 thereafter) virus emerged in China and caused human infections, some of which were associated with severe disease and death (2). The majority of laboratory-confirmed human cases of H7N9 virus infection reported recent exposure to live poultry, typically in the setting of live poultry markets in urban area (3). These defined occasions for exposure have permitted estimation of the incubation period distribution. The incubation period is particularly important for defining the period of public health observation of exposed contacts of confirmed H7N9 cases, with the upper 95th percentile of the estimated incubation period distribution considered a reasonable threshold for the duration of such observation, while even higher percentiles of the distribution might be chosen in some circumstances. Various estimates of the incubation period distribution for human infections with H7N9 virus have been published (4–9). The objective of our study was to describe alternative approaches for estimation of the incubation period, and to identify reasons for discrepancies between different published estimates.

Materials and Methods

Sources of data

All laboratory-confirmed human cases of H7N9 virus infection were notified to the Chinese Center for Disease Control and Prevention and relevant clinical and epidemiological data was recorded in a electronic database (4). Data extracted for this study included age, sex,

geographical location, and dates of exposure, illness onset and hospital admission. In the majority of cases the information on exposure was recorded as intervals of 2 or more days during which infection was thought to have occurred rather than exact dates of presumed infection.

Statistical analyses

For each case *i*, if infection occurred at time X_i and symptom onset occurred at time Z_i, the incubation period is defined as $T_i = Z_i - X_i$. However, estimation of the incubation period is often complicated because infection events cannot be directly observed. If patient *i,* reported that infection most likely occurred in a period of exposure between times L_i and U_i, where $L_i \leq X_i \leq U_i$, the incubation time therefore is bounded by the interval ($Z-U_i$, $Z- L_i$). These data are a special type of survival data, and a natural approach would be to "reverse" the time axis setting Z as the origin and X as the outcome time. "Reversing" the time axis is valid only when the density function for infection is uniform in chronologic time (10–12). This condition should be reasonable here in the setting of H7N9, with each exposure interval being relatively short. Moreover, in order to allow for the coarseness of exposure data reported on a daily basis, we added 0.5 to each upper bound and subtracted 0.5 from each lower bound (13).

A subset of cases reported single dates of exposure of 7, 8, 9 or 10 days. On further investigation of the original case notification forms or the medical records, it was found that an exact date of exposure at 7 days actually indicated exposure at some uncertain time in the previous week, i.e. an incubation period between 0 and 7 days. To account for the

possibility that these longer single exposure times were inaccurate, we explored the sensitivity of incubation period distribution estimates by extending the potential period of infection from 0 to 3 days after the single-exposure date.

The most basic approach to deal with interval-exposure data is to impute the infection dates as the midpoint of any exposure intervals, which then permits empirical estimation (13). However this approach may lead to overestimation of the incubation period distribution, which tends to be right-skewed (14). The "gold standard" approach for non-parametric estimation of a distribution based on interval-censored data is the generalized non-parametric maximum likelihood estimator extension of the Kaplan-Meier estimator developed by Turnbull (15), which simplifies to the empirical distribution function if all exposure times are exactly observed. The incubation period can often be appropriately characterized by a parametric model, which can easily accommodate interval-censored data. The gamma (16), Weibull (4), lognormal (10), exponential (17), and log-logistic (18) distributions have previously been used to describe incubation period distributions. Comparison between models may be made qualitatively through visual comparison with a non-parametric estimate, and quantitatively by a metric such as Akaike's Information Criterion (AIC) (19). In this study, the incubation period distribution was estimated using first the interval-censored data and compared between the different parametric models suggested above and the Turnbull model (16). For the parametric models, 95% confidence intervals for mean incubation times and 95th percentiles of the incubation distribution were estimated using a parametric bootstrap with 10,000 resamples (20). Secondly, the incubation period was also estimated based on the empirical distribution of incubation

times with the midpoint approximation used for interval-censored exposures. We also explored the precision of estimates of the mean and 95th percentile of the incubation period distribution based on cumulative data available at various calendar times. All analyses presented here were conducted using R version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria) and the packages "Interval" and "survival".

Results

As of 5 August 2014, a total of 438 laboratory-confirmed cases of H7N9 were reported in mainland China, of whom 229 had available data on exposure dates. The median age of the 229 cases was 58 years old, 68% were male, and 57% lived in urban areas, which was similar to all 438 confirmed cases. The data on exposure intervals are shown in **Web Figure 1**, and 104/229 (45%) had single exposure data while the remainder reported exposure intervals of 2 days or longer. Among the 104 cases with single exposure dates, 31 had single exposures at 7, 8, 9 or 10 days.

First, we estimated the incubation period distribution for the crude original data without accounting for problems of exact exposure dates (**Table 1**). Using the gamma parametric model (best AIC value), the estimated mean was 4.5 days, the variance 11.1 days and the 95th percentile 11.0 days. Under the midpoint approximation for interval-censored exposures using the original data the mean was 5.5 days and the 95th percentile was 8 days.

Then, we estimated the incubation period distribution using the modified data. **Figure 1A** compares the various fitted parametric models for the incubation period distribution with the non-parametric maximum likelihood estimator. Visual inspection of the parametric curves against the Turnbull estimate in **Figure 1A** confirms that all of the two-parameter distributions provided reasonable fits, while the exponential distribution was slightly inferior. According to the value of AIC (**Table 1**), the best-fitting parametric distribution was the Weibull (AIC=327), while the gamma had a very similar fit (AIC=328) followed by the lognormal (AIC=337) and log-logistic distributions (AIC= 347). For the non-parametric Turnbull estimate, the mean was 3.4 days (95% confidence interval: 1.5-6.7 days), the variance was 2.9 days and the 95th percentile was 6.2 days. For the fitted Weibull distribution (**Figure 1C**), the mean and variance were 3.4 days (95% confidence interval: 3.0-3.7 days) and 2.9 days respectively, and the 95th percentile was 6.5 days.

In **Figure 1B**, the midpoint approximation clearly led to overestimation of the incubation period distribution compared to the non-parametric Turnbull estimate and the Weibull model, and the mean of the empirical distribution under the midpoint approximation was 5.5 days with a 95th percentile of 6.0 days.

We reviewed published estimates of the incubation period distribution, and found generally higher estimates from studies that used the midpoint approximation (**Table 2**). Early estimates based on restricted sample size data and median method estimation provided the longest incubation times (5,6), compared to other studies based also on restricted sample size but with single exposure data (7,8). Our results estimated with interval-censored data

are consistent with estimates from larger sample size studies, with a shorter incubation time (3,4,21), while Gao et al. estimated a higher median incubation time based on cases with single exposures (9).

We estimated the mean and the 95th percentile of the incubation period distribution at various times since the beginning of the epidemic using the Weibull distribution (**Figure 2**). Both estimates were steady over time, with similar point estimates after late April 2013, and increasing precision as sample size increased. This analysis did not account for delays from illness onset to notification which were approximately 1-3 weeks.

To examine the sensitivity of our results to inclusion of adjustments for patients with single-exposure data, we fitted the different distributions to the data using a different correction for exact exposure dates by extending the potential period of infection from 0 to 3 days after and before the single-exposure date, and we observed similar results (**Web Table 1**).

Discussion

Using all available data on exposures from 229 patients with laboratory-confirmed H7N9 virus infection, we estimated that the mean incubation period was around 3.4 days, and 95% of infections led to symptoms within 6.5 days. This latest estimate of the incubation period distribution is consistent with some previous estimates (mean: 3.1 days (4), median: 2.0 days (7) and median: 2.5 days (rural)/4.0 days (urban) (8)) based on exposure data but somewhat shorter than some other estimates (median: 6.0 days (5), median: 7.5 days (6)

and median: 5.0 days (9)) (**Table 2**). These studies with longer incubation periods led the public health authorities to extend the period of medical surveillance or quarantine for close contacts of confirmed cases from 7 days initially to 10 days (22,23). These discrepancies in estimates could be due to differences in estimation methods and handling of raw data. The midpoint method used in some studies was shown to overestimate the incubation period distribution (**Figure 1B**), while cleaning the raw data on longer exposures (**Web Figure 1**) also led to shorter estimates. Our estimates are concordant with smaller sample size studies based first on parametric methods with interval exposure data (4), and also on inference from ecological data, based on the impact of live poultry market closures in reducing incidence of human infections (3,21). Moreover, we showed that our estimates were steady over time, and reasonable estimates were available based on data from 50 cases (**Figure 2**). Our results suggest that incubation periods of 8-10 days are unlikely, while medical surveillance for exposed persons would be appropriate for no more than 7 days or 8 days since 97% and 99% of cases respectively would present symptoms within those periods. The Chinese Center for Disease Control and Prevention and the World Health Organization now recommend a 7-day observation period for exposed persons (24,25), although some other organizations continue to recommend 10 days (22,23).

Similar observations between midpoint imputation and parametric estimates were already observed in the case of influenza A(H5N1). Despite the small number of available data, Huai et al. (26) reported in 2008 an overall median incubation period of 5 days (range: 2-9.5 days) for a cohort of 24 patients using midpoint imputation whereas Cowling et al. (4) reported more recently a mean incubation period of 3.3 days (95% confidence interval: 2.7-

3.9 days) for a cohort of 41 patients accounting for interval censoring. Although midpoint imputation can provide practical estimates during the early stages of an emerging epidemic with potentially scarce data, this similar difference shows the advantage of assessing the incubation period distribution with appropriate techniques.

Our study presents some limitations, as only a subset of the patients registered in the Chinese Center for Disease Control and Prevention database had available data on potential exposures (229/438; 52%). Moreover, a substantial number of patients reported wide exposure intervals (**Web Figure 1**). With very small sample size it would be difficult to use parametric or non-parametric methods to estimate the incubation period distribution with accuracy and precision, and one of the priorities in an emerging infection is comprehensive investigation of the early cases to define the epidemiologic parameters.

In conclusion, for emerging infectious diseases, accurate and precise estimates of the distribution of incubation times are necessary to advise public health policy and to specify case definitions. Robust inference accounting for interval censoring of exposures is recommended when estimating the incubation period distribution (10).

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Figure Legends

Figure 1. **Parametric and non-parametric estimates of the incubation period distribution for human infections with avian influenza A(H7N9) virus based on data from 229 laboratory-confirmed cases with available data on exposure times.** Panel A: Comparison of alternative parametric (Lognormal, Gamma, Weibull, Exponential and Log-logistic) models with the non-parametric maximum likelihood estimator (Turnbull). For the non-parametric estimate (Turnbull), gray rectangles show intervals where the estimate was not unique. Panel B: comparison of the non-parametric maximum likelihood estimator (Turnbull) and best fitting parametric model (Weibull) with the empirical distribution using a midpoint approximation for interval-censored exposures (Midpoint). Panel C: Probability density function of the Weibull distribution used to estimate the incubation period distribution of the 229 cases. The solid black line represents the fitted Weibull distribution and the grey lines represent the uncertainty range estimated by bootstrapping with 1,000 resamples.

Figure 2. Estimation of mean incubation time and 95th percentile estimated based on cumulative data available at different times in the epidemic, plotted by calendar time of symptom onset. Panel A: The black solid lines show the mean incubation period over time and the black dotted line shows the 95th percentile of the incubation period distribution, while gray solid and dotted lines show the corresponding 95% confidence intervals, to be read off of the left-hand y-axis. Panel B: Cumulative number of cases with available data on exposure.

Web Figure 1. Raw data on exposures, and description of the adjustment of longer single exposures for 31/229 patients (14%) included in the dataset. The scale is inverted, where 0 corresponds to the day of illness onset for each patient, and higher numbers on the x-axis indicate earlier exposures. The red lines show the patients with single exposures reported at 7 days or longer, represented with red points, and the adjustments made prior to analysis (red dotted lines).

Table 1. Alternative parametric estimates of the mean of the incubation distribution based on all available exposure data (N=229) of influenza A(H7N9) cases reported in mainland China from February 2013 through August 2014..

	Mean (days)		95th percentile (days)		99th percentile (days)		
Distribution	**Estimate**	**95% CI[b]**	**Estimate**	**95% CI[b]**	**Estimate**	**95% CI[b]**	**AIC**
Modified data[a]							
Weibull	3.4	(3.0 - 3.7)	6.5	(5.9 - 7.1)	8.0	(7.3 - 8.8)	326
Gamma	3.3	(2.6-5.9)	8.8	(7.0 - 15.1)	12.8	(10.4 - 21.7)	328
Lognormal	3.2	(2.9 - 3.6)	7.2	(6.4 - 7.9)	10.8	(9.5 - 11.9)	336
Log-logistic	3.4	(3.0 - 3.9)	7.7	(6.8 - 8.5)	13.4	(11.6 - 15.3)	347
Exponential	3.2	(3.0 - 3.5)	9.6	(8.9 - 10.3)	14.8	(13.7 - 15.8)	410
Original data							
Weibull	4.4	(4.0 - 4.9)	8.9	(8.3 - 9.5)	11.2	(10.3 - 12.0)	537
Gamma	4.5	(2.8 - 16.2)	11.0	(7.2 - 37.0)	15.6	(10.4 - 51.1)	535
Lognormal	4.2	(3.8 - 4.7)	10.2	(9.2 - 11.1)	16.0	(14.1 - 17.7)	561
Log-logistic	4.7	(4.2 - 5.2)	11.2	(10.0 - 12.4)	20.9	(17.8 - 24.0)	571
Exponential	4.1	(3.8 - 4.4)	12.2	(11.3 - 13.1)	18.7	(17.3 - 20.2)	617

[a]Modified data are the data where exact reported exposures of 7, 8, 9 or 10 days were modified to exposures on [0,10], [0,11], [0,12] or [0,13] days, respectively.

[b] 95% CIs calculated by bootstrapping with 10,000 repetitions.

AIC: Akaike Information Criterion.

CI: Confidence interval

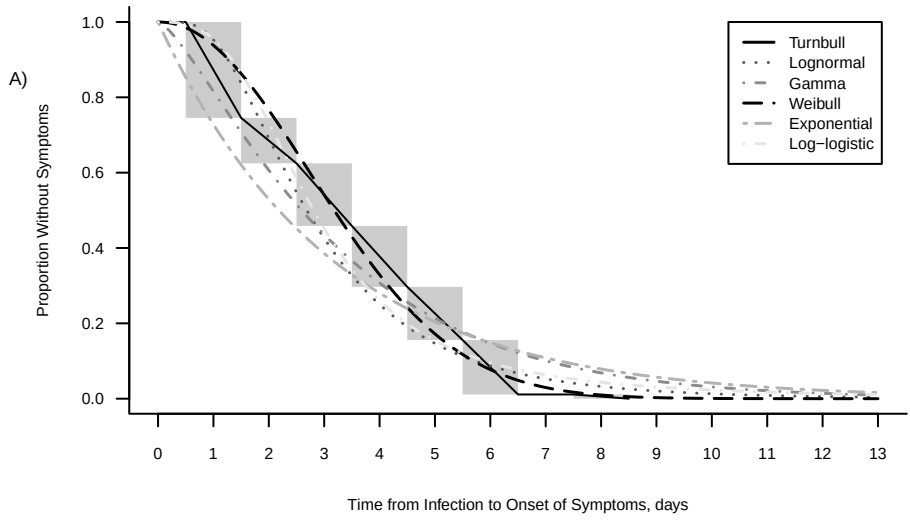
Table 2. Published estimates (2013-2014) of the incubation period of human infections with avian influenza A(H7N9) virus.

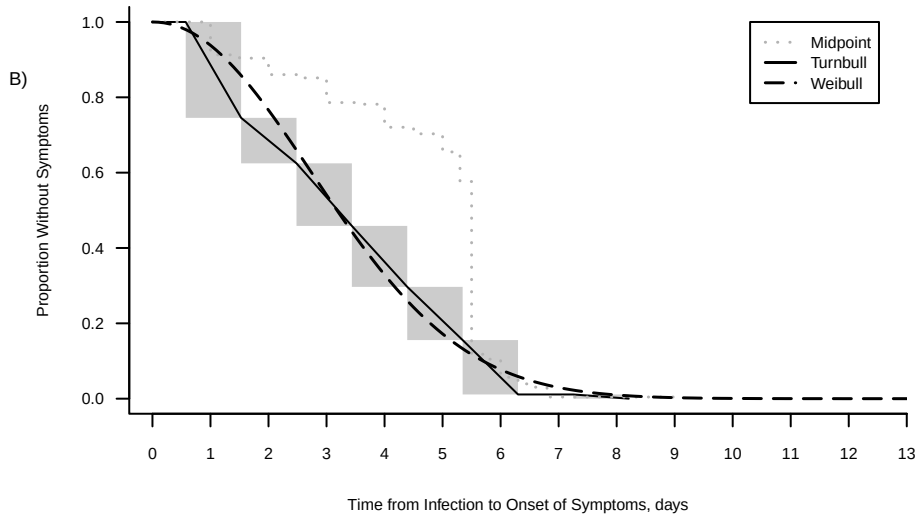
First author and reference	Patients analyzed	Method	Mean	95% confidence interval for mean	Median	Range
Current study	229	Parametric	3.4 days	3.3 - 3.6 days	-	-
Wu, 2014 (21)	NA[a]	Parametric	3.4 days	2.2 – 5.0 days	-	-
Yu, 2014 (3)	NA[a]	Parametric	3.3 days	1.4 - 5.7 days	-	-
Cowling, 2013 (4)	32	Parametric	3.1 days	2.6 - 3.6 days	-	-
Gao, 2013 (9)	62	Midpoint	-	-	5.0 days	2 - 8 days
Gong, 2014 (7)	30	Midpoint	-	-	2.0 days	-
Sun, 2014 (8)	16[b] 30[c]	Midpoint	- -	- -	2.5 days[b] 4.0 days[c]	- -
Li, 2014 (5)	23	Midpoint	-	-	6.0 days	1 - 10 days
Huang, 2014 (6)	22	Midpoint	-	-	7.5 days	2 - 12.5 days

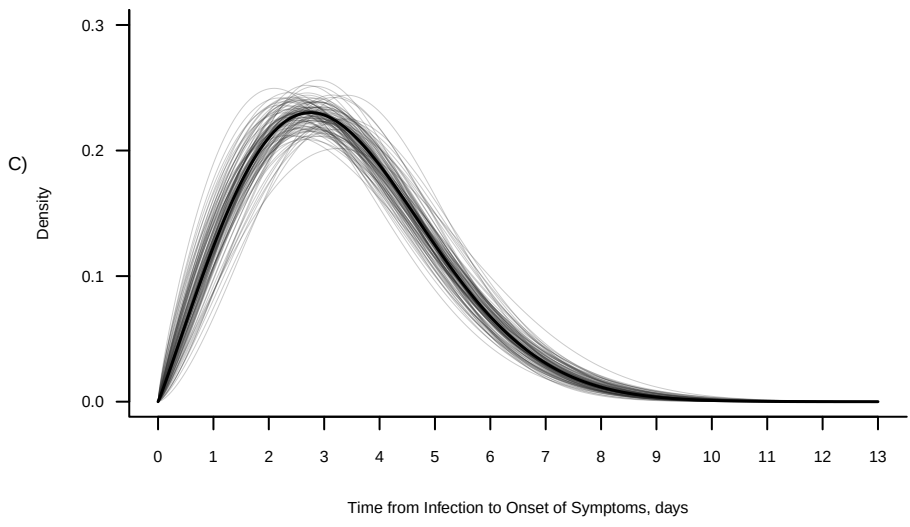
[a]*The Yu et al. and Wu et al. studies estimated the incubation period distribution indirectly, via the delay in impact of live poultry market closures on incidence of human infections in urban areas in the first wave in 2013 and the second wave in 2013-14, respectively. These studies did not include any data on exposure dates for individual cases.*

[b] *Rural H7N9 cases*

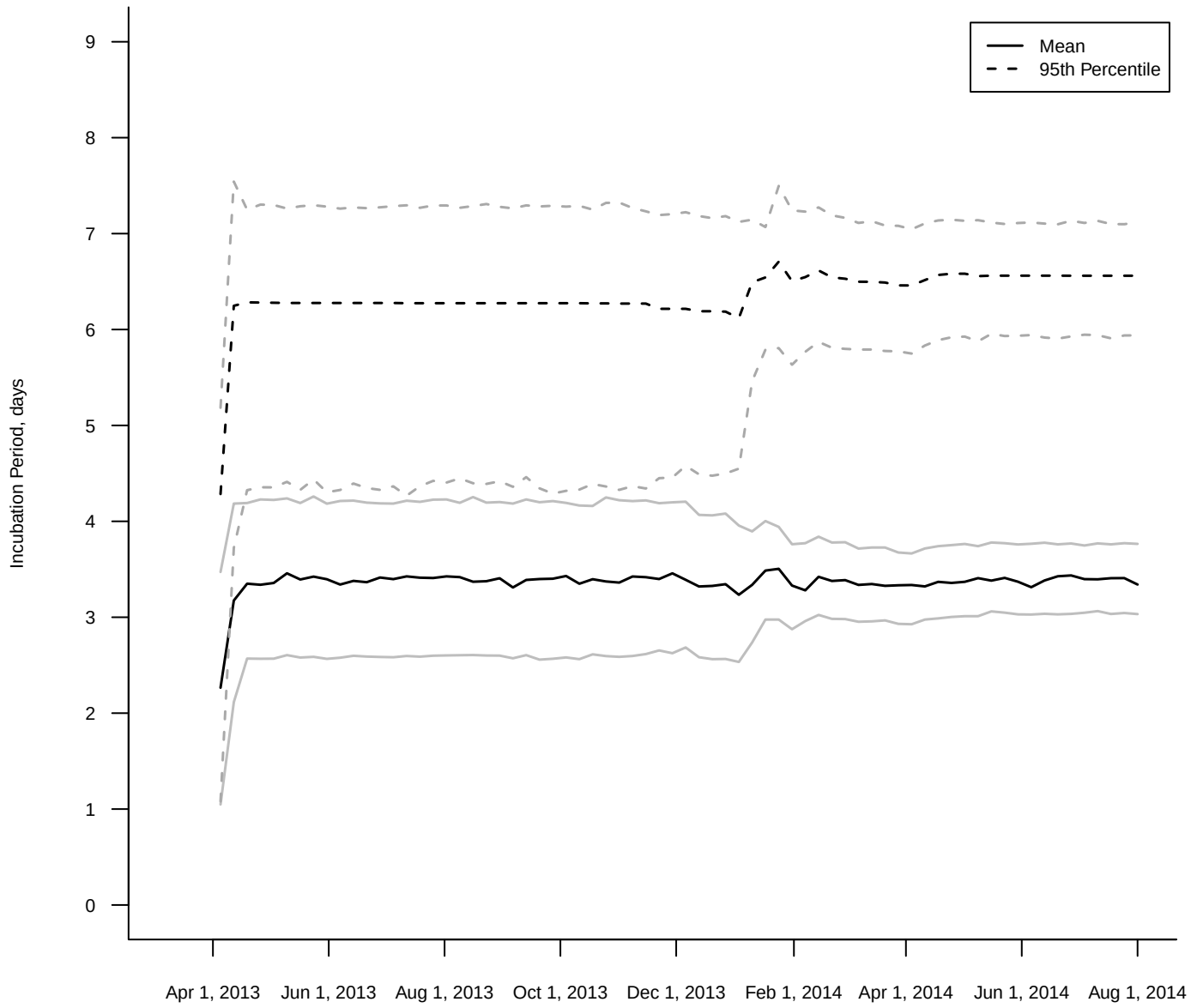
[c] *Urban H7N9 cases*


A)
Proportion Without Symptoms
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
6
7
8
9
10
11
12
13
Time from Infection to Onset of Symptoms, days
Turnbull
Lognormal
Gamma
Weibull
Exponential
Log−logistic

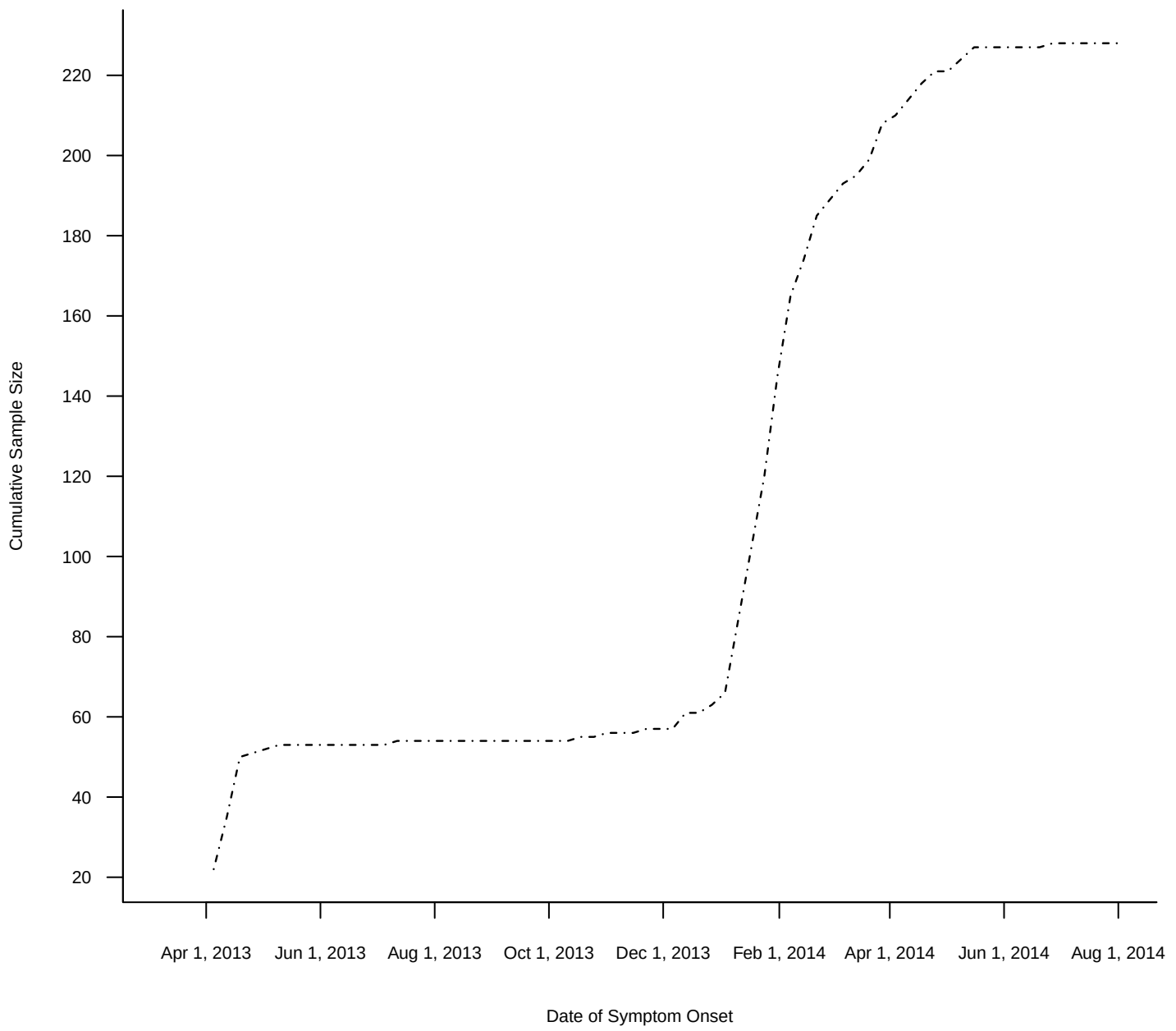

B)
Proportion Without Symptoms
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
6
7
8
9
10
11
12
13
Time from Infection to Onset of Symptoms, days
Midpoint
Turnbull
Weibull

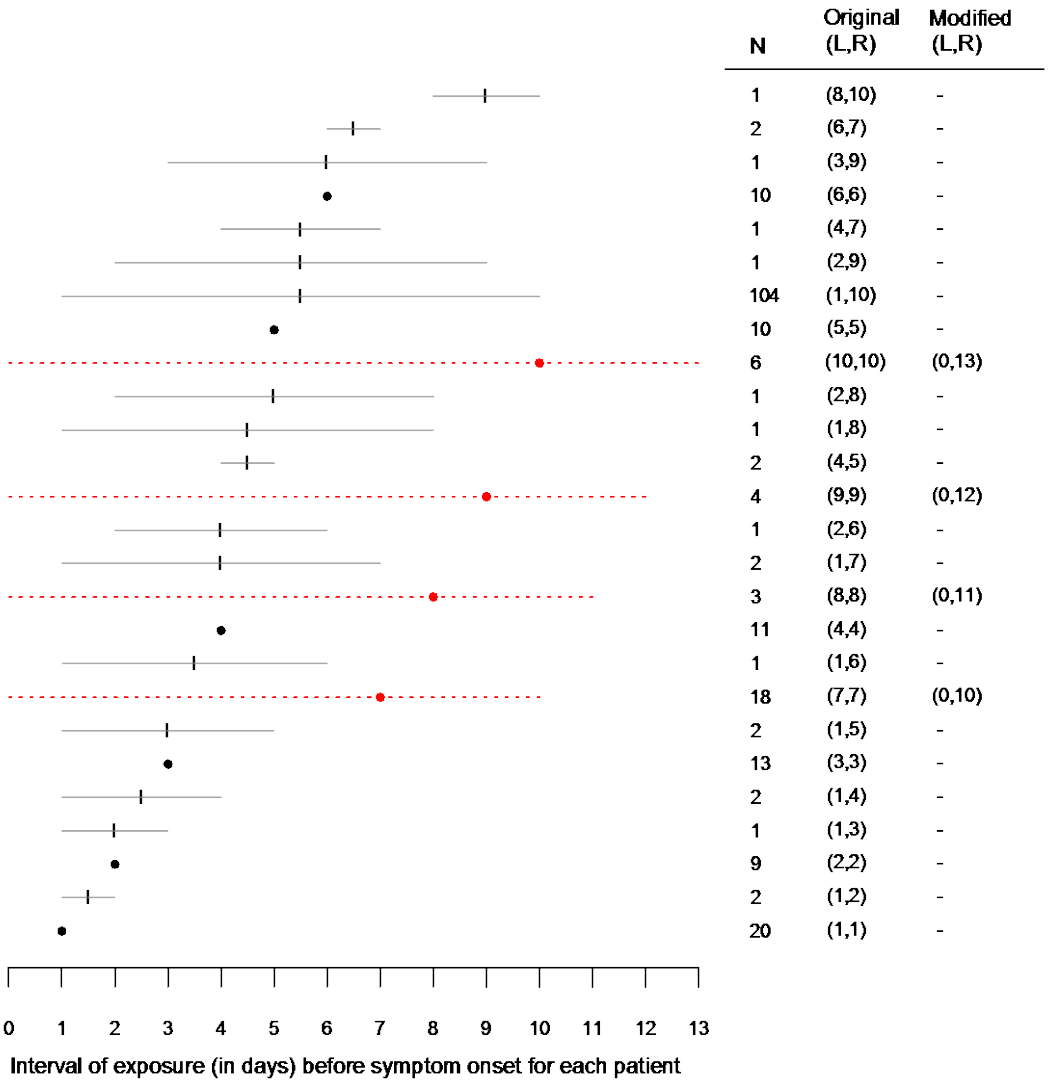

C)
Density
0.3
0.2
0.1
0.0
0
1
2
3
4
5
6
7
8
9
10
11
12
13
Time from Infection to Onset of Symptoms, days

A)


Mean
95th Percentile
Incubation Period, days
0
1
2
3
4
5
6
7
8
9
Apr 1, 2013
Jun 1, 2013
Aug 1, 2013
Oct 1, 2013
Dec 1, 2013
Feb 1, 2014
Apr 1, 2014
Jun 1, 2014
Aug 1, 2014
Date of Symptom Onset

B)


Cumulative Sample Size
20
40
60
80
100
120
140
160
180
200
220
Apr 1, 2013
Jun 1, 2013
Aug 1, 2013
Oct 1, 2013
Dec 1, 2013
Feb 1, 2014
Apr 1, 2014
Jun 1, 2014
Aug 1, 2014
Date of Symptom Onset



Web Figure 1. Raw data on exposures, and description of the adjustment of longer single exposures for 31/229 patients (14%) included in the data set. The scale is inverted, where 0 corresponds to the day of illness onset for each patient, and higher numbers on the x-axis indicate earlier exposures. The red lines show the patients with single exposures reported at 7 days or longer, represented with red points, and the adjustments made prior to analysis (red dotted lines).

Web Table 1. Alternative parametric estimates of the mean of the incubation distribution based on all available data (N=229).

	Mean (days)		95th percentile (days)		99th percentile (days)		
Distribution	**Estimate**	**95% CI[1]**	**Estimate**	**95% CI[1]**	**Estimate**	**95% CI[1]**	**AIC**
Modified data*							
Weibull	4.1	(3.7 - 4.5)	7.9	(7.2 - 8.5)	9.7	(8.8 - 10.5)	400
Gamma	4.0	(3.6-4.4)	8.4	(7.7 - 9.0)	11.1	(10.2 - 12.1)	406
Lognormal	4.0	(3.6 - 4.4)	9.1	(8.3 - 9.9)	13.8	(12.3 - 15.5)	422
Log-logistic	4.3	(3.9 - 4.7)	9.8	(8.8 - 10.8)	17.4	(14.8 - 20.2)	429
Exponential	3.9	(3.6 - 4.2)	11.7	(10.8 - 12.6)	17.8	(16.6 - 19.4)	489
Without exact exposure dates (7, 8, 9 and 10 days, N=198)							
Weibull	3.4	(3.0 - 3.7)	6.5	(5.9 - 7.1)	8.0	(7.2 - 8.8)	326
Gamma	3.3	(2.9 - 3.7)	6.8	(6.1 - 7.4)	9.0	(8.1 - 9.9)	328
Lognormal	3.3	(2.9 - 3.6)	7.3	(6.5 - 8.0)	10.9	(9.6 - 12.2)	314
Log-logistic	3.5	(3.0 - 3.9)	7.8	(6.9 - 8.7)	13.8	(11.8 - 15.9)	345
Exponential	3.3	(3.0 - 3.5)	9.8	(9.1 - 10.5)	15.1	(13.9 - 16.1)	403

**Modified data are the data where exact reported exposures of 7, 8, 9 or 10 days were modified to exposures on [4,10], [5,11], [6,12] or [7,13] days, respectively.*
[1] 95% CIs calculated by bootstrapping with 10,000 repetitions.
AIC: Akaike Information Criterion.