Supplementary Online Content

Ge Y, Martinez L, Sun S, et al. COVID-19 transmission dynamics among close contacts of index patients with COVID-19: a population-based cohort study in Zhejiang Province, China. *JAMA Intern Med.* Published online August 23, 2021. doi:10.1001/jamainternmed.2021.4686

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Additional Methodological Information

National Guidelines brief description

There were six versions (v1 - v6) of Covid-19 National Guidelines announced during Zhejiang's major outbreak period. Each version of the National Guidelines (v.1 to 6) were published on the The National Health Commission of the People's Republic of China[1] website on January 15, January 22, January 28, February 7, February 21, March 7, respectively, in 2020. Across these guidelines, the definitions of confirmed Covid-19 cases and their contacts were broadly similar. A confirmed Covid-19 case was defined as either positive detection of SARS-CoV-2 nucleic acid by real-time RT-PCR, or viral genes highly homologous to SARS-CoV-2 by sequencing of specimens.

Contact tracing protocol.

Contacts were defined as individuals who contacted with confirmed Covid-19 cases. The contact events could be living together, studying together, working together or other types occurring in enclosed areas, or healthcare providers such as doctors, nurses. Health professions in the local Centers for Disease Control and Prevention (CDC) identified and traced contacts in multiple ways. Epidemiological investigations related to the contact event's details and basic demographic information were performed to the case and traced contacts.

We collected all the information related to the contact events and recoded that into eight categories (Conversion, Dine Together, Enclosed Space Without Direct Contact, Healthcare Setting, Live Together, Multiple, Shared Transportation, and Others). For each category, we listed the definition as follows:

1) Conversion: Individuals having any conversation with a diagnosed and confirmed Covid-19 patient
2) Dine Together: Individuals who dined with the Covid-19 patient (either outdoors or indoors)

3) Enclosed Space Without Direct Contact: Individuals who stayed with the Covid-19 patient in an enclosed area (e.g., classroom, office, elevator, etc.) without conversation or direct contact
4) Healthcare Setting: Healthcare professions who provided healthcare services to a Covid-19 patient
5) Live Together: Individuals who lived with the Covid-19 confirmed patient as a family member, relative, or roommate, etc.
6) Multiple: Individuals who contacted the Covid-19 patient in more than one way, such as living together, eating together, and shared transportation.
7) Shared Transportation: Individuals who commuted with Covid-19 patients, including in trains, cars, airplanes, ships, etc.
8) Others: Other scenarios including but not limited to living in a community or food delivery, etc.

Close contacts were centrally quarantined for at least 14 days except in areas with limited resources where home self-quarantine was alternatively suggested. They were required to stay quarantined even if their Covid-19 test was negative within the 14 days. During the quarantine period, health professionals checked each contact's symptoms daily, including fever, cough, etc. RT-PCR tests were administered to any contact who had respiratory symptoms or was considered as a suspect infection by a physician. If any contact was diagnosed and confirmed with Covid-19, contact tracing would be given to his/her contacts in a similar fashion. Those with no symptoms or whom tested negative were released after 14 days.

eAppendix 2. Definition of COVID-19 Severity

According to the severity of Covid-19, the disease was classified as mild, moderate, and severe (including critically ill) conditions at the time of diagnosis as follows:

Mild Covid-19

–Very mild clinical symptoms with no abnormality in radiology of the lungs.

Moderate Covid-19

– Some clinical symptoms, such as fever, coughing, and other respiratory symptoms, and radiology scan shows pneumonia.

Severe Covid-19

Adults having any of the following conditions:

– Shortness of breath, respiratory rate ≥ 30 breaths per minute (bpm);
– Resting peripheral capillary oxygen saturation (SpO2) ≤ 93%;
– The ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO2/FiO2) ≤ 300 mmHg.

Or children having any of the following conditions:

– Shortness of breath not caused by fever or crying: respiratory rate (RR) ≥ 60 bpm for infant less than 2 months; RR ≥ 50 bpm for infant aged 2-12 months; RR ≥40 bpm if aged 1-5 years; RR ≥ 30 bpm if older than 5 years
– Resting peripheral capillary oxygen saturation (SpO2) ≤ 92%
– Trouble breathing, cyanosis, or apnea
– Lethargy or convulsion
– Dehydration

Critically ill Covid-19

Patients with any of the following conditions:

– Respiratory failure and require mechanical respiration
– Shock
– Failure of other organs and require intensive care.

eAppendix 3. Distributed Lag Non-Linear Models (DLNMs)

Distributed lag non-linear models (DLNMs) allow for both exposure-response functions and lag-response functions, and are widely used in environmental studies to compare the risk of exposures prior to the outcome [2, 3]. Follow the idea of exposure–lag–response [4, 5], we estimated the Covid-19 infection risk with the history of exposure using the R package of dlnm [6].

In the DLNMs, suppose the outcome Y_{it} is the status of Covid-19 infection of *i*th individual at time of t, and let $\mu_t \equiv E(Y_{it})$ represents the expected probability of infection at day *t*. Specifically, the exposure–lag–response associations in Figure 2 and Figure S6 were estimated with a Poisson Generalized Linear Model of form:

$$log(\mu_t) = \alpha + \sum_{l_0}^{L} f \cdot w(x_{t-l}, l) + \sum_{k=1}^{K} \gamma_k u_k \text{ (eq 1)},$$

where α is the intercept; $f \cdot w(x_{t-l}, l)$ is the bi-dimensional exposure-lag-response function which is composed with two marginal functions: the exposure-response function $f(\cdot)$, and the additional lag-response function $\mathrm{w}(\cdot)$ [4]. Since we included up to a lag of 25 days (from -14 to +10 day), $l = [0, \ldots, 24]^T$. The variable u_k represents the k-th covariate in our model to adjust for, i.e., age of case, age of contact, cases severity, contact gender, and contact type, and γ_k is the coefficient of the covariate u_k.

Generally, in DLNMs, the relative risk of the Covid-19 infection related to the timing of exposure was defined on a grid of values of exposure and number of lag days [6]. More specifically, the comparison of transmission risk from Covid-19 exposure versus no exposure at a specific time point with the adjustment of other covariates is then estimated in equation (eq 1) by the exposure-lag-response associations measured by the term $\sum_{l_0}^{L} f \cdot w(x_{t-l}, l)$.

eReferences.

1. National Health Commission of the PRC [Internet]. [cited 2021 Jan 2]. Available from: http://en.nhc.gov.cn/

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3. Gasparrini A, Guo Y, Sera F, Vicedo-Cabrera AM, Huber V, Tong S, Coelho MD, Saldiva PH, Lavigne E, Correa PM, Ortega NV. Projections of temperature-related excess mortality under climate change scenarios. The Lancet Planetary Health. 2017 Dec 1; 1 (9): e360-7.

4. Gasparrini A, Scheipl F, Armstrong B, Kenward MG. A penalized framework for distributed lag non-linear models: Penalized DLNMs. Biom. 2017;73(3):938-948. doi:10.1111/biom.12645

5. Gasparrini A. Modeling exposure–lag–response associations with distributed lag non-linear models. Statistics in Medicine. 2014;33(5):881-899. doi:https://doi.org/10.1002/sim.5963

6. Gasparrini A. Distributed Lag Linear and Non-Linear Models in R: The Package dlnm. J Stat Soft. 2011;43(8). doi:10.18637/jss.v043.i08

eTable 1. Sample Size of Each Flow Step for the Larger Sample Analysis of Risk Factor Analyses of Asymptomatic Disease and Intensity of Exposure (Table 1, Table 2, Figure 4 in the main manuscript).

	N: cases	N: Contact events	N: contacts	Contact quarantine date range
Total	1,495	…	…	Until August 22
Performed contact tracing	827	15,254	14,856	2020-01-02 to 2020-07-29
Excluded contacts who had never been tested for COVID-19	733	9,056	8,908	2020-01-10 to 2020-07-29
Excluded contacts events ended 14 days before the index case's symptom onset date (for an asymptomatic case, we used diagnostic date)	730	8,999	8,852	2020-01-10 to 2020-07-29

eTable 2. Sample Size of Each Flow Step for the Analysis of Exposure Time (Figure 2 and Figure 3 in the main manuscript).

	N, cases	N, contact events	N, contacts	Contact quarantine date range
Total	1,495	…	…	Until August 22
Performed contact tracing	827	15,254	14,856	2020-01-02 to 2020-07-29
Excluded contacts who had never been tested for COVID-19	733	9,056	8,908	2020-01-10 to 2020-07-29
Excluded contacts events ended 14 days before the index case's symptom onset date (for an asymptomatic case, we used diagnostic date)	730	8,999	8,852	2020-01-10 to 2020-07-29
Excluded asymptomatic infections (no symptom onset date available)	645	7,846	7,724	2020-01-10 to 2020-04-03
Excluded contacts had an earlier symptom onset date compared to the index cases	632	7,793	7,672	2020-01-10 to 2020-04-03
Exclude contacts who linked to multiple cases	593	7,544	7,544	2020-01-10 to 2020-04-03
Focused on -14 to 10 days from symptom onset to case-contact exposure	588	7,116	7,116	2020-01-10 to 2020-03-30

eTable 3. Comparison of Basic Demographics Between Included and Excluded Index Cases

	Demographics	Excluded	Included	P-value	Test method
Sample size		97	730		
Median index age, years (IQR)		47 [36–55]	46 [36–56]	0.687	Kruskal–Wallis test
Severity (n, %)	Asymptomatic	7 (7.2)	81 (11.1)	0.391	Pearson's Chi-squared Test
	Mild	43 (44.3)	336 (46.0)		
	Typical	47 (48.5)	313 (42.9)		
Case's Gender	Female	44 (45.4)	356 (48.8)	0.601	Pearson's Chi-squared Test
	Male	53 (54.6)	374 (51.2)		

eTable 4. Comparison of Basic Demographics Between Included and Excluded Contacts

	Demographics	Excluded	Included	P-value	Test method
Sample size		6,004	8,852		
Contact's age (median, IQR)		43.00 [30.00, 54.00]	41.00 [28.00, 54.00]	<0.001	Kruskal–Wallis test
Contact's Gender	Female	2,779 (46.3)	4,173 (47.1)	0.313	Pearson's Chi-squared Test
	Male	3,225 (53.7)	4,679 (52.9)		
Contact setting*	Household	1,846 (30.7)	2,484 (28.1)	<0.001	Pearson's Chi-squared Test
	Non-household	4,160 (69.3)	6,370 (71.9)		

* Two contacts had two types of setting.

eTable 5. Adjusted Relative Risks Shown in Figure 2

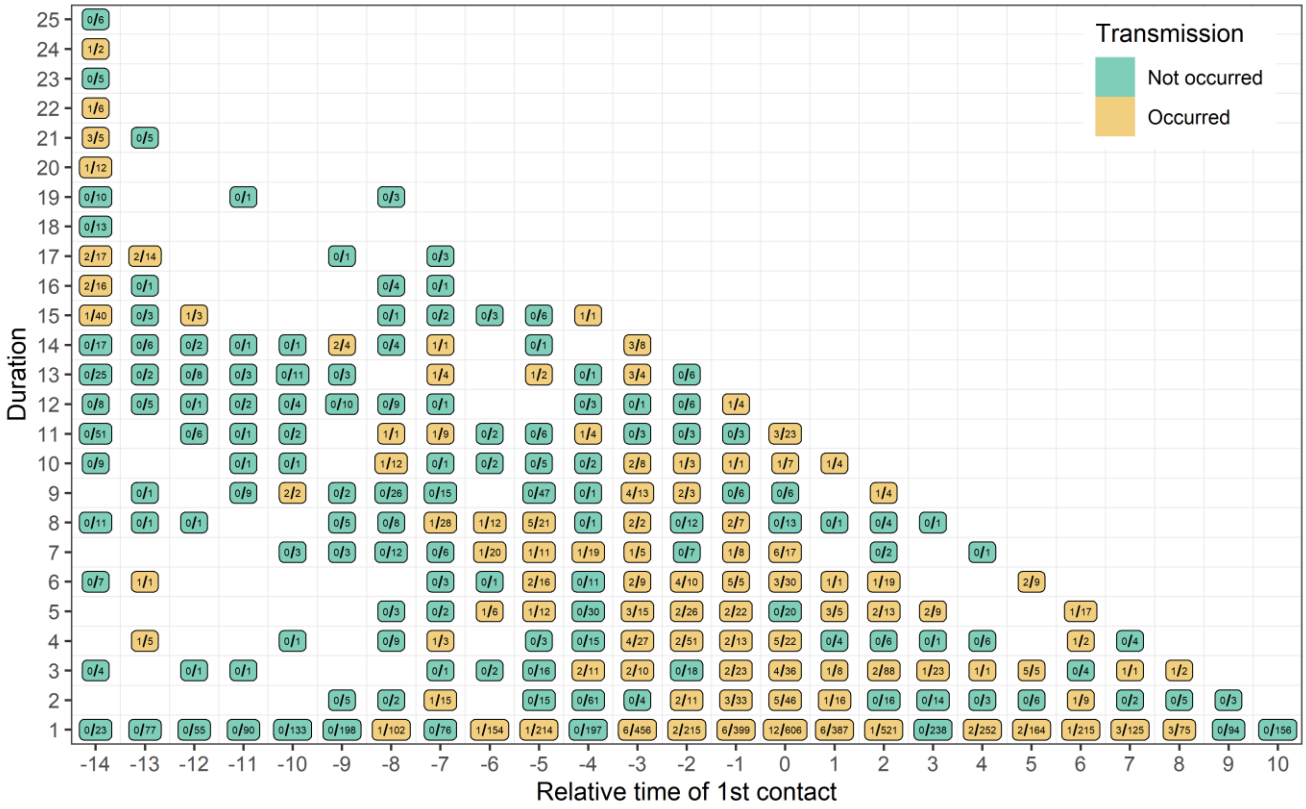
Day	Adjusted Relative Risk (95% CI)	Day	Adjusted Relative Risk (95% CI)
-14	0.86 (0.39–1.91)	0	1.34 (1.18–1.54)
-13	0.98 (0.63–1.52)	1	1.33 (1.19–1.49)
-12	1.09 (0.90–1.31)	2	1.27 (1.15–1.4)
-11	1.16 (0.91–1.48)	3	1.19 (1.07–1.32)
-10	1.16 (0.81–1.66)	4	1.11 (0.98–1.26)
-9	1.07 (0.75–1.54)	5	1.05 (0.92–1.2)
-8	0.95 (0.72–1.26)	6	1.01 (0.89–1.14)
-7	0.84 (0.70–1.02)	7	0.99 (0.88–1.11)
-6	0.78 (0.65–0.94)	8	0.98 (0.84–1.15)
-5	0.78 (0.63–0.96)	9	0.99 (0.76–1.27)
-4	0.86 (0.72–1.04)	10	0.99 (0.69–1.43)
-3	1.02 (0.90–1.15)		
-2	1.18 (1.05–1.34)		
-1	1.30 (1.13–1.49)		

The risk of Covid-19 at each specific day was compared with the risk at all corresponding days (i.e., reference was all other days other than that specific day).

eFigure 1. Contact Events Description (PCR Positive Counts/Total Number of Contacts)

Contact event and PCR testing.

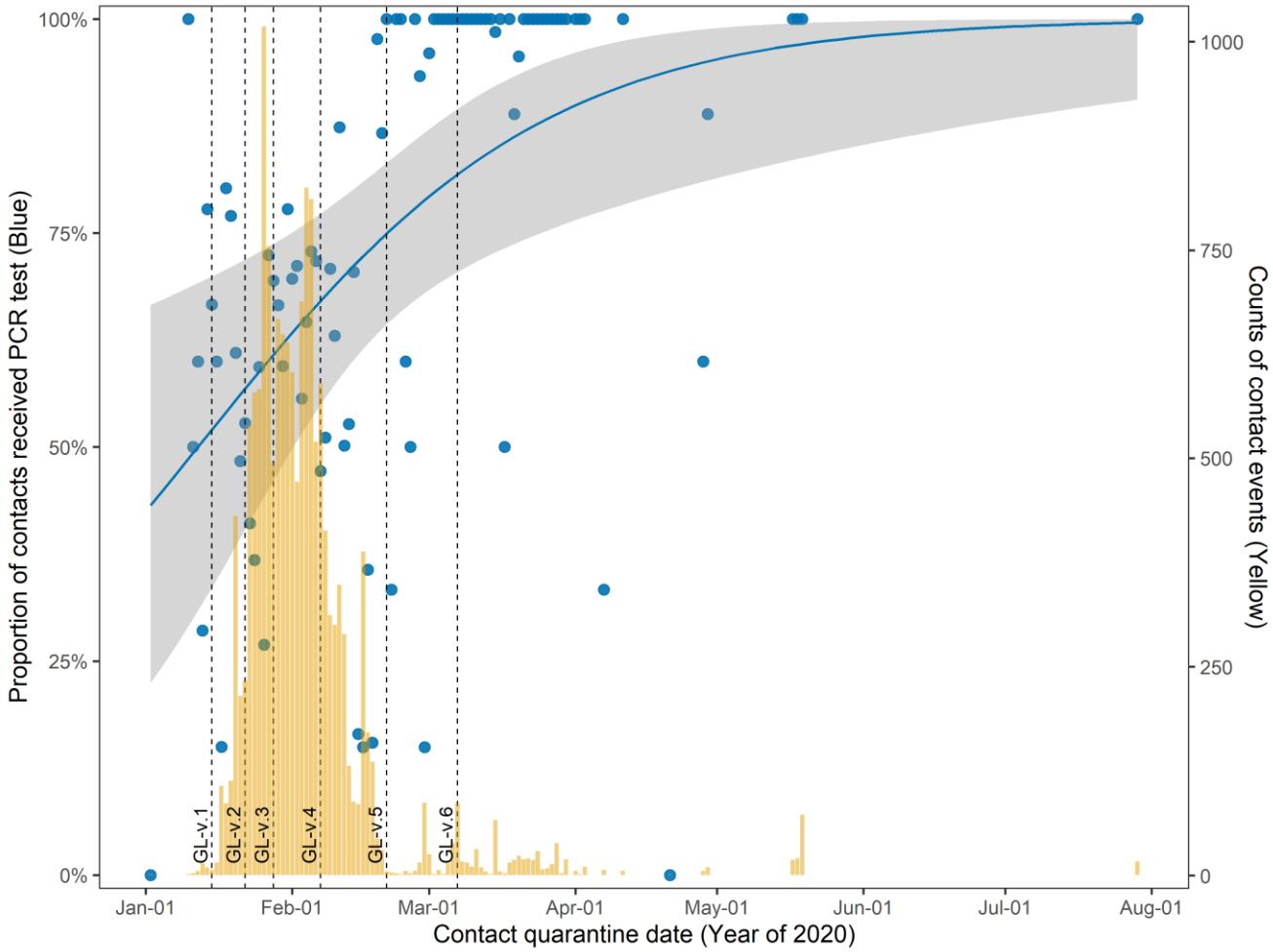
The contacts with the number of PCR positive and negative were presented in Figure S1. We colored different days by whether an infection was detected among contacts. Infections mainly occurred in events that happened between 8 days before and after the index case symptom onset day. A higher positive proportion was observed in events with longer contact duration. We had a limited sample size of events with very early and extremely long exposure.



The x-axis was the exposure time window. The 0 was the symptom onset day of the index case. The y-axis was the duration of the event. The yellow-area suggested at least an infection was detected in that event. Counts in each cell: number of positive over the total number of positive and negative.

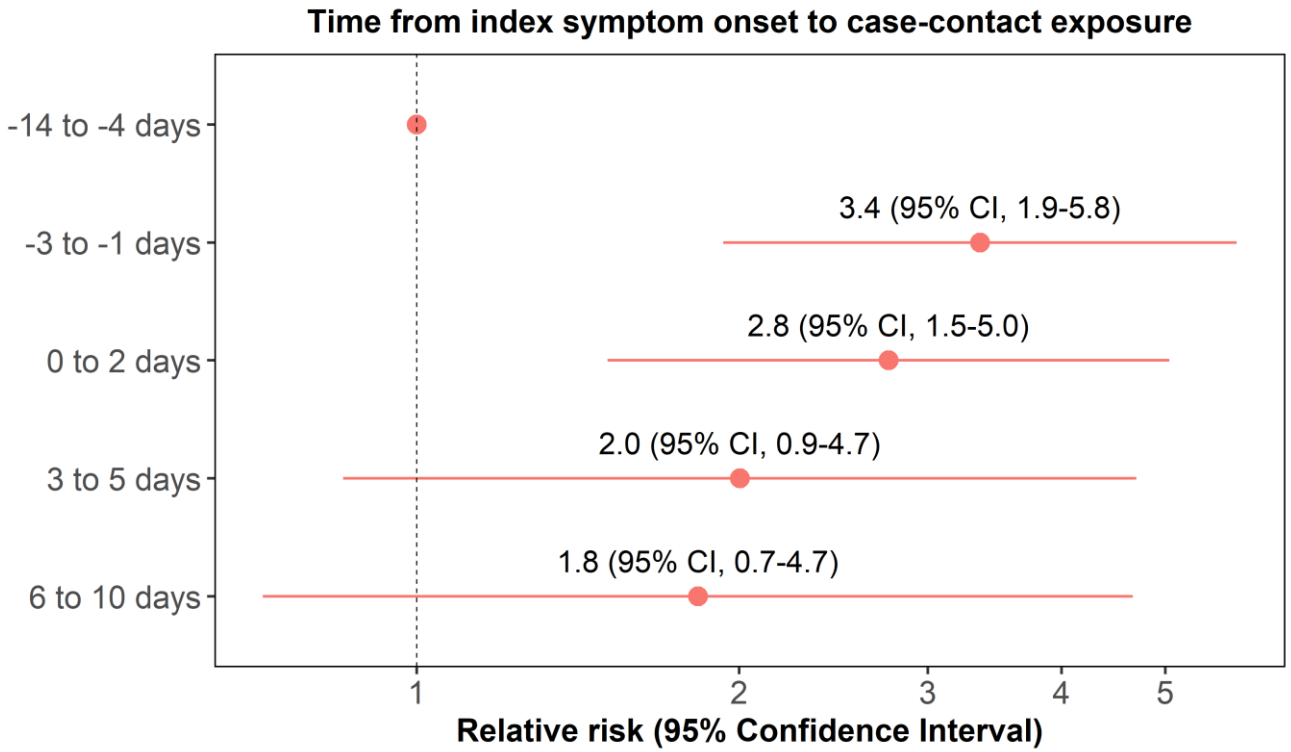
The distribution of daily contact events (yellow) and the proportion of contacts receiving PCR testing (blue) were shown in figure S2. The majority of contact events occurred between late January and early February, with the first investigated contact event recorded on 9th January. After the major outbreak, only sporadic cases were found after March causing the contact events also decreased to a low level. The proportion of contacts receiving PCR tests increased quickly over time from lower than 50% at the beginning to close to 100% later.

eFigure 2. Proportion of Contacts Received PCR Tested for COVID-19

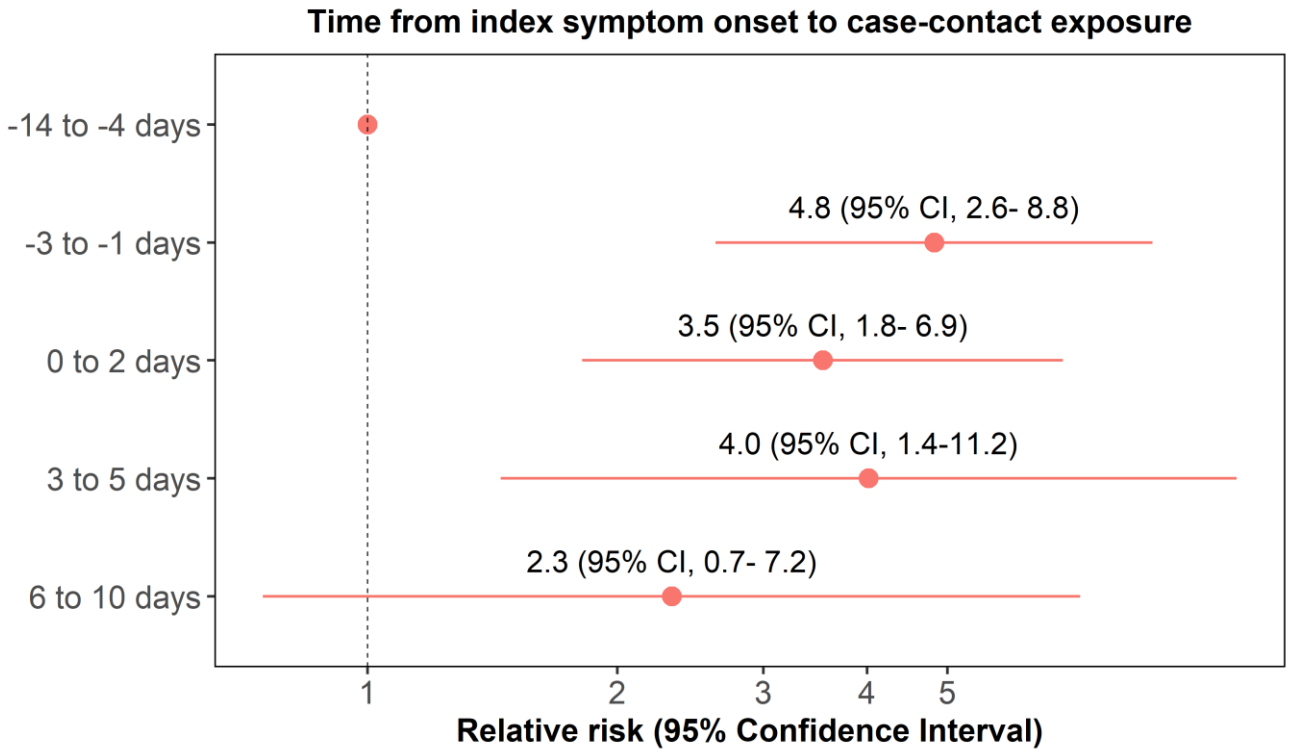


Abbreviations: GL, National Guidelines.
GL-v.1 means 1st version of national COVID-19 guideline. The vertical dot line pointed out the date when the national COVID-19 guideline was announced. A logistic regression was used to estimate the mean (blue curve) and 95% confidence band (grey band) of the daily PCR testing proportion.

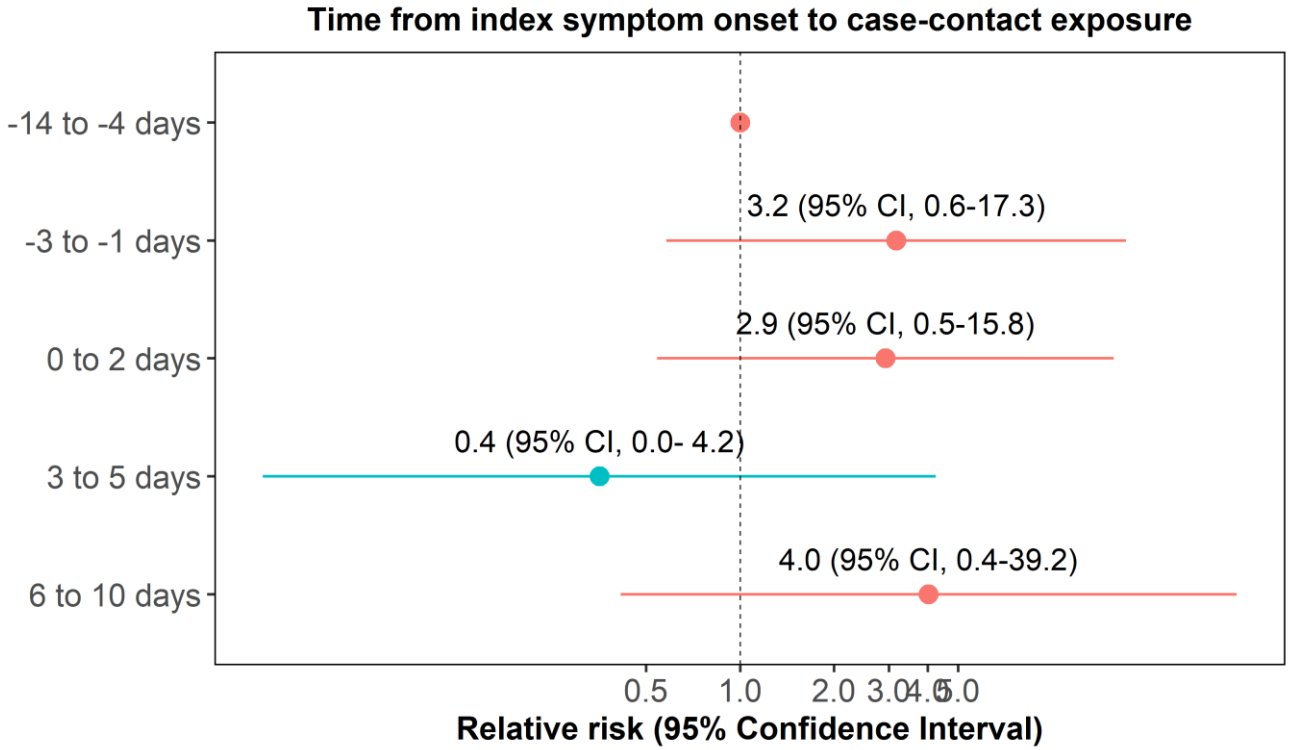
eFigure 3. Relative Risk of Covid-19 Infection Among Contacts Between Different Exposure Time. The reference group and model approach were distinct from Figure 2, therefore relative risks from this Figure may not be directly comparable to Figure 2.



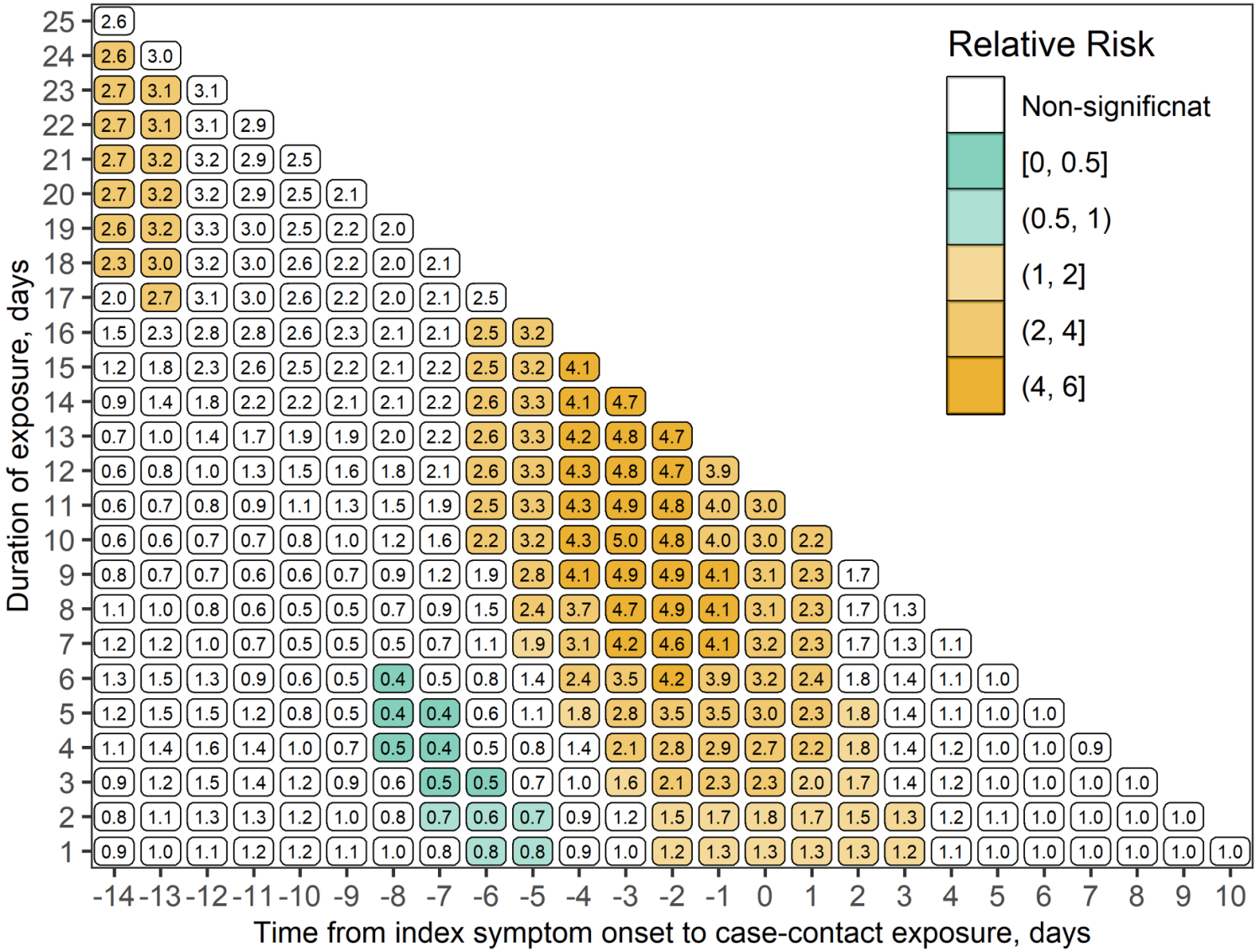
eFigure 4. Relative Risk of Covid-19 Infection Among Household Contacts Between Different Exposure Time. The reference group and model approach were distinct from Figure 2, therefore relative risks from this Figure may not be directly comparable to Figure 2.



eFigure 5. Relative Risk of Covid-19 Infection Among Non-Household Contacts Between Different Exposure Time. The reference group and model approach were distinct from Figure 2, therefore relative risks from this Figure may not be directly comparable to Figure 2.



eFigure 6. The Risk of Covid-19 in Close Contacts of Index Cases by the Duration and Timing of Exposure



The x-axis is the exposure time window. The 0 was the symptom onset day of the index case. The y-axis was the duration of exposure between the index case and close contact defined as the difference in days between date of first and last contact. The yellow-area was where the relative risk statistically significant. If one cell had significant high (>1) relative risk, the contact had an elevated risk of being infected compared to other exposure time points. For example, if a contact event occurred at day -2 and the exposure lasted for 13 days, the adjusted relative risk of Covid-19 among contacts was 4.7 (95% CI, 1.9–11.4). If one cell had significant low (<1) relative risk, the contact had a low risk of being infected. A low risk suggested less likely to be an COVID-19 infection compared to other exposure time points (it may still much higher than those never contact with COVID-19 cases).