Article

One possible reinfection with SARS-CoV-2 validated by 205-days interval of re-detection in Sapporo City, Japan

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Abstract: Since SARS-CoV-2 has spread all over the world, one of the key questions is how long immunity works for protecting hosts from infection. However, it was difficult to distinguish reinfection from re-detected positive cases caused by other reasons. We confirmed 23 re-detected positive cases in Sapporo City in 2020, and among them, the case with 205-days interval from initial onset to the second confirmation date was found. We calculated the probability of observing more than one case with over d-days interval of re-detection, p_{obs}, to find out whether the case with 205-days interval had the similar epidemiological characteristic with others or not. We found that 5th percentile and its 95% confidence interval of p_{obs} was 118 (45, 216) for Sapporo City data and 92 (86, 98) for KCDC data. This result indirectly suggested the case with 205-days interval was reinfection.

Keywords: SARS-CoV-2; COVID-19; reinfection; re-detected positive; Japan

1. Introduction

Since SARS-CoV-2 has spread all over the world, one of the key questions is how long immunity works for protecting hosts from reinfection. Immunity response after infection is important because establishment of herd immunity, predicting number of cases of SARS-CoV-2 and vaccine strategy are heavily influenced. Reports of secondary infection with SARS-CoV-2 have been published from Ecuador [1], Nevada [2], Belgium [3] and Hong-Kong [4]. These reinfections were confirmed by genetic information.

Re-detected positive cases did not just mean reinfections: many case reports [5–8] and systematic reviews [9–11] declared that re-detected positive cases were mainly not caused by reinfection but by re-activation, persistent infection or laboratory errors. The underlying mechanism of re-detected positive cases remains unknown.

In the present study, we report one case with 205-days interval from initial onset to the second confirmation date. This interval length of re-detection was longer than the length of other reported re-detected positive cases [9,10]. We used statistical method to validate the case with 205-days interval of re-detection as a very rare event if this case had similar epidemiological characteristics as other re-detected positive cases and showed that this case was probably exposed to second infection, indirectly.

2. Materials and Methods

2.1. Case history

The case was a 28-year-old female who was a resident of Sapporo City, to be infected with SARS-CoV-2 confirmed by PCR test on day X (in April 2020). She had symptoms of fever, cough and fatigue on day X-5 and after two days, she developed loss sense of taste and smell. The case had no previous medical history. Symptoms of the case resolved on the same date of the confirmation date. Until October 2020, she had no complications. On day X+205 (in October), she was again tested to be positive by PCR test. At this time, she developed fever on day X+202. Next day, fever resolved but she had sore throat and cough. Symptom of the case resolved in the end. The length of the interval from initial onset to the second confirmation date was 205 day. This length of the interval was longer than that of other re-detected positive cases in Sapporo City.

2.2. Data description

Data was provided by the public health office of Sapporo City in Hokkaido, Japan. The first confirmed case in Sapporo City was 14 February 2020. Until 31 December 2020, 8585 cases were confirmed. Among them, 23 cases including the case with 205-days interval from initial onset to the second confirmation date were confirmed as re-detected positive (RP) cases. Here we defined RP cases as ones tested to be positive after isolation due to the first confirmation of SARS-CoV-2 with PCR tests.

In the early phase of the epidemic, two consecutive negative results of PCR tests were needed for discharge in Japan. However, on 29 May 2020, the Japanese government decided that SARS-CoV-2 cases were able to leave the hospital basically 14 days after onset date [12]. Since length of the interval from initial onset to the second confirmation date was affected by the criteria of discharge of cases with SARS-CoV-2, we focused on RP cases whose first confirmation date was before 29 May 2020.

We also used data reported by KCDC on 19 May 2020 for comparison [5]. In this report, 285 RP cases were investigated, and viral cell culture testing was done for 108 RP cases and all of them were proven to have negative results. We utilized the histogram about days from initial onset to testing positive after discharge for our analysis.

2.3. Calculation of the probability of observing more than one case with over d-days interval of re-detection

For the purpose of validation of the case with 205-days interval of re-detection as a rare event, the probability of observing more than one case with over d-days interval of re-detection, p_{obs}, was calculated as follows.

First, we estimated the distribution of the interval from initial onset to the second confirmation date, g, by the maximum likelihood method. We used normal, gamma, lognormal and Weibull distribution for fitting, and the model with the minimum AIC value was used for the following analysis. RP cases reported before 29 May 2020 in Sapporo City excluding the reported case with 205-days interval were used for estimation.

Second, the possibility of observing at least one RP case with over d-days interval of re-detection, p_{re}, is calculated by

$$p_{re}(d) = 1 - G(d \mid \hat{\theta})$$

where d is interval length of re-detection, $\hat{\theta}$ is maximum likelihood estimators, and G is a cumulative distribution of g.

Finally, the probability of observing at least one case with over d-days interval of re-detection, p_{obs}, is a complementary event of observing no case with over d-days interval of re-detection. The probability, p_{obs}, is given by

$$p_{obs}(d) = 1 - P.M.F. \, of \, binom(p_{re}(d), n, 0),$$

where the second term of the right hand of the equation represents the probability mass function of binomial distribution with no observation of cases under the probability, p_{re}, among n cases. n for Sapporo City data was set to be 677, the cumulative number of cases as of 28 May 2020, and n for KCDC data was set to be 11078, the cumulative number of cases as of 19 May 2020. This probability, p_{obs}, can be regarded as how likely a case with d-days interval is observed when n cases are reported.

The bootstrap method was used for calculation of 95% confidence intervals of p_{obs}. We resampled the same size of interval lengths from original data for 5000 times and calculated p_{obs} for each. Then 2.5 and 97.5 percentile of the set of p_{obs} were adopted to be lower and upper bound of confidence interval for each d.

The maximum likelihood estimation was performed by L-BFGS-B method implemented in scipy version 1.5.0., one of the python packages [13].

3. Results

3.1. Characteristics of confirmed and re-detected positive cases

The total number of confirmed and re-detected positive (RP) cases before 29 May 2020 was 677 and 8, respectively, and its proportion was 1.182% (Table 1). The total number of confirmed and RP cases during 29 May 2020 and 31 December 2020 was 7908 and 15, and its proportion was 0.190%. Age was significantly different for data before 29 May 2020. Proportion of RP cases are slightly higher in the younger population. Sex was not significantly different for both terms.

Table 1. Attributes of reported cases and re-detected positive cases in Sapporo City.

	14 February 2020 to 28 May 2020				29 May 2020 to 31 December 2020			
	Cases[*1]	Re-detected positive cases	Proportion (%)	p-value[*2]	Cases[*1]	Re-detected positive cases	Proportion (%)	p-value[*2]
Total	677	8	1.182		7908	15	0.190	
Age								
0-19 years	23	1	4.348	0.0150	987	1	0.101	0.240
20-39 years	130	5	3.846		2971	9	0.303	
40-59 years	203	1	0.493		1895	3	0.158	
60-79 years	213	0	0.000		1223	2	0.164	

≧ 80 years	108	1	0.926		832	0	0.000	
Sex								
Male	312	3	0.962	0.792	3833	10	0.261	0.319
Female	357	5	1.401		3970	5	0.126	
Unknown	8	0	0.000		105	0	0.000	

[*1] For re-detected positive cases, the first confirmation date was used for classification and the second confirmed cases were not counted in this table.

[*2] p-value was calculated with G-test.

For 2 cases with missing initial onset date, the first confirmation date minus 4 days was imputed. 4 days was a mean of reporting delay in Sapporo City in 2020. Days from initial onset to the second confirmation date were statistically significant in term (p=0.0027) where p-value was calculated by Mann-Whitney U test (Figure1). For data before 29 May 2020, the minimum and maximum value was 22 and 205, whereas for data after 28 May 2020, the minimum and maximum value was 11 and 42. The proportion of data after 28 May 2020 less than 22 is 11/15 = 60.0%, meaning that majority of RP cases reported after 28 May 2020 were less than the minimum length of the interval before 29 May 2020.
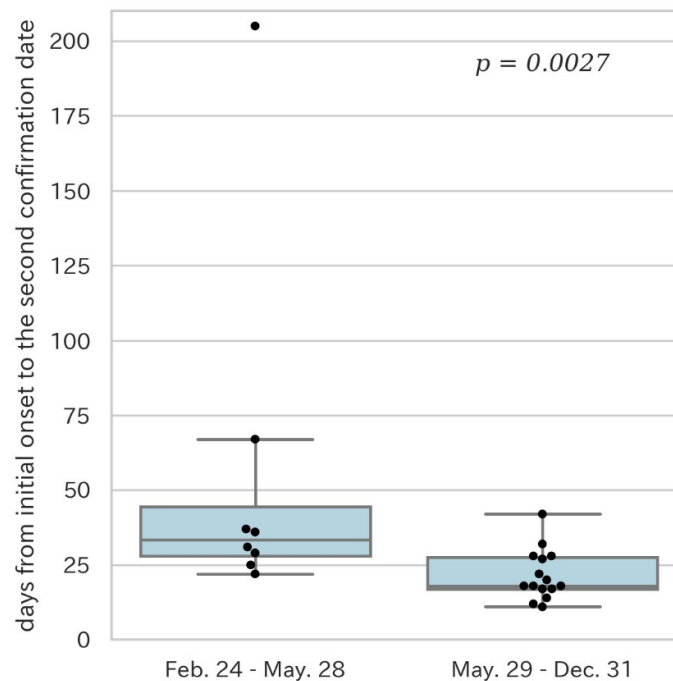

Figure 1. Swarmplot and boxplot of the first onset to the second confirmation date reported in Sapporo City stratified by term. P-value is calculated by Mann-Whitney U test.

3.2. Probability of observing at least one case with over d-days interval from initial onset to the second confirmation date

The estimation results of distributions of interval length from initial onset to the second confirmation date were shown in Table 2. The best fitted model was log normal and Weibull distribution for Sapporo City and KCDC, respectively. Although the mean of the interval length of KCDC data was 10 days longer than that of Sapporo City, the 5th percentile of p_{obs} for Sapporo City was longer than that of KCDC. This is because a Weibull distribution belongs to exponential family whereas a log normal distribution is one of the heavy-tailed distributions.

Table 2. The mean and standard deviation of the interval from initial onset to the second confirmation date and 5th percentile of p_{obs}, and p_{obs} at 205 days with its 95% confidence interval.

Data	n	Distribution	mean	sd	5th percentile of p_{obs} (95% conf.)	p_{obs} at 205 day (95% conf.)
Sapporo City	7	Log normal	35.075	12.076	118 (45, 216)	<0.0001 (<0.0001, 0.0828)
KCDC	225	Weibull	45.013	12.526	92 (86, 98)	<0.0001 (<0.0001, <0.0001)

The probability that one case with over d-days interval of re-detection, p_{obs}, is shown in Figure 2. 5th percentile and 95% confidence interval of p_{obs} was 118 (45, 216) for Sapporo City and 92 (86, 98) for KCDC data (Table 2). Although p_{obs} at 205 days was less than 0.0001 for Sapporo City, the 97.5th percentile of p_{obs} was 0.0828. p_{obs} at 205 days and its confidence interval for KCDC data were all less than 0.0001.
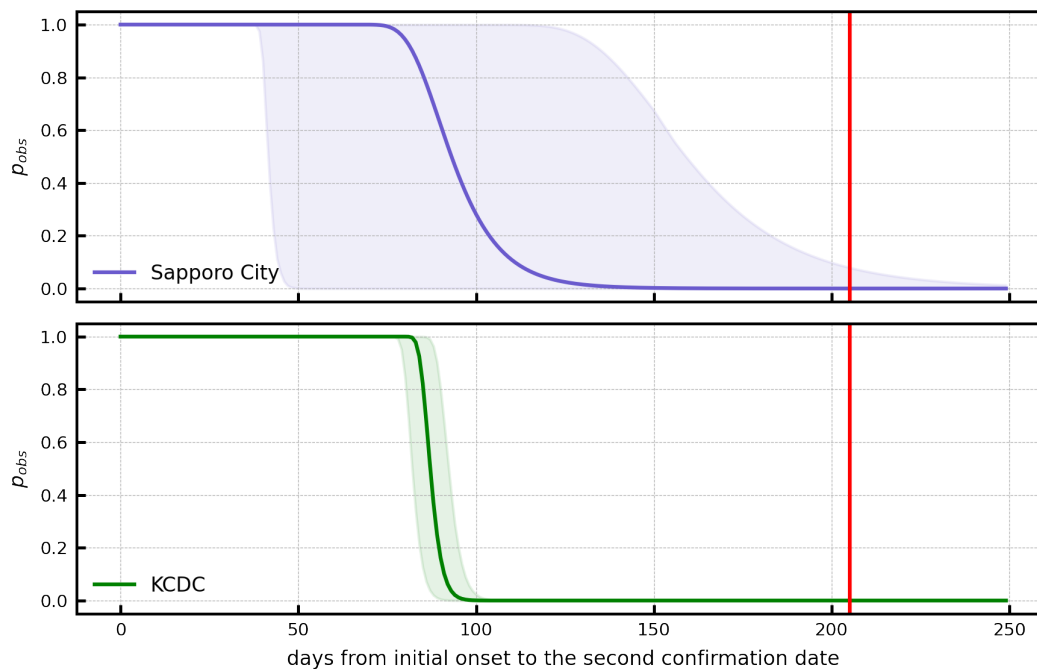

Figure 2. The probabilities that more than one re-detected positive case with over d-days interval from initial onset to the second confirmation date, p_{obs}, was observed. Shaded areas are 95% confidence intervals calculated by the bootstrap method. The red line

is drawn on 205 day, which was the length for the reported case suspected to be reinfection and this case was excluded from the calculation of p_{obs} for Sapporo City.

4. Discussion

The present study showed that one RP case with 205-days interval from initial onset to the second confirmation date was a rare event assuming that this case had the similar epidemiological characteristics with other RP cases. Although 95% confidence interval of 5th percentile of p_{obs} for Sapporo City included 205 days, estimated 5th percentile of p_{obs} was sufficiently low (<0.0001) for both Sapporo City and KCDC data. Therefore, this case would have the different underlying mechanism of re-detection from other RP cases, and we suspected this case to be reinfected one.

The one systematic review [10] argued with RP cases in detail and listed up the following possible explanations for RP cases, i) reactivation of the virus, ii) persistent in-fection, iii) new infection with the same or another strain, iv) laboratory errors. As for i), ii), the case with 95 days from initial onset to the second confirmation date [14] and the case with 82-days interval from Korea [5] were reported. Some report suspected that host immune status affected the length of viral shedding [15]. However, the case with the 205-days interval length reported in the present study was much longer than them and she had no medical history. As for iv) laboratory errors, false-positivity rate changes as a function of time [16]. The case was tested to be positive after 5 and 3 days after onset for the first and second confirmation, respectively, and this period did not have high false-positive rate. Moreover, the case had light symptom for both the first and the sec-ond time.

Therefore iii) new infection with the same or another strain was plausible explana-tion for this case. Among 4 reinfected cases validated by genetic information, the longest interval between the first and the second confirmation date was 142 days [2], which was still shorter than the case in this study.

Our study was not free from limitations. First, we did not have genetic information for this case so that we could neither confirm reinfection nor which strain the case was infected with. Also, we could not know whether reinfection existed among reported RP cases other than the case with 205-days interval. Second, p_{obs} for KCDC data were biased toward lower because of short observation period. Although there is a statistical method to correct this bias [17], we could not apply in this study due to lack of the interval length from discharge to the last observation date for each case in KCDC data. Finally, epidemic situation affects the probability of reinfection [18], but this is not considered in our study. Despite the above limitations, we believe that the report of this case supports the possibility of reinfection with SARS-CoV-2.

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