



Research article

COVID-19 cases with a contact history: A modeling study of contact history-stratified data in Japan

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Abstract: The purpose of the present study was to develop a transmission model of COVID-19 cases with and without a contact history to understand the meaning of the proportion of infected individuals with a contact history over time. We extracted epidemiological information regarding the proportion of coronavirus disease 2019 (COVID-19) cases with a contact history and analyzed incidence data stratified by the presence of a contact history in Osaka from January 15 to June 30, 2020. To clarify the relationship between transmission dynamics and cases with a contact history, we used a bivariate renewal process model to describe transmission among cases with and without a contact history. We quantified the next-generation matrix as a function of time; thus, the instantaneous (effective) reproduction number was calculated for different periods of the epidemic wave. We objectively interpreted the estimated next-generation matrix and replicated the proportion of cases with a contact $p(t)$ over time, and we examined the relevance to the reproduction number. We found that $p(t)$ does not take either the maximum or minimum value at a threshold level of transmission with $R(t) = 1.0$. With $R(t) < 1$ (subcritical level), $p(t)$ was a decreasing function of $R(t)$. Qualitatively, the minimum $p(t)$ was seen in the domain with $R(t) > 1$. An important future implication for use of the proposed model is to monitor the success of ongoing contact tracing practice. A decreasing signal of $p(t)$ reflects the increasing difficulty of contact tracing. The present study findings indicate that monitoring $p(t)$ would be a useful addition to surveillance.

Keywords: COVID-19; contact history; reproduction number; next-generation matrix; statistical estimation

1. Introduction

Coronavirus disease 2019 (COVID-19) first appeared in Wuhan, China in late 2019 and resulted in a worldwide pandemic that has lasted for more than 2 years at this writing. According to the World Health Organization, the pandemic has led to 615 million confirmed cases and 6.5 million deaths globally as of October 2, 2022 [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is highly transmissible in indoor settings with limited ventilation [2], spreading from human to human, and has evolved rapidly, with the emergence of several variants, including Alpha (B.1.1.7), Delta (B.1.617), and Omicron (B.1.1.529) [3]. A published study indicated that there are a number of risk factors for COVID-19 death including the gross domestic product (GDP) per capita, healthcare spending and air pollution of nations [4]. Due to stringent non-specific (non-pharmaceutical) countermeasures, socioeconomic activities were hampered in many parts of the world [5]. During the early stage of the COVID-19 pandemic, Wu et al. [6] pointed out that the travel history, as well as contact history of cases, represent key information in containment efforts. Contact tracing, quarantine and other non-pharmaceutical interventions (NPIs) were proven to be sufficiently effective to contain virus transmission in several settings [7–11] and the combination of multiple NPIs was shown to be more effective compared with single choice of control [12,13]. Ruhomally et al. [14] maintained that vaccination combined with NPIs is indispensable to restrain epidemic prevalence. Nevertheless, another published study [15] showed that the rollout of vaccinations would be influenced by the level of public health governance. Liu et al. [16] proposed a landscape network entropy method to identify the pre-outbreak stage when NPIs should be prepared to implement, and Yuan et al. [17] employed a linear spline model to estimate the NPIs effectiveness.

Kretzschmar et al. [18] indicated that application (app)-based tracing could be more effective than conventional tracing, considering the impact of delays in the effectiveness of contact tracing strategies. Ferretti et al. [19] also proposed the use of a smartphone app from which contact data can be obtained instantly, automatically, and anonymously by recording proximity events between two phones and via which users with a COVID-19 diagnosis can be asked to self-isolate. According to a systematic review [20], digital tracing methods using mobile applications have been adopted in many regions, and logistic regression and SIR models are most commonly used for supervised learning. But many problems remained in its implementation, including the protection issue of personal privacy [21–24]. Furthermore, if digital tracing method was taken, it would be necessary to handle the huge amount of information correctly and efficiently under systematical management to avoid drawing distorting conclusions [25]. It is also generally understood that controlling COVID-19 via forward contact tracing alone might be unfeasible because a certain fraction of infections remains asymptomatic. Moreover, even among symptomatic cases, a substantial proportion of secondary transmissions occur during the pre-symptomatic (incubation) period [26]. According to recent studies, at least 40% of people infected with COVID-19 remain asymptomatic throughout the course of infection, and the rate of asymptomatic infection with the Omicron variant is estimated at 80–90% [27,28]. A considerable number of infections are therefore undiagnosed or unreported, implying that a notable proportion of infected individuals are very likely to be infected by an unrecognized primary case; thus, these secondary cases do not have a contact history. Arun et al. [29] suggested that using IoT (Internet of things)-based devices and sensors could be a possible way of detecting and monitoring asymptomatic patients.

Despite the asymptomatic and mild nature of many COVID-19 infections, it is important to understand why and how information regarding contact history can be utilized in COVID-19 control.

In a modeling analysis, Aleta et al. [30] indicated that a response system of enhanced testing and tracing have a major role in relaxing social distancing interventions when there is a lack of herd immunity against SARS-CoV-2. Tian et al. [31] calculated a number of indicators for patients with COVID-19 in Beijing, including the proportion with a contact history, with the aim to put forward reasonable isolation policy recommendations. Mizumoto et al. [32] estimated the reproduction number for market-to-human and human-to-human transmission in quantitative modeling analyses using incidence data from a wet market in China, stratified according to contact history. Lan et al. [33] identified occupations with a high risk of infection, analyzing work-related cases with a contact history and identifying local settings with a high transmission risk. Published studies in different countries have also indicated that contact history plays an important role in public health and social measures [34–40].

Questions regarding the meaning of having or not having a contact history for each diagnosed case have yet to be clarified. For example, what does the proportion of cases with a contact history indicate over the time course of an epidemic? In Japan, retrospective and prospective contact tracing have been conducted from the start of the first wave [41]. Accordingly, the line list of cases during the early stage of the pandemic (by July 2020) included information of contact history for each confirmed case. These data offer the opportunity to explore the relationship between transmission dynamics and the proportion of infected individuals with contact history in an explicit manner. The daily number of new cases can be stratified according to the presence of a contact history, and the relationship between the reproduction number and contact history can then be investigated.

The purpose of the present study was to develop a transmission model of COVID-19 cases with and without a contact history to understand what the proportion of infected individuals with a contact history indicates over time. We attempted to understand the relationship between contact history and the reproduction number and demonstrate that monitoring the proportion of cases with a contact history would be a useful addition to surveillance. Using our simple model, we analyzed first-wave data in Osaka from January 15 to June 30, 2020.

2. Materials and methods

2.1. Sample and data

In Japan, COVID-19 is a notifiable disease according to the Infectious Disease Law, and all cases confirmed by means of RT-PCR are notified to the government via local health centers. We analyzed an epidemiological dataset comprising the daily number of infected individuals as a function of the date of illness onset, stratified by the presence of a contact history in Osaka for the period January 15 to June 30, 2020. All confirmed infected individuals were checked for their contact histories and recorded respectively during that period. The original data are openly shared by the Osaka prefectural government [42] and are presented as Supplementary Data 1.

2.2. Measures of variables

We denote the daily number of infected individuals without a contact history at calendar time t as $c_0(t)$ and the number with a contact history as $c_1(t)$. We calculated the proportion of infected individuals with a contact history, which is denoted as

$$p(t) = \frac{c_1(t)}{c_0(t) + c_1(t)} \quad (1)$$

Figure 1 shows the original dataset according to contact history. Whereas the number of COVID-19 cases with a contact history was larger at the beginning of the epidemic wave, those without a contact history exceeded that number, and the relationship was recovered in the middle of the declining phase. Thus, the qualitative pattern in the proportion of cases with a contact history $p(t)$ exhibited a U-shape. It should be noted that the proportion $p(t)$ in the figure only reflects the dataset from March 6 to May 10 because the daily number of infected individuals was low and $p(t)$ were not calculable prior to March 6 and also after May 10.

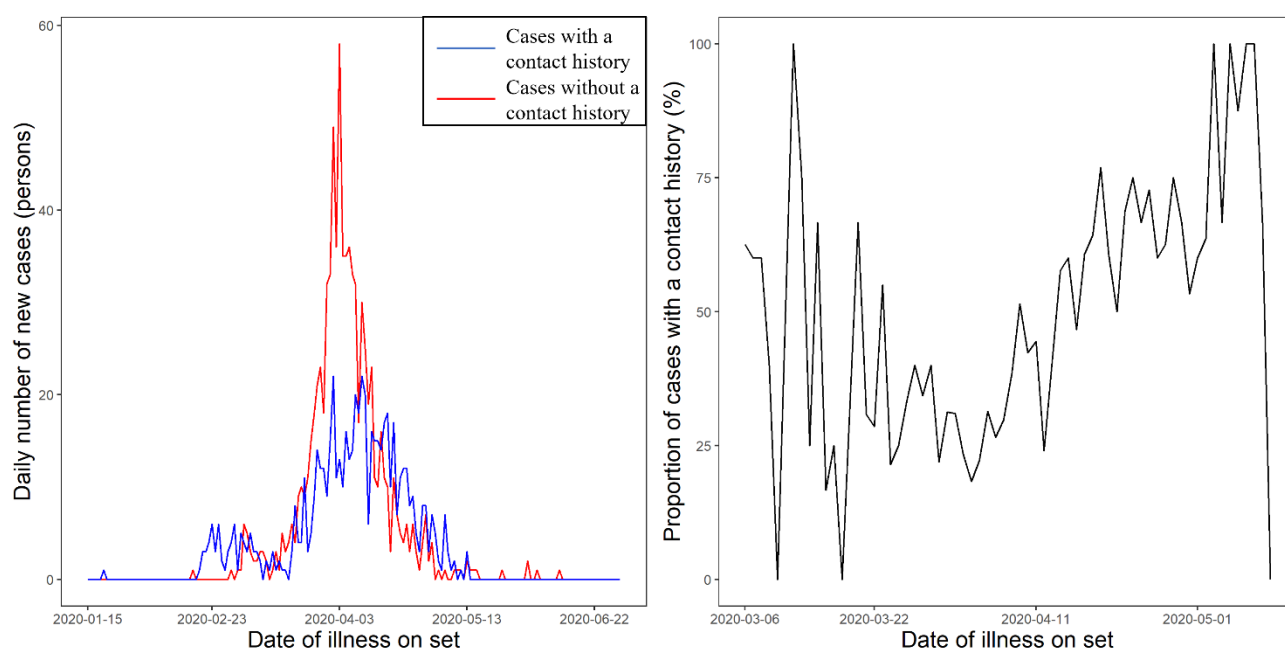


Figure 1. COVID-19 cases with a contact history in Osaka, 2020.

The blue line in the left panel represents the daily number of new cases (individuals) with a contact history; the red line represents the daily number of new cases (individuals) without a contact history. Both datasets are from January 15 to June 30, 2020, in Osaka. The right panel shows the proportion of cases with a contact history (%) calculated from March 6 to May 10, 2020.

2.3. Models and data analysis procedure

To clarify the epidemiological meaning of the proportion of cases with a contact history, we used a renewal process model to reconstruct the transmission dynamics. The bivariate process is described as

$$\begin{pmatrix} c_0(t) \\ c_1(t) \end{pmatrix} = K(t) \begin{pmatrix} \int_0^\infty c_0(t-s)g(s)ds \\ \int_0^\infty c_1(t-s)g(s)ds \end{pmatrix}, \quad (2)$$

where $t = 1, 2, 3, \dots$ denotes the calendar day starting from January 15, 2020 (day 1). The next-generation matrix at calendar time t , $K(t) = \begin{pmatrix} R_{00}(t) & R_{01}(t) \\ R_{10}(t) & R_{11}(t) \end{pmatrix}$, describes how transmission to and from cases with/without a contact history takes place (e.g., $R_{10}(t)$ stands for the average number of traced secondary cases generated by a single untraced primary case). $g(s)$ is the probability density function of generation time, assumed to be captured by a gamma distribution with a mean of 4.8 days and standard deviation at 2.4 days [43].

Because retroactive contact tracing was in place, when there was a very small number of cases owing to containment efforts during the first epidemic wave in Japan, cases with a contact history were thought to be all traced, implying that there was no transmission from the traced cases to other cases who were later diagnosed but were untraced, $R_{01}(t) = 0$ and $R_{11}(t) > 0$. Otherwise, no constraint was imposed on the estimate of the next-generation matrix. Among untraced cases, their secondary cases would be partly traced and otherwise remain untraced; thus, we assume that $R_{10}(t) = k(t)R_{00}(t)$ where $k(t)$ is the ratio of traced to untraced among secondary cases. With these assumptions, the bivariate renewal process becomes

$$\begin{cases} c_0(t) = R_{00}(t) \int_0^\infty c_0(t-s)g(s)ds \stackrel{\text{def}}{=} \lambda_0(t), \\ c_1(t) = k(t)R_{00}(t) \int_0^\infty c_0(t-s)g(s)ds + R_{11}(t) \int_0^\infty c_1(t-s)g(s)ds \stackrel{\text{def}}{=} \lambda_1(t). \end{cases} \quad (3)$$

Assuming that variations of $c_0(t)$ and $c_1(t)$ are sufficiently captured by a Poisson distribution, i.e., $c_0(t) \sim \text{Poisson}(\lambda_0(t))$ and $c_1(t) \sim \text{Poisson}(\lambda_1(t))$, the likelihood function to estimate unknown parameters of the system (2) L_0 and L_1 is

$$\begin{cases} L_0 = \frac{\lambda_0(t_1)^{c_0(t_1)} \dots \lambda_0(t_n)^{c_0(t_n)}}{c_0(t_1)! \dots c_0(t_n)!} e^{-(\lambda_0(t_1) + \dots + \lambda_0(t_n))} \\ L_1 = \frac{\lambda_1(t_1)^{c_1(t_1)} \dots \lambda_1(t_n)^{c_1(t_n)}}{c_1(t_1)! \dots c_1(t_n)!} e^{-(\lambda_1(t_1) + \dots + \lambda_1(t_n))} \end{cases} \quad (4)$$

where $t_1, t_2, \dots, t_n \in [1, 168]$ (from January 15 to June 30, 2020). The total likelihood L is

$$L = L_0 L_1 \quad (5)$$

which can be log-linearized as:

$$\begin{aligned}
\ln(L) = & \sum_{i=1}^n c_0(t_i) \ln(R_{00}(t_i) \int_0^\infty c_0(t_i - s)g(s)ds) + \\
& \sum_{i=1}^n c_1(t_i) \ln(k(t_i)R_{00}(t_i) \int_0^\infty c_0(t_i - s)g(s)ds + R_{11}(t_i) \int_0^\infty c_1(t_i - s)g(s)ds) - \\
& \sum_{i=1}^n R_{00}(t_i) \int_0^\infty c_0(t_i - s)g(s)ds - \sum_{i=1}^n (k(t_i)R_{00}(t_i) \int_0^\infty c_0(t_i - s)g(s)ds + \\
& R_{11}(t_i) \int_0^\infty c_1(t_i - s)g(s)ds) - \sum_{i=1}^n \ln(c_0(t_i)!) - \sum_{i=1}^n \ln(c_1(t_i)!)
\end{aligned} \tag{6}$$

Maximum likelihood estimation of unknown quantities $(R_{00}(t), R_{11}(t), k(t))$ can be achieved by minimizing the negative expression of the loglikelihood (6). Using the estimated parameters, we reconstructed the transmission dynamics.

Quantitatively, we explored the relationship between $p(t)$ and the instantaneous reproduction number of the entire population $R(t) = \max(R_{00}(t), R_{11}(t))$, the latter taking the maximum because the reproduction number is calculated as the largest eigenvalue of $K(t)$ [44]. All analyses were performed with R software Version 4.2.0 (The R Project for Statistical Computing, Vienna, Austria).

2.4. Ethics approval of research

This study was approved by the Medical Ethics Board of the Graduate School of Medicine at Kyoto University (no. R2676). The present study used publicly available data that were de-identified.

3. Results

3.1. Three-phase analysis

On March 24, 2020, the governor of Tokyo decided to postpone the Tokyo Olympic Games for 1 year. The Tokyo government then announced that Japan's capital cities were at risk of having an exploding number of COVID-19 cases [45]. On March 27, 2020, the governor of Osaka requested people to refrain from going out over the weekend because the number of cases was showing an increasing trend [46]. On April 7, a state of emergency was declared by the government of Japan, requesting people to reduce contacts, adopt a stay-home policy, cancel mass gatherings and events, and refrain from crossing prefectural borders [46,47]. These were considered to have had an impact on the SARS-CoV-2 reproduction number [43,46]. Following the published studies, we calculated the reproduction numbers employing a piecewise constant model for three periods of calendar time, i.e., on and before March 26, March 27–April 6, and April 7 and later. For simplicity, we considered $k(t)$ as a constant for the entire period of time. During the initial period (up to March 26), the next-generation matrix K_1 was estimated at

$$K_1 = \begin{pmatrix} 1.70 & 0 \\ 0.36 & 0.99 \end{pmatrix}.$$

Transmission was mainly owing to people without a contact history, and the transmission among cases with a contact history contributed to 0.99 secondary transmissions. Bootstrap-based 95% confidence intervals (CIs) based on a multivariate normal distribution were (1.42, 1.97), (0.30, 0.41),

and (0.76,1.20) for R_{00} , R_{10} , and R_{11} , respectively.

The next-generation matrix K_2 for the second period (from March 27 to April 6) and K_3 for the third period (from April 7 to June 30) were estimated as

$$K_2 = \begin{pmatrix} 1.41 & 0 \\ 0.30 & 0.63 \end{pmatrix},$$

and

$$K_3 = \begin{pmatrix} 0.67 & 0 \\ 0.14 & 0.68 \end{pmatrix},$$

with $R_{00} \in [1.28, 1.55]$, $R_{10} \in [0.27, 0.33]$, and $R_{11} \in [0.41, 0.83]$ for the second period and $R_{00} \in [0.60, 0.74]$, $R_{10} \in [0.12, 0.15]$ and $R_{11} \in [0.58, 0.77]$ for third period. Once the restriction of contacts was requested by the Japanese government, R_{00} decreased slightly but not substantially during the second period. Instead, R_{11} decreased more abruptly than R_{00} . During the third period, both R_{00} and R_{11} took a value below 1, and the epidemic in the entire population was brought under control.

3.2. Step-function model

Next, we estimated the parameter $(R_{00}(t), R_{11}(t), k(t))$ for every 3 days during the entire period to recover the observed dynamics of $c_0(t)$ and $c_1(t)$ and then calculated the estimated $p(t)$.

Figure 2 presents a comparison of observed and predicted cases with and without a contact history as well as the estimated proportion of cases with a contact history. Bootstrap-based 95% CIs were computed by resampling the two types of infected individuals from a Poisson distribution, each for 1000 times. The predicted cases and predicted proportion contained most of the observed data within the 95% CI (Figure 2).

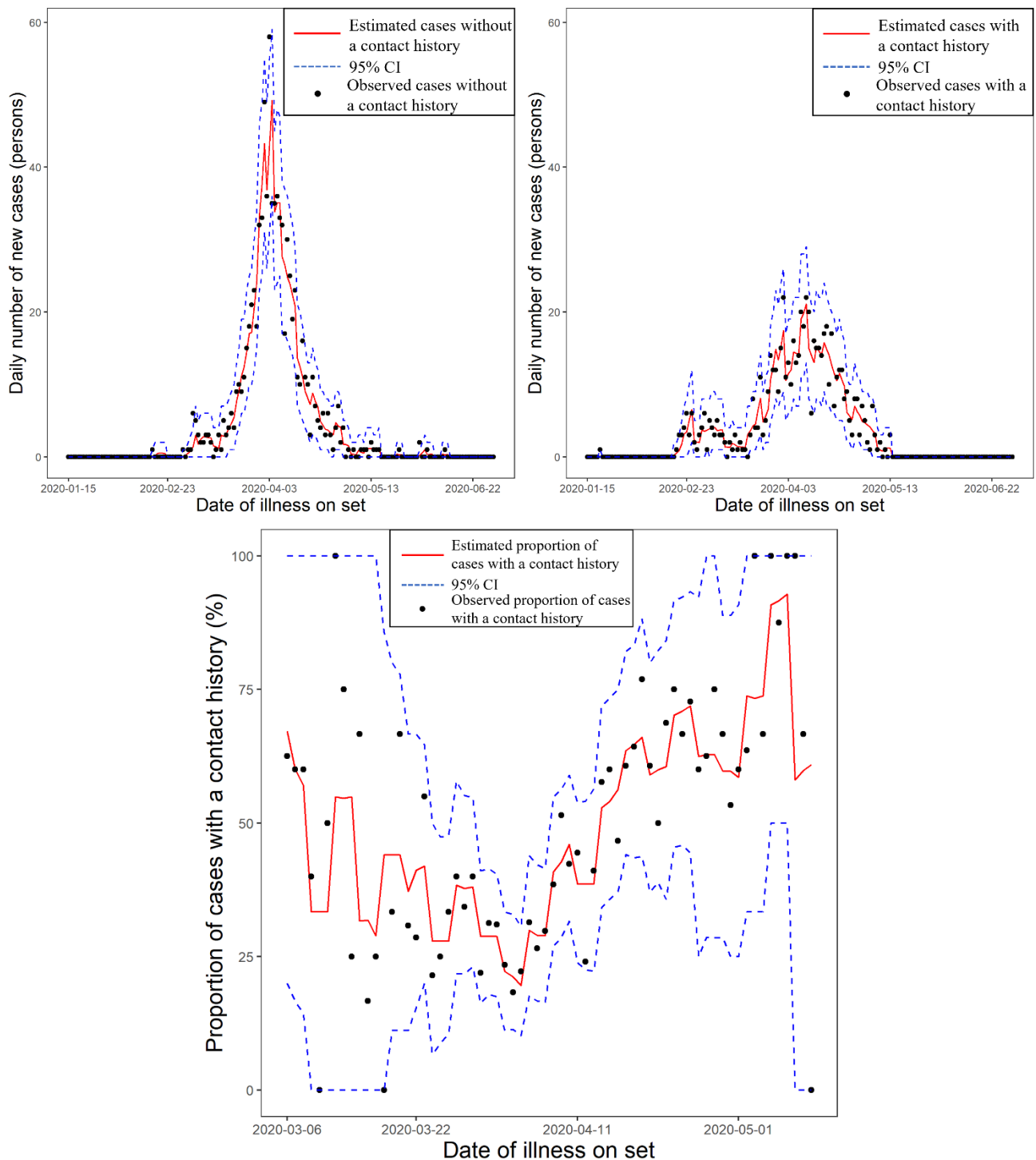


Figure 2. Predicted and observed COVID-19 cases by contact history in Osaka, 2020.

In all panels, the observed data are shown as dots, and the predicted mean is shown as a red line. Blue dashed lines represent 95% confidence intervals as computed by the bootstrap method. The top left panel shows the daily number of new cases (individuals) without a contact history, the top right panel shows the daily number of new cases (individuals) with a contact history, and the panel at the bottom shows the proportion of cases with a contact history (%) over time.

By fitting the model to the observed data using a piecewise constant model for all three parameters ($R_{00}(t), R_{11}(t), k(t)$) every 3 days, we could compute both the proportion of cases with a contact history $p(t)$ and the dominant eigenvalue of the next-generation matrix $R(t)$. Figure 3 shows the relationship between the two as a function of $R(t)$ on the horizontal axis. It can be seen that $p(t)$ does not take either the maximum or minimum value at a threshold level of transmission with $R(t) = 1.0$; there was no apparent threshold property observed for $p(t)$. The empirically estimated proportion of infected individuals with a contact history was 60.4% at $R(t) = 1.0$. With $R(t) < 1$ (subcritical level), $p(t)$ was a decreasing function of $R(t)$. Qualitatively, the minimum $p(t)$ was seen in the domain with $R(t) > 1$. For instance, although not theoretically ensured as a global minimum, the empirically estimated proportion minimum was 28.8% when the reproduction number was 2.0. It appears that $p(t)$ was slightly recovered for $R(t) > 2$, but it must be noted that the period with $R(t) > 2$ corresponded to the transmission dynamics in early March when a small number of secondary transmissions began with superspreading events. In fact, the well-cited basic reproduction number of SARS-CoV-2 is 2.5 [48].

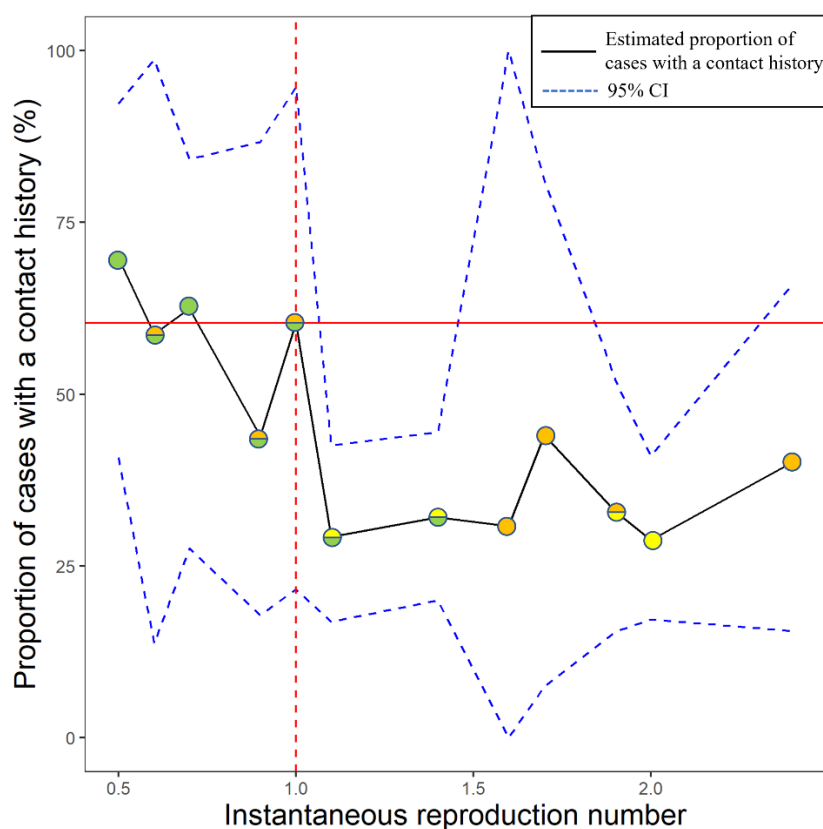


Figure 3. Relationship between the instantaneous reproduction number and proportion of cases with a contact history.

The black line shows the mean of estimated proportions of cases with a contact history (%), corresponding to the instantaneous reproduction number and the blue dotted lines show 95% confidence intervals computed using the bootstrap method. The colored points on the black line show the estimated instantaneous reproduction numbers that appeared from March 6 to May 10 with orange representing March 6–March 26, yellow representing March 27–April 6 and green representing

April 7–May 10, respectively. The points combined by two colors represent that the reproduction numbers at these points appeared in two of the three periods. The horizontal red line indicates the proportion of cases with a contact history when the instantaneous reproduction number is 1, as indicated by the vertical red dotted line.

4. Discussion

In the present study, we extracted epidemiological information regarding the proportion of COVID-19 cases with contact history. To clarify the relationship between transmission dynamics and contact history, we used a bivariate renewal process model to describe transmission among cases with and without a contact history. Analyzing the first wave dataset in Osaka from January 15 to June 30, 2020, we quantified the next-generation matrices as a function of time; thus, the instantaneous (effective) reproduction number was calculated for different periods during the epidemic wave. We objectively interpreted the estimated next-generation matrix and replicated the proportion of cases with contact $p(t)$ over time, and we examined the relationship to the reproduction number. In the subcritical condition with $R(t) < 1$, $p(t)$ was a decreasing function of $R(t)$. $p(t)$ was minimum with $R(t) > 1$. Even when the reproduction number was at the threshold level $R(t) = 1$, $p(t)$ did not take either the maximum or minimum value, and $p(t)$ was minimum with $R(t) > 1$.

An important point in the present study is that the dataset for the proportion of cases with a contact history does not simply reflect the transmission dynamics. As shown in Figure 3, $p(t)$ takes the minimum value with $R(t) > 1$, implying that in practice, contact tracing might have collapsed at some point with $R(t) > 1$. With an increasing value of $R(t)$ in a supercritical condition, $p(t)$ declined and gradually plateaued, perhaps reflecting an epidemiological situation that precludes the ability to maintain contact tracing for a broad range of cases (instead, only close contacts within households and in elderly care and health care facilities were constantly monitored). At a subcritical level $R(t) < 1$, the qualitative pattern of $p(t)$ still showed a decreasing trend with an increase in $R(t)$. This might be consistent with the explanation that contact tracing capacity is slightly but gradually reduced as a function of the number of secondary transmissions. To our knowledge, the present study is the first to have demonstrated the abovementioned relationship, using the simple yet tractable bivariate renewal process model.

From the next-generation matrices estimated for three distinct time phases, which correspond to the three different phases of governmental policy, we can see how the reproduction number changed during this period in relation to contact history. During the initial period, transmission between individuals with a contact history was near critical (R_{11} was 0.99), and transmission from individuals without a contact history to those with a contact history was limited (i.e., R_{10} was below 1). Transmission between individuals without a contact history was not under control, with $R_{00} > 1$. In the second period after the government's request to limit contacts, R_{00} diminished slightly but still took a value > 1 . Finally, after the declaration of the state of emergency, R_{00} fell to 0.67 and R_{10} and R_{11} also both remained below 1, indicating that the epidemic had been brought under control. We found that transmission to individuals with a contact history was below 1 for the entire course of the epidemic wave. Transmission among individuals without a contact history was substantially reduced only after declaration of the state of emergency. In this way, we showed that the bivariate model allows for the determination of the type of individuals (i.e., traced or untraced cases) contributing to transmission in relation to the epidemic period and the interventions in place.

An important future implication for use of the proposed model is to understand whether containment efforts can be successful in real-time. In addition to estimating the instantaneous reproduction number over time, we showed that $p(t)$, and also the next-generation matrix stratified by the presence of contact history, allows us to monitor the success of ongoing contact tracing (and other interventions) in practice with respect to containing an outbreak. A decreasing signal of $p(t)$ reflects increasingly difficult contact tracing. The present study findings indicate that monitoring $p(t)$ would be a useful addition to surveillance.

Several limitations of the present study must be discussed. First, our next-generation matrix might have been oversimplified, e.g., $R_{01}(t) = 0$, in advance of the estimation. In Japan, retroactive and prospective contact tracing was conducted during the first epidemic wave; thus, it was unlikely that traced cases contributed to producing untraced cases. However, this might not be applicable in other countries, and in fact, the use of four unknown quantities in the next-generation matrix increased uncertainty with regard to the heterogeneous transmission dynamics, which is the biggest disadvantage of our approach. Second, we did not account for undiagnosed cases. Unascertained cases must have existed [49], and our next-generation matrix does not show how undiagnosed cases contributed to secondary transmissions. Transmission from untraced cases could have been overestimated. Third, the study setting was restricted to the first COVID-19 wave in Osaka, although we have seen similar patterns of $p(t)$ in subsequent epidemic waves across Japan (data not shown). We can establish the generalizability of the findings in a quantitative sense by exploring multiple waves; however, the consistently traced data owing to the practice of backward and forward contact tracing in Japan was limited to the first wave. Fourth, we relied on contact tracing data taken during interviews conducted by healthcare workers. If other approaches are followed and the tracing capacity is not overwhelmed (e.g., by using smartphone apps, as described in the Introduction), quantitatively different patterns of relationships between $p(t)$ and $R(t)$ might be identified.

5. Conclusions

Many take-home lessons exist in designing control strategies for COVID-19 [50,51]. For instance, a longer duration of NPIs, e.g., lockdown, does not necessarily lead to smoothly decreasing confirmed cases, and the negative aspects of stringent NPIs on public health such as psychological distress are induced. As an alternative, specific mitigation policies that aim to diminish contact among people in specific high-risk settings (e.g., bar, cafeteria, gym, etc.) could also decrease transmission and potentially act as an alternative of NPIs for the entire population, but that calls for early diagnosis and isolation of secondary cases assisted by contact tracing. It should be noted that even if the digital tracing method is adopted, fully automated digital tracing without a manual tracing method may not be the most effective [52]. Combining digital and manual contact tracing methods would be perhaps required to confront the risk of the next pandemic.

Despite several technical limitations, we believe that the theoretical foundation regarding the proportion of cases with a contact history in relation to transmission dynamics was successfully described in the present study. We showed that a decreasing signal of $p(t)$ over time could reflect an increasing difficulty in further tracing of contacts. By stratifying the surveillance data of cases according to contact history, public health agencies can monitor the success of ongoing contact tracing practices.

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Conflict of interest

The authors declare no conflicts of interest.

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