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Research article

Estimating the transmissibility of SARS-CoV-2 VOC 202012/01 in Japan using travel history information

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Abstract: Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has rapidly spread across the globe. The variant of concern (VOC) 202012/01 (B.1.1.7, also known as the alpha variant) bearing the N501Y mutation emerged in late 2020. VOC 202012/01 was more transmissible than existing SARS-CoV-2 variants and swiftly became dominant in many regions. More than 150 cases of VOC 202012/01 were reported in Japan by 26 February 2021. During the very early stage of introduction, only a subset arose from domestic transmission. If the reproduction number R (i.e., the average number of secondary transmission events caused by a single primary case) is greater than 1, the corresponding proportion should converge to 1 in a short period of time, and thus it is critical to understand the transmissibility of VOC 202012/01 based on travel history information. The present study aimed to estimate R of VOC 202012/01 using overseas travel history information. A mathematical model was developed to capture the relationship between travel history and R. We obtained travel history data for each confirmed case of VOC 202012/01 infection from 26 December 2020 to 26 February 2021. Maximum likelihood estimation was used to estimate R, accounting for right censoring during real-time estimation. In the baseline scenario, R was estimated at 2.11 (95% confidence interval: 1.63, 2.94). By 26 February 2021, an average of nine generations had elapsed since the first imported case. If the generation time of VOC 202012/01 was assumed to be longer, R was increased, consistent with estimates of R from case data. The estimated R of VOC 202012/01 in Japan exceeded 1 on 26 February 2021, suggesting that domestic transmission events caused a major epidemic. Moreover, because our estimate of R was dependent on generation time and ascertainment biases, continuous monitoring of contact tracing data is crucial to decipher the mechanisms of increased VOC 202012/01 transmissibility.

Keywords: Coronavirus; Statistical estimation; Epidemiological model; Mathematical model; Variant of Concern; Mutation

1. Introduction

The emergence of new variants of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the causative agent of coronavirus disease (COVID-19), has affected many industrialized countries that are already struggling to control the infection. The variant of concern (VOC) 202012/01, also known as the alpha variant (lineage B1.1.7), has received special attention since the end of 2020, when it began to rapidly replace preexisting variants and eventually dominated in many European countries and the United States [1–4]. SARS-CoV-2 causes acute infection of the upper and/or lower respiratory tracts [5]. The basic reproduction number of SARS-CoV-2 (typically defined as the average number of secondary cases generated by a single primary case in a fully susceptible population) was estimated to range from 1.5 to 3.5 based on analyses conducted during the early phase of the pandemic [6,7]. Because secondary transmission of COVID-19 generally occurs through clustering of cases in close contact settings, public health and social measures (PHSMs) have been implemented to halt chains of transmission [8]. Although the delta variant (B.1.617.2) has already replaced the alpha variant around the world, the introduction of SARS-CoV-2 VOC 202012/01 was remarkable and led to implementation of a concerted series of stricter PHSMs. Some studies suggested that the transmissibility of SARS-CoV-2 VOC 202012/01 is at least 50% higher compared with that of previously circulating variants [9–11]. In addition, infections caused by the alpha variant were at least 50% more lethal than non-VOC 202012/01 infections [12–14].

In Japan, the first cases of VOC 202012/01 were detected in quarantine and not in a local health facility on 26 December. Following the initial detection, more than 150 VOC 202012/01 cases had occurred as of 26 February 2021 (Figure 1). Because of increasing concerns regarding the surge of VOC202012/01 incidence, Japan intensified capacity for sequencing virus samples to detect the N501Y mutation in each prefecture. Moreover, the government required all incoming travelers to submit proof of a negative test result from throat swab samples starting on 13 January 2021 [15]. Despite these efforts, the number of confirmed domestic VOC 202012/01 cases gradually increased starting at the end of January 2021. There is a need for reliable methods to estimate the transmissibility of the SARS-CoV-2 alpha variant in Japan.

The number of confirmed imported cases of VOC 202012/01 reflects only a proportion of infected individuals. Thus, it is necessary to devise an estimation method that does not rely solely on counts of confirmed cases. Published studies have explored the transmission potential of zoonotic influenza virus using data on contact history with animals [16,17], offering key insights into the handling of travel history data for each confirmed case. The present study aimed to develop a method to estimate the reproduction number for domestic transmission of SARS-CoV-2 VOC 202012/01 in real-time using data from confirmed imported and domestic cases.

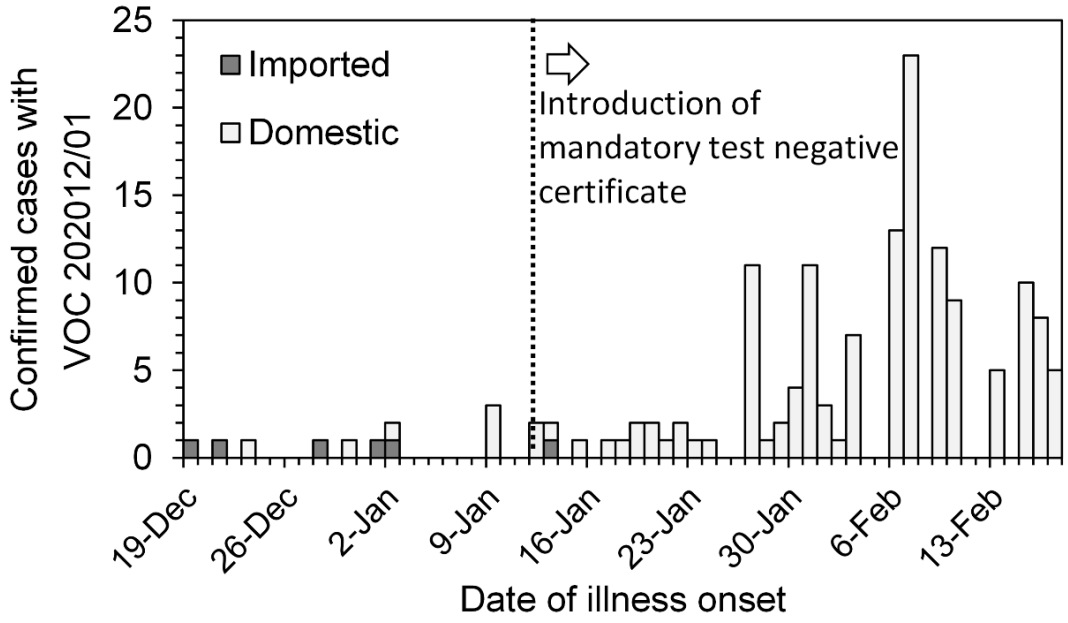

Figure 1. Daily number of confirmed SARS-CoV-2 alpha variant infections in Japan. Daily numbers of confirmed imported and domestic cases of COVID-19 caused by VOC 202012/01 in Japan are shown. Cases detected in airport quarantine station were excluded. All cases are plotted according to the date of symptom onset back projected from the empirical data. The vertical dashed line shows the date on which mandatory submission of test-negative document was introduced as part of quarantine measures13 January 2021 in Japan. SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; COVID-19, coronavirus disease 2019; VOC, variant of concern.

2. Materials and methods

2.1. Epidemiological data

To estimate the transmissibility of VOC 202012/01, we used data on cases of SARS-CoV-2 alpha variant (N501Y mutation) confirmed by reverse transcription polymerase chain reaction from 26 December 2020 to 26 February 2021 in Japan. Cases were detected in airports or during quarantine; in addition, more than 40% of confirmed COVID-19 cases were screened for the N501Y mutation [18] and the testing results are publicly available on the website of the Ministry of Health, Labour and Welfare (MHLW) of Japan [19]. To explore the transmissibility of domestic cases of SARS-CoV-2 VOC 202012/01, cases of VOC 202012/01 identified in quarantine (i.e., at airports) were excluded from the analysis; these cases were placed under strict observation and no chains of transmission emerged. In this study, an imported case of VOC 202012/01 was defined as an individual with confirmed VOC 202012/01 infection who had a history of overseas travel within 7 days prior to symptom onset. A domestic case of VOC 202012/01 was defined as an individual who had no history of overseas travel within 7 days prior to symptom onset. Cases detected in airport quarantine station were excluded, because their movement was restricted upon diagnosis and it is thus very hard for them to contribute to domestic spread of infection.

2.2. Mathematical model

To calculate the reproduction number for domestic transmission of VOC 202012/01 in Japan, a simplistic model was developed. For this purpose, here we define domestic transmission as the transmission that takes place within Japan, regardless of primary case being imported or domestically acquired infection. If the domestic transmission leads to a substantial number of secondary cases and subsequent generations, the series of transmission implies that the reproduction number $R>1$ and the proportion of domestic cases out of all cases would of course increase. Let R and n represent the reproduction number of the alpha variant and the number of generations caused by an imported case, respectively. Because infections occur in geometric series, the cumulative number of cases by generation n caused by a single imported case is calculated as $\frac{1-R^{n+1}}{1-R}$ [16,17]. If $R \ll 1$ and n is large, the cumulative number of cases converges to $1/(1-R)$. Out of $1/(1-R)$, only 1 case was the imported case. Thus, the proportion of imported cases out of total cases is calculated as $(1-R)$.

To estimate the reproduction number in real-time without using the abovementioned convergence result, we need to account for multiple primary cases (i.e., multiple imported cases w) as well as the time delay of the number of generations of transmission that have elapsed since the previous imported case. Let the probability mass function of the elapsed number of generations be f_n. The total number of domestic cases would be written as:

$$C_{domestic} = w\left(\sum_{n=0}^{N} f_n \frac{1-R^{n+1}}{1-R} - 1\right), \tag{1}$$

where $C_{domestic}$ represents the total number of domestic VOC 202012/01 cases generated by imported VOC 202012/01 cases, and N is the maximum number of generations by the latest observation time. In equation (1), w represents the total number of imported VOC 202012/01 cases; it should be noted that w is not fully observable because of unrecognized introductions. During the course of introduction of VOC 202012/01 from December 2020 to February 2021 (Figure 1) we assumed that imported cases decreased exponentially over time because of strengthened travel restrictions. Thus, we first developed a model to describe the incidence of imported cases i at calendar time t, which we assumed could be described by $i(t) = ke^{rt} (r < 0)$; here, k was a constant, r was the increasing/decrease rate of imported cases per day and t was the time of infection among imported cases. The exponential trend of imported cases was assumed, as part of an approximation of the increasing/decreasing number of cases with alpha variant abroad, and even under quarantine measures, we employed this approximation, because the observed number of imported cases in Japan represents documented (confirmed) infections that escaped from detection at airport and shows only a portion of actual number of imported cases. $i(t)$ describes the infection-age distribution of imported cases. Let T_g be the mean generation time (assumed as 5 days), the probability mass function of the possible number of elapsed generations n of imported cases f_n is given by:

$$f_n = \frac{\int_{(n-1)T_g}^{nT_g} kexp(rt)dt}{\int_0^{n_{max}T_g} kexp(rs)ds} = \frac{e^{rnT_g} - e^{r(n-1)T_g}}{e^{rn_{max}T_g} - 1} \tag{2}$$

$$= \frac{e^{r'n} - e^{r'(n-1)}}{e^{r'n_{max}} - 1}.$$

where $r'=rT_g$ that approximates the growth rate of imported cases per generation and n_{max} represents the maximum number of generations of cases. The number of primary cases (i.e., imported cases) is w. From w imported cases, $C_{domestic}$ domestic cases arose. Thus, the proportion of imported cases out of all cases would be:

$$p_{imported} = \frac{w}{w\left(\sum_{n=0}^{N} f_n \frac{1-R^{n+1}}{1-R} - 1\right) + w}. \quad (3)$$

There may be ascertainment bias in the detection of VOC 202012/01 cases. To assess the impact of ascertainment bias on the analysis, we incorporated different biases α and β for imported and domestic cases, respectively.

$$p_{imported} = \frac{\alpha w}{w\left(\sum_{n=0}^{N} f_n \frac{1+(\beta-1)R^2-\beta R^{n+1}}{1-R} - 1\right) + \alpha w}$$

$$= \frac{\alpha}{\alpha + \sum_{n=0}^{N} f_n \frac{1+(\beta-1)R^2-\beta R^{n+1}}{1-R} - 1}. \quad (4)$$

for $n>0$. Biases α and β ($0 < \alpha \leq 1$ and $0 < \beta \leq 1$) represent the relative ascertainment bias of detecting imported and domestic cases. In this model, imported cases are α times less likely to be identified than domestic cases. We assumed that secondary and subsequent generations of domestic cases are more likely to be diagnosed with relative frequency β, leading to generation of the series of cases $A_n = 1 + R + \beta R^2 + \beta R^3 + \cdots + \beta R^n$. Let i and j represent the number identified imported and domestic cases, respectively. Supposing that the elapsed number of generations n_u is known for each imported case u, using equation (2) and $p_{imported}$, the following likelihood function can be employed to estimate R from the observed proportion of imported cases:

$$L(R; i, j, r, k, \alpha, \beta) \propto \left(1 - p_{imported}(u_1)\right)^j \prod_{u=1}^{i} p_{imported}^{i}(u) f_{n_u}. \quad (5)$$

It should be noted that (1-$p_{imported}$) used the time elapsed since first imported case, because primary cases (or ancestor case) of each observed case without travel history cannot be manually identified. Under this assumption, the estimation would allow us to obtain a pessimistic estimate of the reproduction number of VOC. In this analysis, the elapsed number of generations n_u was calculated from the difference between the date of illness onset of the first identified primary case (i.e., the very first imported VOC 202012/01 case on 19 December 2020) and the latest date of illness onset in a domestic case divided by the mean generation time. The reproduction number was estimated by minimizing the negative logarithm of equation (5). The 95% confidence intervals (CI) were computed using a parametric bootstrap method. After resampling r and k 1,000 times each from a multivariate normal distribution with a variance-covariance matrix generated by maximum likelihood estimation, we obtained a total of 1,000 estimates of the reproduction number to provide an uncertainty bound.

Each ascertainment bias α and β was set to 1 for the baseline scenario in our analysis. The mean generation interval of SARS-CoV-2 VOC 202012/01 was assumed to be 5 days based on data for preexisting variants in the baseline scenario [20], although the biological characteristics of SARS-CoV-2 VOC 202012/01 have not yet been explicitly clarified. When necessary, the mean time delay from symptom onset to reporting, which was used for back calculating illness onset date, was assumed to be 9 days based on surveillance datasets. To explore the impacts of those parameters on the estimated reproduction number for domestic transmission of VOC202012/01, various scenarios were examined including varying the generation time from 4 to 6 days, elongating the mean delay from illness onset to reporting from 7 to 11 days, and increasing ascertainment biases from 0.6 to 1.0

2.3. Ethical considerations

This study was approved by the Medical Ethics Board of the Graduate School of Medicine, Kyoto University (R2676). The study used data published online by public health jurisdictions in Japan.

3. Results

A total of six imported cases, excluding those diagnosed during airport quarantine, and 146 domestic cases were used for the analysis for the period between 26 December 2020 and 26 February 2021. For the baseline scenario, we estimated the reproduction number for domestic transmission of SARS-CoV-2 VOC 202012/01 in Japan using data from 26 December 2020 to 26 February 2021. The Japanese government declared a state of emergency from 7 January to 21 March 2021 and imposed movement restrictions. In the presence of these countermeasures, the reproduction number of the alpha variant was estimated to be 2.11 (95% CI: 1.63, 2.94). The mean (standard deviation [SD]) number of generations that had already elapsed was estimated at 9.6 (1.8).

Figure 2 shows the estimated reproduction number for domestic transmission of VOC 202012/01 at different time points (i.e., for different periods of estimation). Datasets were updated in real-time from 29 January to 26 February 2021. The reproduction number was estimated to be 1.75 (95% CI: 1.44, 2.26) during the first estimation period on 29 January, and continuously increased and reached

2.23 (95% CI: 1.75, 3.06) on 19 February. The estimated reproduction number then slightly dropped to 2.11 (95% CI: 1.63, 2.94) on 26 February. During these periods, Japan was under the stage of emergency, and multitudes of interventions, including the restriction of mobility, were in place.

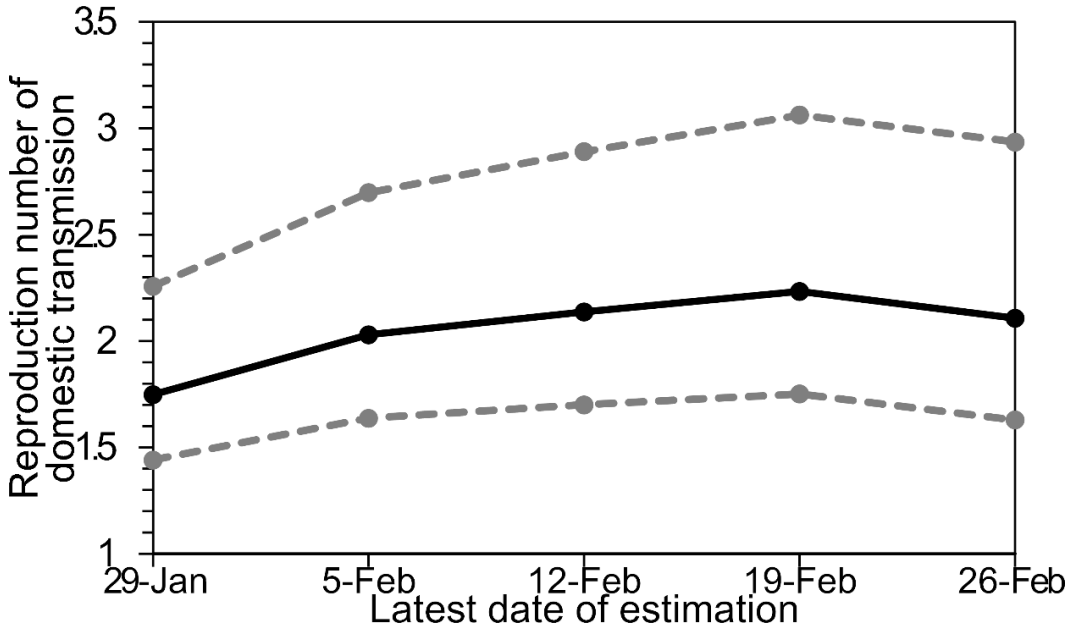

Figure 2. Estimated reproduction number for domestic transmission of SARS-CoV-2 alpha variant in Japan at different times of estimation. The black line shows the maximum likelihood estimate for the reproduction number of the alpha variant (mean generation time 5 days, delay from symptom onset to reporting of 9 days, and ascertainment biases α and β both 1) from 29 January to 26 February 2021. The gray dotted lines show the 95% CIs of the reproduction number derived from the parametric bootstrap method. SARS-COV-2, severe acute respiratory syndrome coronavirus-2; CI, confidence interval.

Figure 3 shows the sensitivity of the reproduction number R to parameter estimates. R increased linearly from 1.80 (95% CI: 1.46, 1.2.36) to 2.46 (95% CI: 1.82, 3.63) as the mean generation time increased from 4 to 6 days (Figure 3A). The mean generations that had elapsed were estimated at 11.8 (SD: 2.5) and 7.7 days (SD: 1.8) for mean generation times of 4 and 6 days, respectively. As is well known from Euler-Lotka equation, the reproduction number is given by the inverse of moment generating function of the generation time given the intrinsic growth rate [6,9]. The same mechanism applies to our estimation approach. However, the impact of delay from symptom onset to reporting on estimates of the reproduction number appeared to be small: R increased slightly from 2.06 (95% CI: 1.62, 2.82) to 2.24 (95% CI: 1.71, 3.17) using delays of 7 days and 11 days, respectively (Figure 3B). To explore the role of ascertainment bias in the detection of imported and domestic cases of VOC 202012/01, R was estimated using relative ascertainment rates from 0.6 to 1.0 for imported and domestic cases (Figure 3C and 3D, respectively). Compared with ascertainment rate at 1.0, unbiased estimated of R was only slightly elevated as the ascertainment bias for detecting imported VOC 202012/01 cases increased. Conversely, compared with ascertainment rate at 1.0, unbiased estimated of R only marginally decreased as the ascertainment bias for detecting domestic VOC 202012/01 cases increased. We verified the impacts of detection biases for imported and domestic VOC 202012/01 cases on the estimate of the reproduction number analytically by assessing the relative ascertainment rates. With smaller ascertainment rate of domestic cases, it is easier for imported cases to be detected and diagnosed.

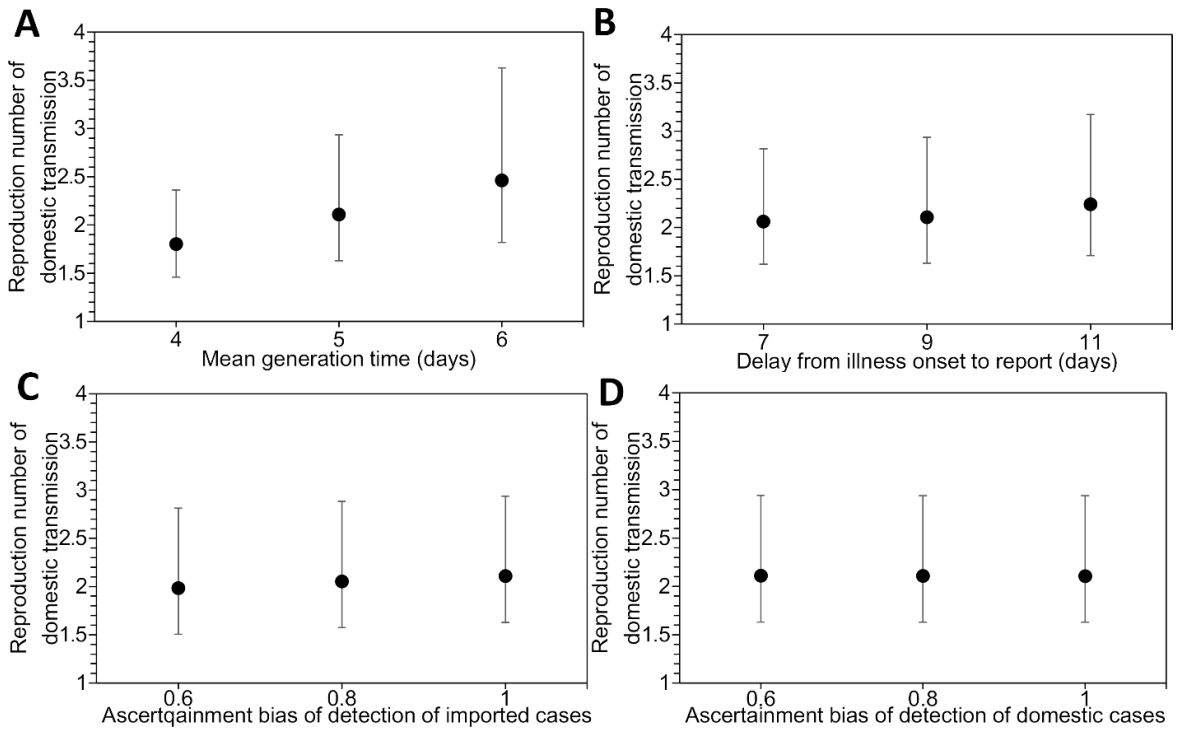

Figure 3. Estimated reproduction number for domestic transmission of SARS-CoV-2 alpha variant in Japan using different values for the generation time and ascertainment bias. Each black dot represents the estimated reproduction number of the alpha variant. The error bars show the 95% CIs derived from bootstrap resampling. The baseline scenario for our estimates was based on the following assumptions: mean generation time of 5 days, delay from symptom onset to report of 9 days, and ascertainment bias for detecting imported (α) and domestic cases (β) both 1. A. The mean generation time was varied from 4 to 6 days. B. The delay from symptom onset to reporting was varied from 7 to 11 days. C. The ascertainment bias for detecting imported cases was varied from 0.6 to 1. D. The ascertainment bias for detecting domestic cases was varied from 0.6 to 1.0. SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; CI, confidence interval.

4. Discussion

The present study explored the domestic transmissibility of SARS-CoV-2 VOC 202012/01 in Japan using travel history information. Our findings revealed that the reproduction number for domestic transmission of VOC 202012/01 was already above 1 as of the end of January 2020, then subsequently increased despite declaration of a state of emergency. The mean generation time of SARS-CoV-2 VOC 202012/01 had a strong impact on estimates of the reproduction number. Ascertainment biases in detecting imported and domestic VOC 202012/01 cases had contrasting influences on estimates of the reproduction number. Even when PHSMs were in place due to excessive number of cases, the resulting estimate of R for alpha variant was estimated to be 1.6–2.9, i.e. supercritical level.

The Japanese government decided to require all incoming travelers entering Japan to submit proof of negative SARS-CoV-2 tests conducted within 72 hours of departure starting on 13 January 2021. This action may have delayed the spread of VOC 202012/01 in the community. Along with quarantine

measures, the government declared a second state of emergency on 7 January 2021. It should be noted that the estimate of the VOC 202012/01 reproduction number in the current study was in the context of a state of emergency. Thus, lifting of strong PHSMs could potentially lead to rapid spread of VOC 202012/01, as demonstrated by the situation in some European countries [1,2,11]. Our findings suggest that the reproduction number for domestic VOC 202012/01 transmission was more than 1 at the end of January; around that time, the spread of VOC 202012/01 was already rampant in Japan. According to the MHLW, as of 9 March 2021 the number of confirmed infections by VOCs (i.e., alpha, beta, and gamma variants) had reached 345 cases including those identified in quarantine. Therefore, the alpha variant was starting to spread and become more prevalent across Japan at that time [21].

Despite implementation of quarantine measures by the government, there are a few reasons why some cases of VOC 202012/01 acquired abroad were confirmed not in quarantine but at local health centers. First, negative test results for SARS-CoV-2 and tests conducted in airports are not guarantees of the absence of the virus [22]. Second, even if undetected cases were required to self-isolate in their homes or hotels for 14 days after entering Japan, they may have been in contact with others. The possibility of such events could lead to generation of secondary cases. Although the estimated reproduction number increased between 29 January and 19 February 2021 (Figure 2), it decreased slightly by 26 February. This may be because our estimate assumed that domestic cases increase with a constant R; thus, a decreasing trend in domestic cases because of reporting delays cannot be well captured by our model.

Sensitivity analyses were conducted using different assumptions for mean generation time and ascertainment biases in detecting imported and domestic cases of VOC 202012/01. Although some estimates of the transmissibility of the B1.1.7 lineage have assumed a shorter mean generation time or the same interval as previous lineages (i.e., approximately 5–6 days [9,11,23]), the reproductive number of VOC 202012/01 increased for longer generation times. Therefore, continuous monitoring and studies exploring the characteristics of new SARS-CoV-2 variants are required. We also quantified how ascertainment biases affected estimates of the VOC 202012/01 reproduction number. If imported cases of VOC 202012/01 were less likely to be detected than domestic cases, the actual value of the reproduction number would be slightly smaller than estimated from empirical data without an adjustment of ascertainment. By contrast, if domestic VOC 202012/01 cases were less likely to be found than imported cases, the actual value of the reproduction number would be only slightly greater than what is estimated without adjusting for ascertainment. Our analyses imply that the estimation of the reproduction number could be stable regardless of the light changes of the ascertainment biases of imported and domestic cases (i.e., from 0.6 to 1). However, considering potential impacts on estimates of the reproductive numbers, cases should be tightly ascertained with caution. To do so, nationwide implementation of random screening for SARS-CoV-2 VOC 202012/01 must be accelerated to more accurately understand transmission dynamics. Some local governments decided to reinforce testing capacity for VOC202012/01. However, random screening should be implemented systematically in all prefectures and the resulting information should be made publicly available [24].

Our study had several limitations. First, we assumed that the proportion of imported cases of VOC 202012/01 among all confirmed cases can explain all infections. Thus, estimates of the reproductive number would not fully capture the transmission dynamics of domestic cases if this assumption was violated. Additional data supporting this assumption are required. Second, confirmed VOC 202012/01 cases were not randomly sampled from the population in Japan, which means there could have been selection bias (for example, because of the occurrence of clusters of cases). However, including relative

ascertainment bias in the model allowed us to partially address this problem and assess the potential impacts of these biases. Third, we assumed that the number of imported cases of VOC 202012/01 decreased exponentially over time. Our results may be influenced by the probability mass function of the generations of each imported case. Fourth, because we did not have the date of confirmed infection or symptom onset of each case, we back projected the date of symptom onset using the mean interval between symptom onset and reporting. Although only 27 of 158 cases were available to estimate this delay, our results suggested that variation in reporting delay did not significantly affect the estimate of the reproduction number. Finally, because our analysis relied on a homogeneously mixing population, heterogeneity based on geographical location and age composition was not considered.

Despite some remaining tasks for future studies, our proposed mathematical approach can be used to model the domestic transmissibility of VOC 202012/01 cases in Japan. Our findings indicate that the reproduction number for domestic transmission of VOC 202012/01 was greater than 1 for a period time, and was influenced by several parameters such as the mean generation time and ascertainment biases. Thus, continued monitoring for cases of VOC 202012/01 is critical to provide more accurate estimates and inform efforts to control new variants of SARS-CoV-2.

5. Conclusions

We successfully developed a method for estimating the reproduction number for domestic transmission of SARS-CoV-2 VOC 202012/01 using the confirmed imported (n = 6) and domestic cases (n = 146) in Japan. The reproduction number was estimated as more than 1 at the end of January 2021, and subsequently, the value increased. A sensitivity analysis suggested that the biological characteristics of VOC 202012/01 (i.e., mean generation time) can impact estimates of the reproduction number. We assessed the impacts of ascertainment biases in detecting imported and domestic cases of VOC 202012/01. Systematic monitoring via random sampling nationwide will enable more robust estimation of the reproduction number of VOC 202012/01. Mutation of SARS-CoV-2 must be continuously monitored. Modeling the spread of new variants can inform strategies to control the spread of these variants more efficiently. Our modeling study agreed well with the subsequent outcome of VOC 202012/01 spread and replacement of pre-existing SARS-CoV-2 in Japan.

Conflict of interest

The authors declare no conflicts of interest associated with this manuscript.

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