On a Statistical Transmission Model in Analysis of the Early Phase of COVID-19 Outbreak

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Journal club presentation

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COVID-19

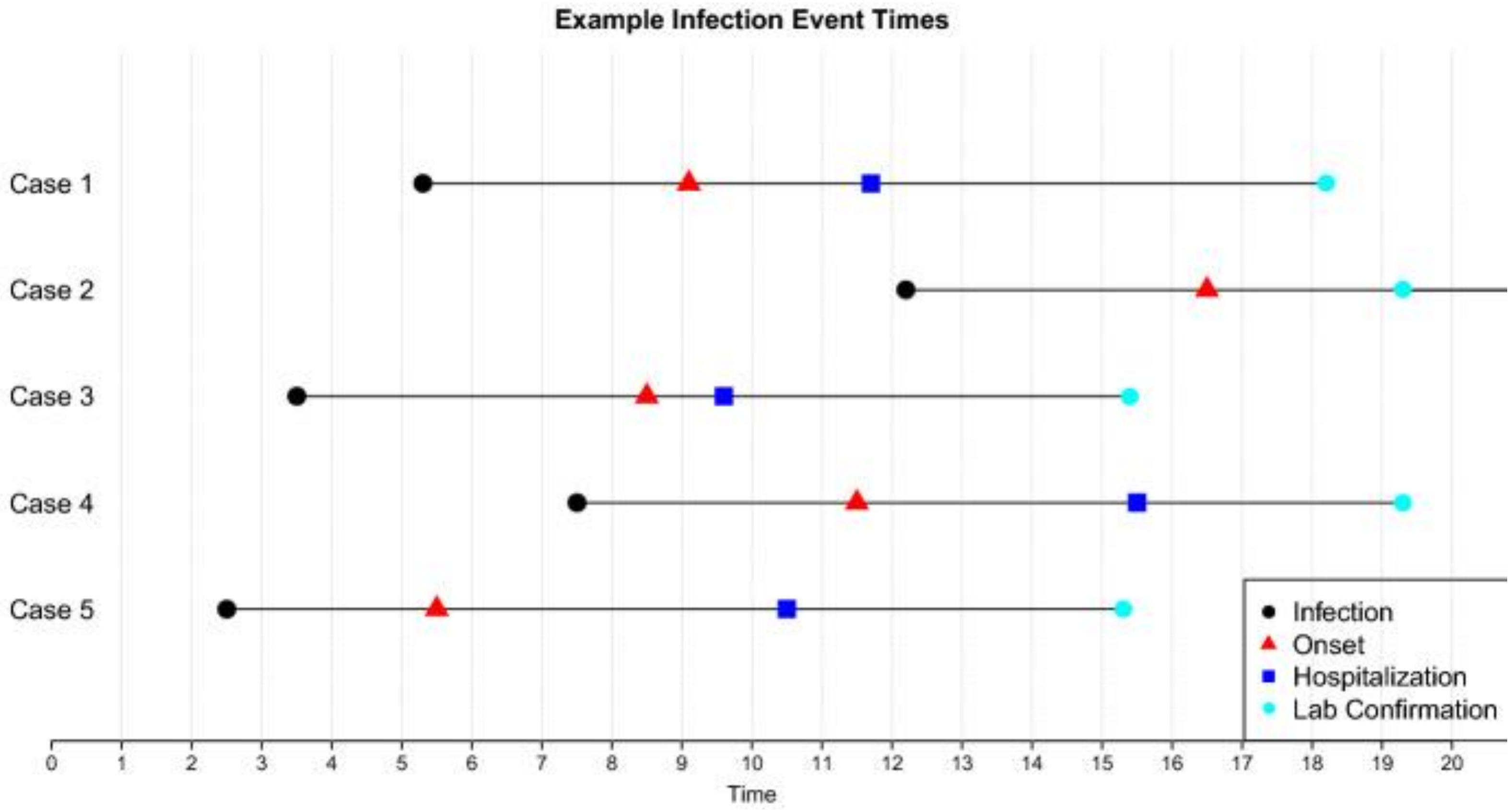
- Disease caused by novel coronavirus (SARS-Cov2)
- Outbreak first reported on December 2019 and lockdown measures were immediately imposed to contain the spread of the virus
- Greatest transmission rate among all human coronaviruses (i.e. SARS-CoV & MERS-CoV)
- In the early stages of the outbreak, it was important to understand the transmissibility of the outbreak

R_0

- Many studies provide crucial information for establishing transmission models to estimate the basic reproduction number (R_0) of COVID-19 (measure of transmission for infectious diseases)
- R_0: average number of secondary cases in an uninfected population that a diseased person would infect during their infectious window
- Estimated R_0's from initial models were generally greater than 2 with values as high as 3.8 for SARS-CoV2
- In this paper, a Poisson transmission model was fitted and evaluated and R0 values were computed

Explanation of data structure

Hypothetical example of case event time review and contact tracing process



Explanation of Data Structure

Define some variables:

For each infected individual i, i = 1,...,N, let:
$\hat{t}_i$: corresponding infection time
$\tilde{t}_i$: symptom onset time
$\bar{t}_i$: case confirmation time
where $\hat{t}_i < \tilde{t}_i < \bar{t}_i$

Incubation period $(\hat{t}_i, \tilde{t}_i)$: time to develop symptoms after being infected

Assumption of Disease Natural History

- Exact infection time is difficult to determine, hence we need a reasonable **assumption** of the incubation period distribution:

$$\text{beta-distributed on } (Inc_{min}, Inc_{min} + \Delta)$$

- The probability of observing symptom onset at t given some infection time is,

$$p_{\text{inc}}(t \mid \hat{t}) = f_{\text{beta}}\left(\frac{t-\hat{t}-\text{Inc}_{\text{min}}}{\Delta_{\text{inc}}}, |, \alpha_{\text{inc}}, , , \beta_{\text{inc}} \right),$$
$$t \in (\hat{t} + \text{Inc}_{\text{min}}, \hat{t} + \text{Inc}_{\text{min}} + \Delta_{\text{inc}}),$$

Assumption of Disease Natural History

- We also **assumed** that the latent period (time length between infection and start of infectiousness) is the same as the incubation period
- The relative infectivity during the infectious period $(\tilde{t}, \tilde{t} + \Delta_{\text{inf}})$ is,

$$p_{\text{inf}}(t \mid \tilde{t}) = f_{\text{beta}}\left(\frac{t-\tilde{t}}{\Delta_{\text{inf}}}, |, \alpha_{\text{inf}}, , , \beta_{\text{inf}}\right), \quad t \in (\tilde{t}, \tilde{t} + \Delta_{\text{inf}})$$

Poisson Transmission Model for Daily Disease Onset Record

- Let γ : the average hazard of secondary infection along the infectious period
- The overall infection hazard from all infected cases in the community is

$$\hat{\lambda}(t) = \sum_{i:t\in[\tilde{t}_i,\tilde{t}_i+\Delta_{\inf}]} p_{\inf}(t|\tilde{t}_i)\,\Delta_{\inf}\gamma$$

- The intensity of disease onset at time t is

$$\tilde{\lambda}(t) = \int_{t-\mathrm{Inc}_{\max}}^{t-\mathrm{Inc}_{\min}} \hat{\lambda}(\tau)\,p_{\mathrm{inc}}(t|\tau)\,\mathrm{d}\tau.$$

Poisson Transmission Model for Daily Disease Onset Record

Let $\tilde{\Lambda}(t) = \int_{s-1}^{s} \tilde{\lambda}(s)\,\mathrm{d}s$: daily cumulative intensity rate of onset

Assume the number of observed symptom onsets for day t is Poisson distributed with intensity $\tilde{\Lambda}(t)$, the likelihood of observing onset record $\tilde{\mathbf{N}} = (\tilde{N}_1, \ldots, \tilde{N}_T)$ is

$$p(\tilde{\mathbf{N}} | \gamma, \theta_{\text{inc}}, \theta_{\text{inf}}) = \prod_{t=1}^{T} \frac{e^{-\tilde{\Lambda}(t)} \tilde{\Lambda}(t)^{\tilde{N}_t}}{\tilde{N}_t!}$$

$\hat{R}_0 = \hat{\gamma}\Delta_{\text{inf}}$ can be estimated using MLE

Probable Infectiousness Before Symptom Onset (Modified Model)

- Previously assumption: latent period is the same as the incubation period
- New assumption: infectiousness develops since time of infection, correspondingly,

$$p^*_{\text{inf}}(t|\hat{t}) = f_{\text{beta}}\left(\frac{t-\hat{t}}{\Delta_{\text{inf}}}|\alpha^*_{\text{inf}}, \beta^*_{\text{inf}}\right), \quad t \in (\hat{t}, \hat{t} + \Delta^*_{\text{inf}})$$

$$\hat{\lambda}(t) = \sum_{i:t\in[\hat{t}_i,\hat{t}_i+\Delta^*_{\text{inf}}]} p^*_{\text{inf}}(t|\hat{t}_i)\, \Delta^*_{\text{inf}}\gamma$$

City Lock Down Intervention

- Assumption:
  - The lock down intervention had an immediate effect to reduce the disease transmissibility
  - As well as a lasting effect that strengthens following the lockdown
- Intervention effect:

$$\theta(t) = \left(\theta_1, e^{-\theta_2(t-t_0)}\right)^{I(t>t_0)}$$

- Incorporation of intervention effect into transmission model:

$$\hat{\lambda}(t) = \sum_{i:t\in[\tilde{t}_i,\tilde{t}_i+\Delta_{\inf}]} p_{\inf}(t|\tilde{t}_i)\,\Delta_{\inf}\gamma\theta(t)$$

Data source

Transmission models were fitted with disease onset sizes recorded daily from December 1, 2019 to January 23, 2020

Data sources used:

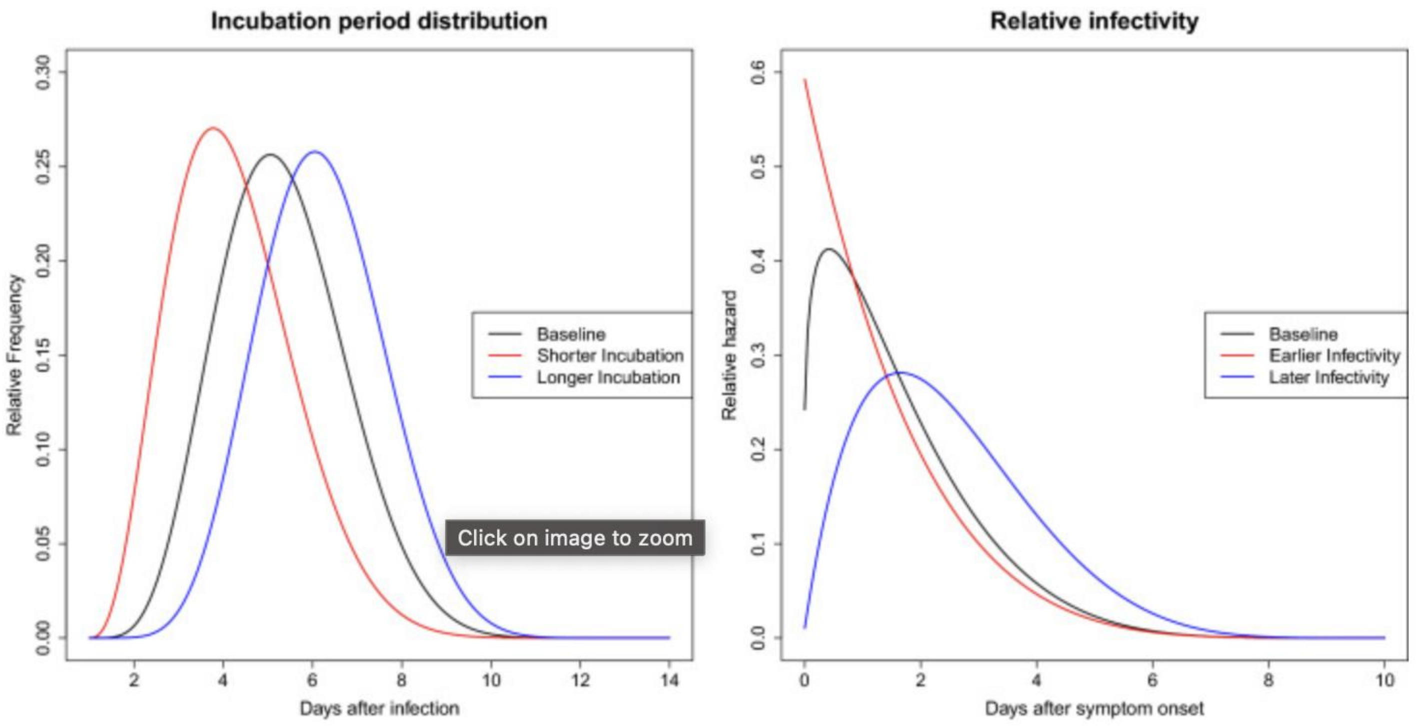
1. Confirmed and suspected daily onset record from China CDC Epidemic update and risk assessment of 2019 Novel Coronavirus
2. Augmented daily onset record using confirmed cases reports from National Health Commission of the People’s Republic of China using delay distribution

Model Assumptions

- Assumed $\alpha_{\mathrm{inc}} = 6$ and $\beta_{\mathrm{inc}} = 12$ for the beta distributed incubation periods, with range of 1 to 14 days and mean incubation of 5.67 days
- Relativity infectivity varied over the infectious period (0-10 days after onset)
- Sensitivity analyses were performed by varying the distribution of the incubation period and relative infectivity over time (next slide)
- For the modified transmission model, $\Delta^*_{\mathrm{inf}} = 24$ after infection, and the relative infectivity was assumed to be highest at or after symptom onset.

Sensitivity Analyses for Original Model

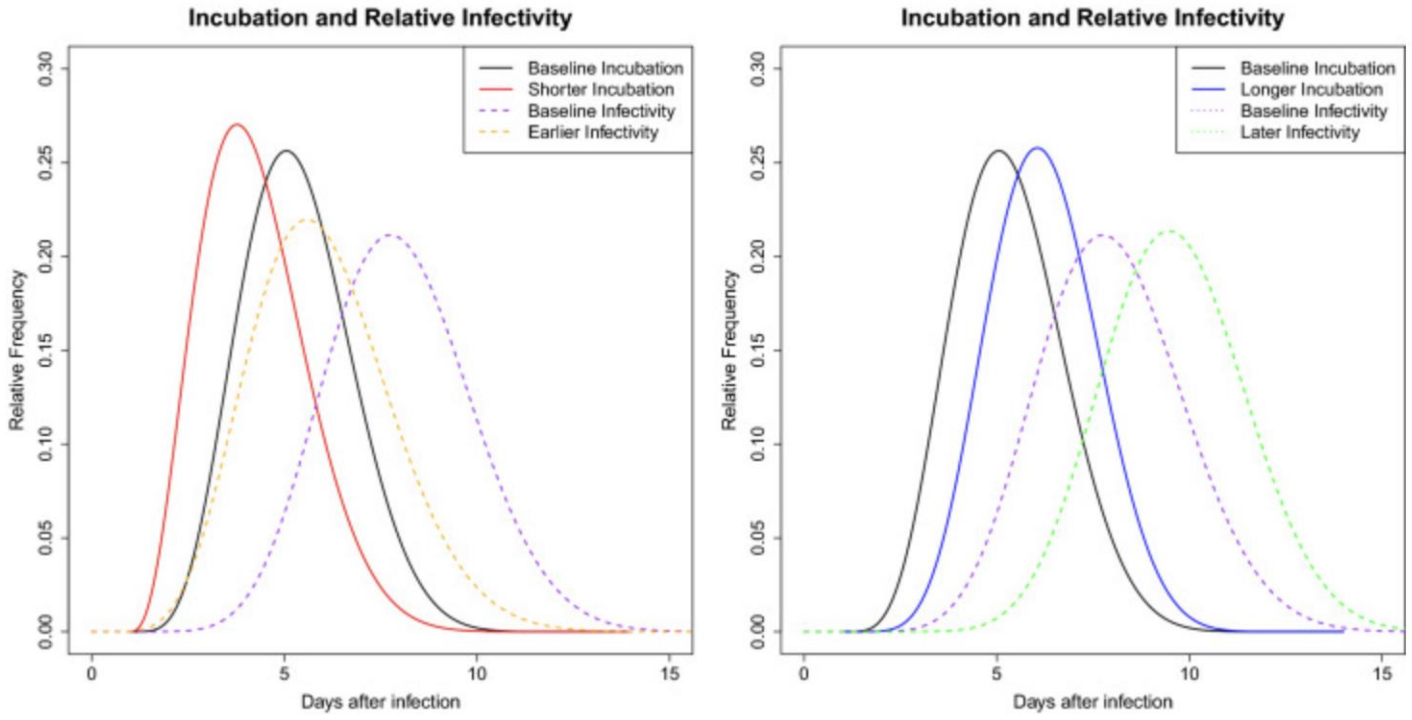
Fig. 2



Assumptions used to model the incubation period length distribution and relative infectivity following patient symptom onset for COVID-19 outbreak in China from 1, December 2019 to 23 January 2020. No asymptomatic infectiousness was possible in this model as cases may infect others only after symptom onset

Sensitivity Analyses for Modified Model

Fig. 3



Modified assumptions used to model the incubation period length distribution and relative infectivity following infection time for COVID-19 outbreak in China from 1, December 2019 to 23, January 2020. Asymptomatic infectiousness exist as the infectious period starts at time of infection

R_0 Results

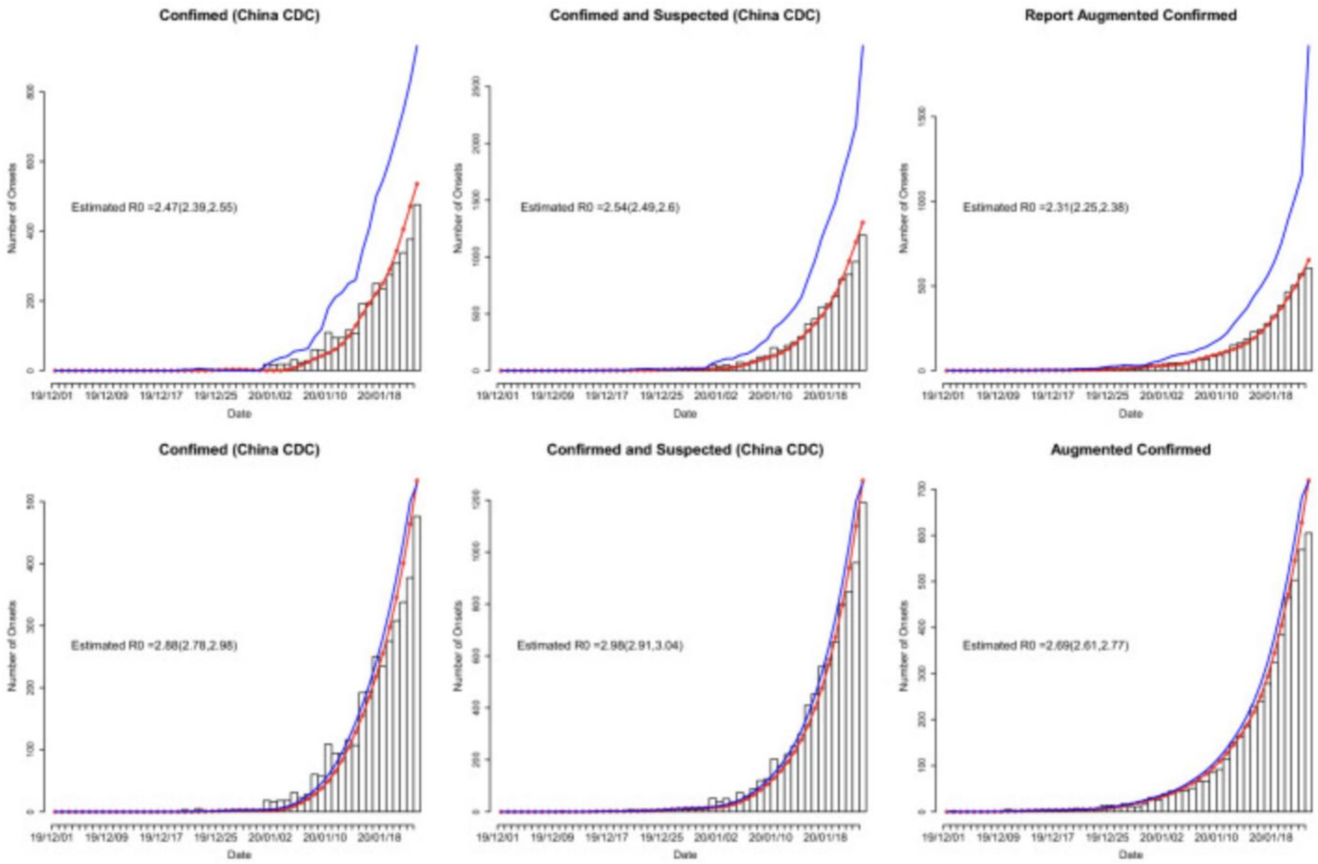
- Poisson Transmission model (baseline assumptions), the estimated R_0 and it’s 95% CI,
  - Confirmed cases only: 2.47 (2.39, 2.55)
  - Both confirmed and suspected cases: 2.54 (2.49, 2.60)
  - Augmented onset record: 2.32 (2.25, 2.38)
- Modified Poisson Transmission model (baseline assumptions), the estimated R_0 and it’s 95% CI,
  - Confirmed cases only: 2.88 (2.78, 2.95)
  - Both confirmed and suspected cases: 2.97 (2.90, 3.04)
  - Augmented onset record: 2.69 (2.61, 2.77)

Model with infectiousness after symptom onset					
p_{inc}	**Baseline**	**Shorter**	**Longer**	**Baseline**	**Baseline**
p_{inf}	**Baseline**	**Baseline**	**Baseline**	**Earlier**	**Later**
Data source					
Confirmed [2]	2.47 (2.39, 2.55)	2.05 (1.98, 2.12)	2.89 (2.80, 2.99)	2.40 (2.32, 2.48)	2.82 (2.73, 2.92)
Confirmed/suspected [2]	2.54 (2.49, 2.60)	2.10 (2.06, 2.15)	2.99 (2.92, 3.05)	2.47 (2.42, 2.52)	2.92 (2.85, 2.98)
Augmented confirmed [5]	2.31 (2.25, 2.38)	1.95 (1.90, 2.01)	2.65 (2.58, 2.73)	2.25 (2.19, 2.32)	2.60 (2.52, 2.67)

Modified model with asymptomatic infection					
p_{inc}	**Baseline**	**Shorter**	**Longer**	**Baseline**	**Baseline**
p_{inf}	**Baseline**	**Baseline**	**Baseline**	**Earlier**	**Later**
Data source					
Confirmed [2]	2.88 (2.78, 2.95)	2.88 (2.78, 2.99)	2.87 (2.77, 2.98)	2.09 (2.02, 2.17)	3.79 (3.66, 3.92)
Confirmed/suspected [2]	2.97 (2.90, 3.04)	2.98 (2.92, 3.05)	2.97 (2.90, 3.04)	2.15 (2.10, 2.19)	3.93 (3.84, 4.03)
Augmented confirmed [5]	2.69 (2.61, 2.77)	2.69 (2.62, 2.77)	2.69 (2.61, 2.78)	2.01 (1.95, 2.07)	3.41 (3.30, 3.53)

Results from the first model assumed same latent period and incubation period. Results from the modified model assumed infectiousness can develop before symptom onset. Estimates of R_0 from sensitivity analyses were also shown, where the assumed distribution of incubation period and relative infectivity was changed shown as in Figs. 2 and 3

Fig. 4

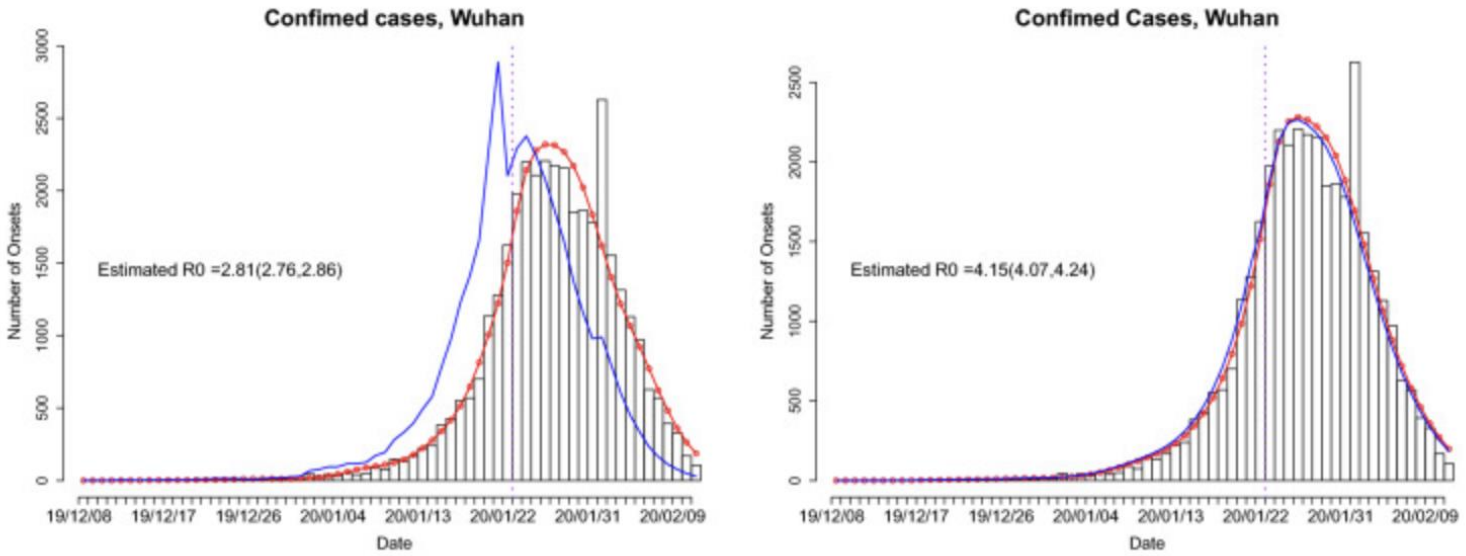


Observed (shown as bars) and fitted (red curve) number of cases with symptom onset over time, and fitted number of infected cases (blue curve) over time. The upper panels show the results from the model that assumed the incubation period and latent period are the same. The lower panels show the results from the modified model where infectiousness can develop before symptom onset

Results with Updated Case Onsets

- Updated data included more than 2 week’s onset records following the lock down of the Wuhan region
- This allowed the estimation of the intervention effect parameters with the updated transmission model
- Shorter incubation assumptions and either baseline or earlier infectivity assumptions were used in the transmission model

Fig. 5



(a) Cases in Wuhan, without asymptomatic infection. **(b)** Cases in Wuhan, with asymptomatic infection.

Observed (shown as bars) and fitted (red curve) number of cases with symptom onset over time, and fitted number of infected cases (blue curve) over time from updated data [12]. Results were with shorter incubation period and baseline infectivity assumptions. The purple vertical dotted line indicates the start of lock down intervention

Estimated model parameters and their 95% CIs for COVID-19 outbreak in Wuhan with updated data [12]

p_{inf}	**Without asymptomatic infection**		**With asymptomatic infection**	
	Baseline	**Earlier**	**Baseline**	**Earlier**
Confirmed cases, Wuhan[a]				
θ_1	0.579 (0.556, 0.599)	0.582 (0.563, 0.602)	0.635 (0.612, 0.659)	0.664 (0.640, 0.690)
θ_2	0.126 (0.122, 0.130)	0.121 (0.117, 0.125)	0.183 (0.179, 0.189)	0.137 (0.133, 0.142)
R_0	2.81 (2.76, 2.86)	2.70 (2.65, 2.75)	4.15 (4.07, 4.24)	2.73 (2.68, 2.79)
Days after intervention to $R_{eff} < 1$	3.85	3.74	5.29	4.35

Shorter incubation period assumption used

Results from Updated Case Onsets

- R_0 with updated data tend to be higher than those from previous results (2.7 to 4.2)
- Intervention effect of lockdown took place gradually. $R_{eff} = R_0\theta(t)$ would fall below 1 after an average of 3.7-5.3 days

Discussion

- Inferred R_0 fall in the same range as results from other researchers who used different sources of data, and was consistent with multiple data sources
- R_0 was sensitive to different assumptions of disease natural history
- Limited resources such as case reporting may have caused a potential underestimation of cases and caused distortion in the distribution of report delay and relative infectivity

Thank you for listening!