Infectiousness in omicron BA.2 (B.1.1.529.2) an effectiveness of the fourth vaccination BA.2 in Japan

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Conflict of Interest:
No author has any conflict of interest, financial or otherwise, to declare in relation to this study.

ICMJE Statement
Contributors JK was responsible for the coordination of the study and responsible for the data setting. YO developed the model and TS illustrated the results. All authors contributed to the writing of the final manuscript.

Abstract

Background: Omicron variant strain dominated since the beginning of 2022. Its infectivity was supposes to be higher than Delta variant strain or strains in past. Moreover, the fourthe vaccination had started in May, 2022.

Object: We estimated prevalence of omicron variant strain, particularly BA.2 (B.1.1.529.2) variant and COVID-19 vaccine effectiveness of the third dose in Japan as well as controlling for waning of second dose of vaccine, other mutated strains, the Olympic Games, and countermeasures.

Method: The effective reproduction number R(*t*) was regressed on shares of omicron variant strain and BA.2 and vaccine coverage of the third dose, as well as along with data of temperature, humidity, mobility, share of the other mutated strains, and an Olympic Games and countermeasures. The study period was February, 2020 through February 21, 2022, as of March 15, 2022.

Results : Estimation results indicated that waning of the second dose vaccine e with 150 days prior was the most appropriate specification. Moreover, BA.2 of omicron variant strain has higher infectively than other variant strain or traditional strain.

Discussion: Because of data limitation since emerging BA.2, the estimated its infectively will change over time.

Keywords: COVID-19, effective reproduction number, omicron, vaccine coverage, vaccine effectiveness, BA.2

1. Introduction

Omicron variant strain dominated since the beginning of 2022 in Japan as well as rest of the world. Though some researched supposed higher infectivity than Delta variant strain or strains in past [1,2] , it was much concern of public health and general in the real world, especially in the community as well as its pathogenicity. Moreover, since February 2020, sublineage BA.2(B.1.1.529.2) of omicron variant strain had emerged [3-5]. After that, sublineage BA.5 also emerged in June, 2022 and spread rapidly.

Before delta variant strain emerging, wide coverage of COVID-19 vaccination has altered outbreak situations in European countries and in the US. Unfortunately, vaccination in Japan started only in February, 2021 using BNT162b2 mRNA (Pfizer Inc., BioNTech) and mRNA-1273 (Moderna, Inc.) vaccines: among the latest of starting dates of vaccination programs in economically developed countries. Later, ChAdOx1 adenoviral vector (Oxford, AstraZeneca) also became available. By the end of November 2021, the rate of completion for second dose vaccine administration had reached almost 80% in Japan (Figure 1) [6,7]. The next challenge posed by vaccine issues in Japan might be waning of vaccine effectiveness.

In fact, waning vaccine effectiveness has been reported [8,9]. One study revealed that the log of IgG antibody titer decreased by a factor of 18.3 when measured six months after second-dose vaccination. Another study revealed vaccine effectiveness as 77.5% at one month after the second vaccination, but it had decreased to about 20% when measured 5–7 months later. In the real world, vaccines of several types have been used. Moreover, vaccinated persons might change their behaviors. Therefore, this study assessed vaccine effectiveness and its waning capabilities against infectively in the real world, particularly in Japan.

By the time vaccinations started in Japan, the alpha variant strain had emerged and had expanded to dominate the recorded infections. Subsequently, a new mutant alpha variant strain appeared in May. Based mainly on data reported by the UK, its infectively and pathogenicity were estimated as 35–90% higher than those of the original strain circulating before the emerging variant strain [10-13]. Therefore, we consider the prevalence of these mutated strains together when evaluating vaccine effects.

The Olympic Games and Paralympic Games of 2020 began on July 23, 2021. A subject of great concern for COVID-19 outbreak effects in Japan was whether audiences would be allowed to attend game events, or not. As part of this controversy, some experts asserted that the Games should be abandoned because they would expand the outbreak explosively [14]. As a result, the game events were held with no live audience. Under the state of emergency declared in Tokyo, effects of the 2020 Tokyo Games must be included to evaluate vaccine effectiveness.

As countermeasures against the COVID-19 outbreak in Japan, school closure and voluntary event cancellation were adopted from February 27, 2020 through the end of March.

Large commercial events were cancelled. Subsequently, a state of emergency was declared for April 7 through 25 May, stipulating voluntary restrictions against leaving home. Consumer businesses such as retail shops and restaurants were shuttered. During this period, the first peak of infection was reached on April 3. Infections subsequently decreased through July 29. The so-called “Go To Travel Campaign” (GTTC) was launched on July 22 as a 50% subsidized travel program aimed at supporting sightseeing and tourism businesses with government-issued coupons for use in shopping at tourist destinations. It was expected that the campaign might expand the outbreak. Thereafter, GTTC continued to the end of December, by which time a third wave of infection had emerged. The third wave in December, which was larger than either of the preceding two waves, reached its highest peak at the end of December. Therefore, GTTC was inferred as the main reason underlying the third wave [15].

To suppress that third wave of infection, a second state of emergency was declared from January 8, 2021 through March 15, 2021. However, a fourth wave emerged at the end of February, probably because of the spread of variant strains. To support hosting of the Olympics and Paralympics games in Tokyo in July, a third state of emergency was declared on April 25, 2021. It had ceased on June 20, 2021 in Tokyo. Nevertheless, the outbreak commenced again before the Tokyo Games 2020 started. Therefore, a fourth state of emergency was declared on July 13, 2021. It continued thereafter until the Tokyo Games 2020 had closed.

Although results have been mixed, some findings from earlier studies suggest that COVID-19 is associated with climate conditions [16–19]. If that were true for Japan, then GTTC might not have been the main factor contributing to the third wave. In fact, mobility was inferred as the main cause of the outbreak dynamics for the first wave in Japan [20] and throughout the world [21–24].

The object of this study was to estimate waning of vaccine effectiveness against SARS-CoV-2 infectively for the outbreak in Japan as a result of the vaccine effectiveness itself, the mutated strain, the Olympic Games, countermeasures, and other factors that might affect infectively.

2. Methods

This study examined the numbers of symptomatic patients reported by the Ministry of Health, Labour and Welfare (MHLW) for February 1, 2020 – February 21, 2022 published [25]as of March 15, 2022. Some patients were excluded from data for Japan: patients presumed to be persons infected abroad or infected as Diamond Princess passengers. Those patients were presumed not to represent community-acquired infection in Japan. For some symptomatic patients with unknown onset dates, we estimated the onset dates from an empirical distribution with duration extending from onset to the report date among patients for whom the onset date had been reported.

Onset dates among patients who did not report this information and a reporting delay were adjusted using the same procedures as those used for earlier studies [26,27]. As described hereinafter, we estimated the onset dates of patients for whom onset dates had not been reported. Letting $f(k)$ represent this empirical distribution of the incubation period and letting N_t denote the number of patients for whom onset dates were not published and available at date t, then the number of patients for whom the onset date was known is t-1. The number of patients with onset date t-1 for whom onset dates were not available was estimated as $f(1)N_t$. Similarly, patients with onset date t-2 and for whom onset dates were not available were estimated as $f(2)N_t$. Therefore, the total number of patients for whom the onset date was not available, given an onset date of s, was estimated as $\Sigma_{k=1} f(k) N_s + k$ for the long duration extending from s.

Moreover, the reporting delay for published data from MHLW might be considerable. In other words, if $s+k$ is larger than in the current period t, then $s+k$ represents the future for period t. For that reason, N_{s+k} is not observable. Such a reporting delay engenders underestimation of the number of patients. For that reason, it must be adjusted as $\Sigma_{k=1}^{t-s} f(k) N_s + k \,/ \Sigma_{k=1}^{t-s} f(k)$. Similarly, patients for whom the onset dates were available are expected to be affected by the reporting delay. Therefore, we have $M_s|_t \,/ \Sigma_{k=1}^{t-s} f(k)$, where $M_s|_t$ represents the reported number of patients for whom onset dates were period s as of the current period t.

We defined R(t) as the number of infected patients on day t divided by the number of patients who were presumed to be infectious. The number of infected patients was calculated from the epidemic curve by the onset date using an empirical distribution of the incubation period, which is $\Sigma_{k=1}f(k)E_{t+k}$, where E_t denotes the number of patients for whom the onset date was period t. The distribution of infectively in symptomatic and asymptomatic cases $g(k)$ was assumed to be 30% on the onset day, 20% on the following day, and 10% for the subsequent five days [28] . Then the number of infectious patients was $\Sigma_{k=1}g(k)E_{t-k}$. Therefore, R(t) was defined as $\Sigma_{k=1}f(k)E_{t+k}/\Sigma_{k=1}g(k)E_{t-k}$.

Data indicating the shares of mutated variants among all cases were published by the Tokyo Metropolitan Government. Unfortunately, detailed information about mutated strains has not been published for the entirety of Japan. We used four measures for the mutant strain shares in Tokyo, Japan: alpha, delta, omicron and BA.2 variant strains [29].

We use average temperature and relative humidity data for Tokyo during the day as climate data because national average data are not available. We obtained data from the Japan Meteorological Agency (https://www.data.jma.go.jp/gmd/risk/obsdl/index.php). Additionally, we identified several remarkable countermeasures in Japan: four state-of-emergency declarations, a travel campaign, and school closure and voluntary event cancellation (SCVEC). The latter, SCVEC, extended from February 27 through March in 2020: this countermeasure required school closure and cancellation of voluntary events, and even cancellation of private meetings. The first state of emergency was declared on April 7, 2020. It ceased at the end of May. It required school closures, shutting down of some businesses, and voluntary restriction against going out. To subsidize travel and shopping at tourist destinations, the "Go To Travel Campaign (GTTC)" started on July 22, 2020. It was halted temporarily at the end of December.

The second state of emergency was declared on January 7, 2021 for the 11 most-affected prefectures. This countermeasure required restaurant closure at 8:00 p.m., with voluntary restrictions against going out, but it did not require school closure. It continued until March 21, 2021. The third state of emergency was declared on April 25, 2021 for four prefectures: Tokyo, Osaka, Hyogo, and Kyoto. Later, the application areas were extended gradually. They never covered the entirety of Japan.

To clarify associations among R(t) and current and the past vaccine coverage in addition to the mutant strains, climate, mobility, the Olympic Games, and countermeasures, we used ordinary least squares regression to regress the daily R(t) on daily current vaccine coverage and daily past vaccine coverage as well as dummy variables for the Games, weekly shares of alpha and delta variant strains, daily climate, mobility, and dummy variables for countermeasures. Temperatures were measured in degrees Celsius. Because mobility data provided by Apple Inc. had been ceased to provide to public in March 13, 2022, we used the prediction by Google provided mobility data (https://www.google.com/covid19/mobility/) for Apple data through

$$(A_{1t}+A_{2t}+A_{3t})/3=a+b_1G_{1t}+ b_2G_{2t}+ b_3G_{3t}+ b_4G_{4t}+ b_5G_{5t}+ b_6G_{6t}+e_t$$

where A_{it} (i=1-3) were three types of mobility data provided by Apple and G_{it} (i=1-6) were six types of mobility data provided by Google. Because Google had started to provide February 15, 2020 though it was started in January 13, 2020 for Apple data, the period for the estimation was since February 15, 2020 until March 13, 2022. We used its prediction value as measure for mobility even before March 13, 2022. It means hybrid measure for mobility both of Apple data and Google data. After March 14, 2022, we can use the mobility data defined as above until that Google will cease to provide the data.

We define vaccine coverage as the completion rate of the second dose without delay. If a vaccine perfectly protects the recipient from infection, then the estimated coefficient of vaccine coverage would be 0.01 if one assumes an average of R(*t*) with no vaccination in the study period. That would indicate that vaccine coverage increased by one percentage point could be expected to reduce R(*t*) by one percentage point. If the estimated coefficient of vaccine coverage were smaller than -0.01, then it might reflect imperfect personal prevention. Conversely, if the estimated coefficients of vaccine coverage were smaller than -0.01, then herd immunity can be inferred to have contributed to prevention of infection among non-recipients.

Waning of vaccine effectiveness was measured by the estimated coefficient of vaccine coverage in the past. Particularly, we examined every 30 days prior until 150 days prior. We expected the estimated coefficient to be positive if waning was occurring. If its estimated coefficient was positive but smaller than the absolute value of the estimated coefficient of current vaccine coverage, then waning was presumed to be partially occurring. Vaccination was presumed to be effective even if a part of effectiveness was waning. If the estimated coefficient of vaccine coverage in the past was positive and almost equal to the absolute value of the estimated coefficient of current vaccine coverage, then waning was presumed to be complete. We might not expect vaccine effectiveness until that time. Conversely, if the estimated coefficient of vaccine coverage in the past was positive and larger than the absolute value of the estimated coefficient of current vaccine coverage, then the vaccine might raise infectively eventually. We supposed waning of vaccine effectiveness in the second and third vaccination because the fourth vaccination had just started in the study period. We also estimate it without any vaccine coverage in the past which implies to be no waning of vaccine effectiveness.

We selected length of lag in vaccine coverage in the past trough adjusted coefficient of determinant which was a measure of goodness of fit when the number of explanatory variables were not the same. We adopted 5% as the significance level.

3. **Results**

3.1 *Data*

Figure 1 depicts vaccine coverage second and third dose with a 14-day delay. The vaccine coverage of the fourth dose with a 14-day delay was not shown in Figure 1, because it had been just started on June 5,2022 , when just one day before from the last day in Figure 1. Its coverage was on June5 and on June 6, 2022. It remained just a 0.0001% and 0.0003% in these days. Adjustments were made for double counting for the number of vaccine recipients. Therefore, the vaccine coverage was sometimes less than it was earlier.

Figure 2 depicts R(*t*) during the study period. Figure 3 shows both of Apple provided mobility data and its prediction by Google provided mobility data. Of course, both variables fluctuate very similarly, though volatility of the predicted value was much smaller than the observed mobility data provided by Apple.

Figure 4 presents an empirical distribution of the duration of onset to reporting in Japan. The maximum delay was 31 days. Figure 5 presents an empirical distribution of incubation periods among 91 cases for which the exposed date and onset date were published by MHLW in Japan. The mode was six days; the average was 6.6 days.

Table 1 presents estimation results. Based on the estimated adjusted R^2, we selected the specification with 120 days lag of waning of the second and third dose vaccination. In this specification, mobility, the 2nd and 3rd state of emergency, vaccine coverage of the second and third dose and those with lag, and vaccine coverage of the fourth dose were significant with the expected sign. Conversely, humidity, SCVEC, the 4th state of emergency, and share of delta or omicron before BA.2 variant strain were significant with unexpected sign. Concerning about GTTC, it was significantly negative and thus it reduced infectively.

Discussion

The obtained estimated results showed that waning of the second and third dose vaccine e with 120 days prior was the most appropriate specification. This duration may be comparable with earlier studies of waning [8,9], which reached their conclusions based on antibody titer or test negative design. Readers must be reminded that waning estimated for the present study might include behavioral changes among the vaccinated persons to adoption of more risky behavior that is prone to exacerbating infectively. Such behaviors and the vaccine itself affect waning results, but they are not separately discernible based on results of this study. Weakening of immunoreaction and behavioral change are separate factors, but their mutual effects might be the most important for management of public health.

Moreover, the estimated effect of the fourth vaccinationBA.2 was quite high. This extremely result may be caused by very short period since the fourth vaccination had started and thus its coverage remained as very small. Therefore, its effect should be decline rapidly with the accumulation of data. Hereafter, expanding of the fourthe vaccination, its estimated effect may be able to decrease over time.

Concerning about prevalence of BA.2, it was not significant. However, because delta or omicron before BA.2 were negatively significant,

Vaccine efficacy was estimated as 95% for the original strain through clinical trials [30]. In the real world, it was also estimated as 46–80% for the first dose and 86–90% for the second dose [31-36] through case control studies or test negative design. However, even in the real world, such studies specifically examine protection for vaccine recipients only and ignore herd immunity, representing vaccine effects on non-vaccine recipients. The latter was not able to be estimated through clinical trials, case–control studies, or test negative design. In this sense, these earlier studies have been incapable of evaluating the overall effects of vaccination on the community. Instead of those methods, we evaluated vaccine effectiveness on the entire community, of course including herd immunity, through its effects on SARS-CoV-2 infectively.

Though Alpha variant strain effects were not significant, the share of delta or omicron before BA.2 variant strain were negatively significant. These results were not consistent with results reported from earlier studies [10-13].

Limitations

First, we assumed implicitly that epidemiological characteristics including incubation period or delay in reports were the same among the original strain, alpha, delta, omicron and BA.2 variant strains. However, results of one study indicated that the delta variant strain has a shorter incubation period than either original strain [37].

Secondly, readers must be reminded when interpreting the obtained results that they do not indicate causality. Results of this study demonstrated that a negative association exists between the vaccine coverage and infectively. That finding does not necessarily mean that the vaccine coverage reduced infectively. The lower infectively might have caused or might have even simply coincided with higher vaccine coverage.

Conclusion

We found that second and third dose vaccine coverage with 120 days prior raises infectively. Because of data limitation since initiation of the fourth vaccination, the estimated its effect will change over time.

The present study is based on the authors' opinions: it does not reflect any stance or policy of their professionally affiliated bodies.

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Ethical considerations

All information used for this study was from official data published on the internet. There is therefore no ethical issue related to this study.

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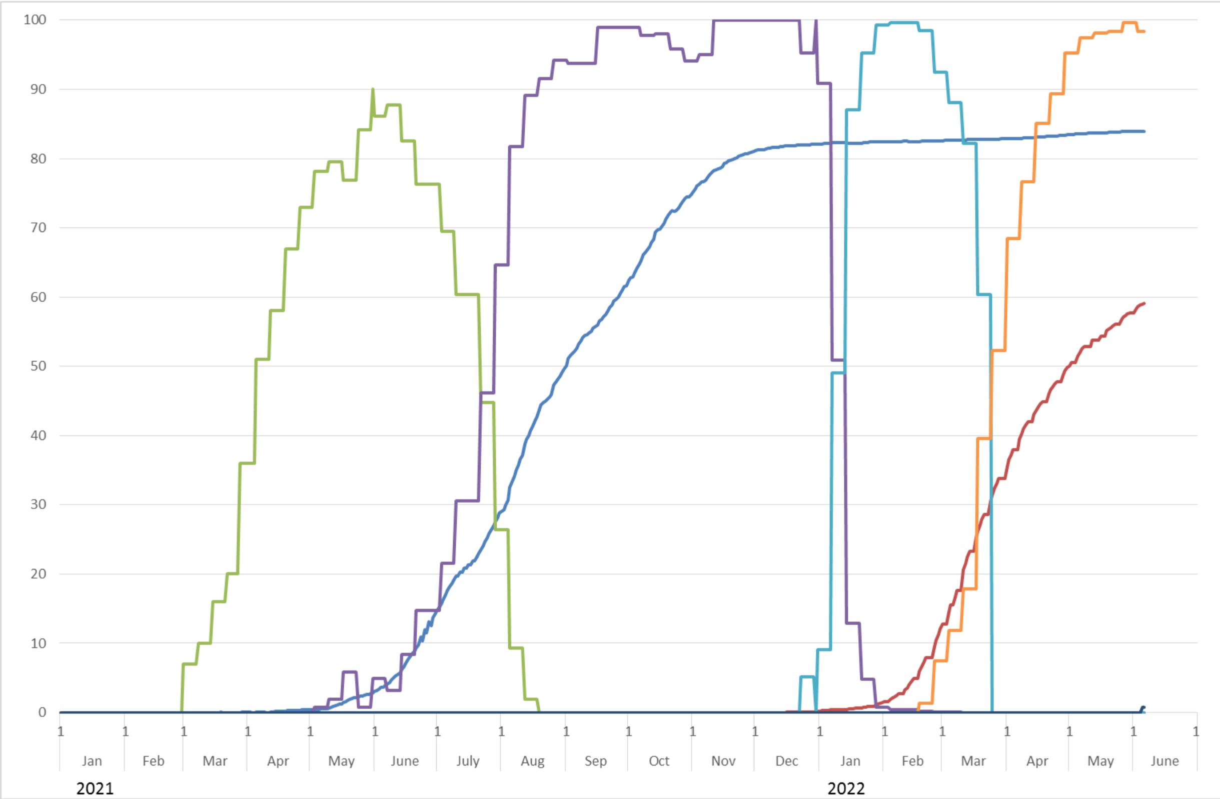
Figure 1: Vaccine coverage and shares of alpha and delta variant strains in 2021 until June 6, 2022.

(%)

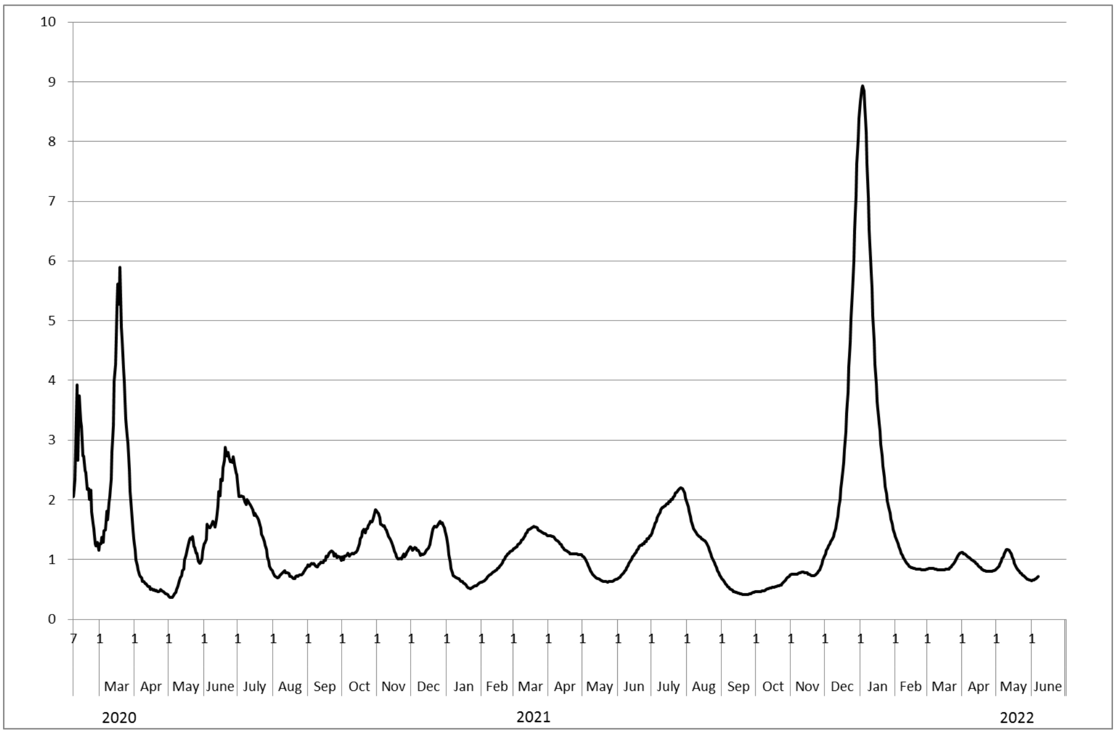


(date)

Note: The gray line represents shares of the alpha variant strain, the yellow line represents shares of the delta variant strain, and light blue line indicates the omicron variant strain before BA.2 in Tokyo. Green line indicates share of BA.2 only variant strain and small dark blue line on June 2022 indicates share of BA.5 only. Blue line denotes completed vaccine coverage as defined by the second dose with a 14-day delay. Red line denotes coverage defined by the third dose. Because the daily vaccine coverage was not reported on weekends or national holidays, data of vaccine coverage are missing for these days. Moreover, there were adjustments for double counting for the number of vaccine recipients. Therefore, the vaccine coverage sometimes slightly decrease from before.

Figure 2: Effective reproduction number from February, 2020 through June 6, 2022.

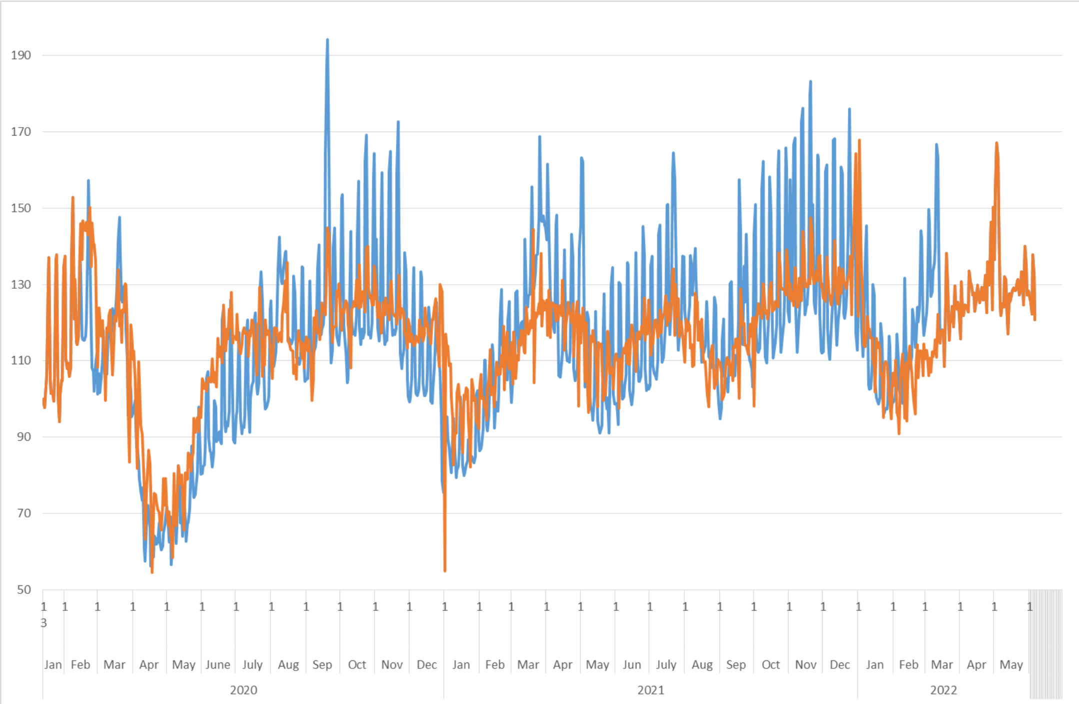
R(t)



(date)

Note: The line represents the effective reproduction number in Japan from February, 2020 through June 6, 2022, as of the end of June, 2022. Calculation procedures are explained in the main text.

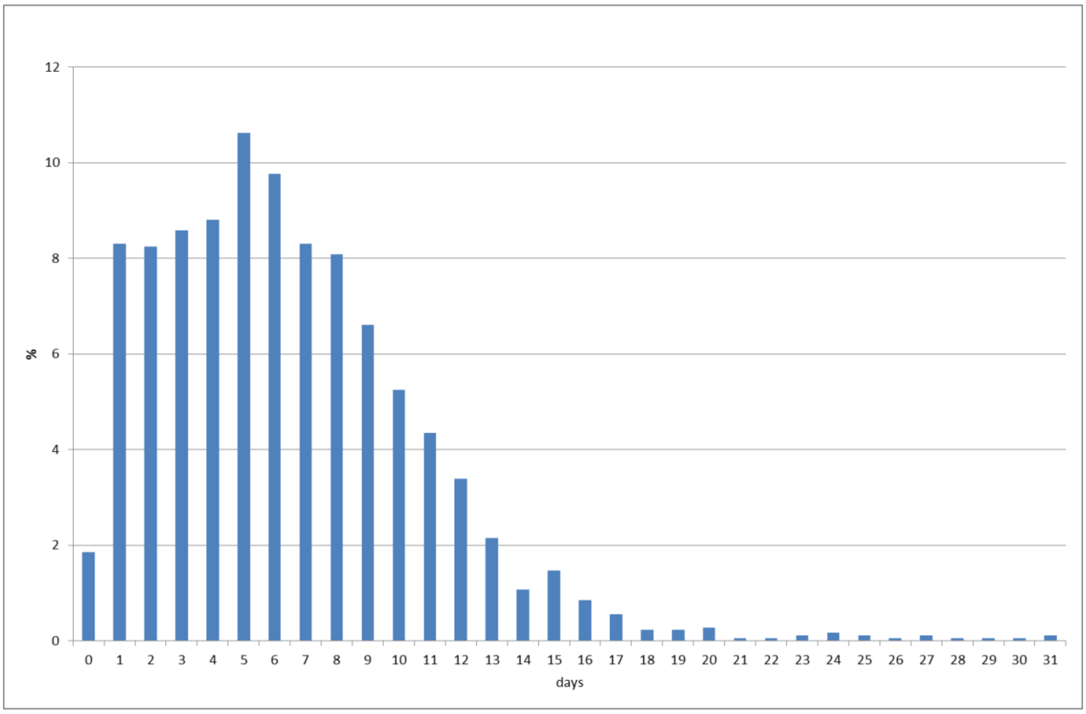
Figure 3: Mobility from Apple data and its prediction by Google data until June 6, 2022



Note: Blue line represents mobility data from Apple data. Orange line indicates its prediction by Google data. Apple data had been ceased to provide to public in March 13, 2022.

Figure 4: Empirical distribution of duration from onset to report by MHLW, Japan.

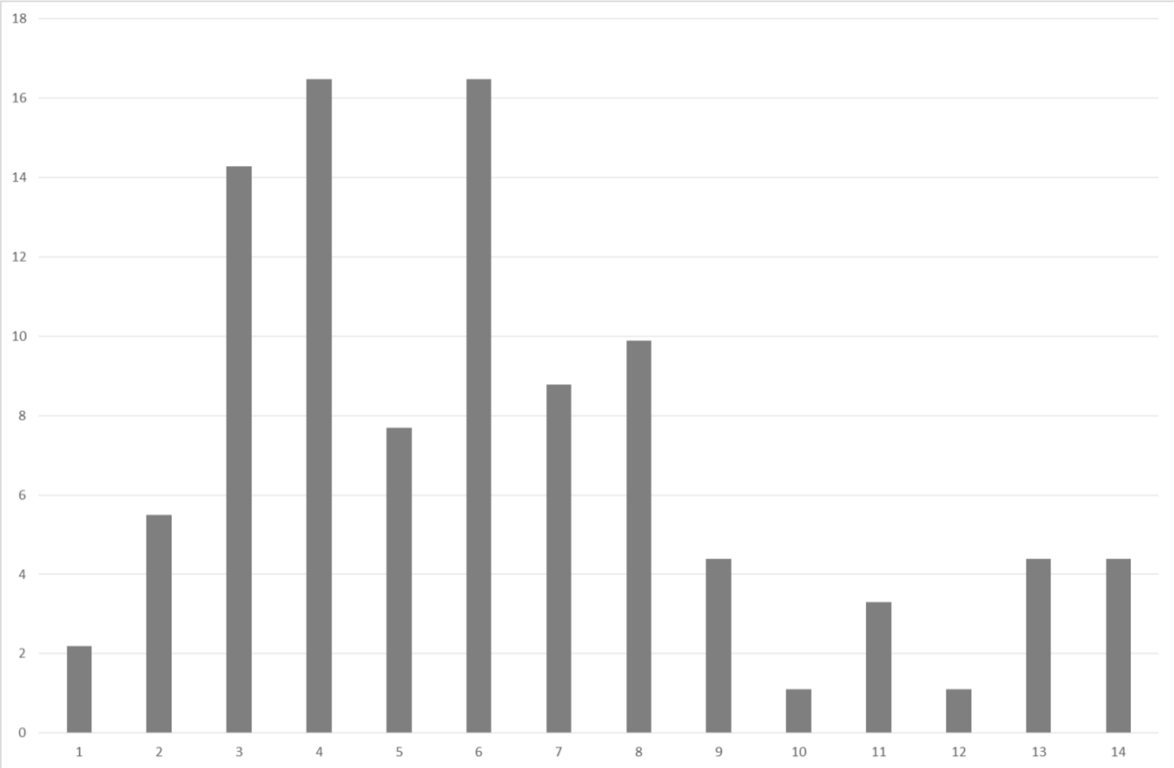
(%)



Note: Bars represent the probability of duration from onset to report based on 657 patients in Japan for whom the onset date was available. Data were obtained from MHLW, Japan.

Figure 5: Empirical distribution of the incubation period published by MHLW, Japan.

(%)



(days)

Notes: Bars show the distribution of incubation periods for 91 cases for which the exposure date and onset date were published by MHLW, Japan. Patients for whom incubation was longer than 14 days are included in the bar shown for day 14.

Table 1: Estimation results of R(t) with vaccine coverage, prevalence of the variant strains, and Olympic Games with the climate condition, mobility, and countermeasures

Lag for waning	Without lag for waning		30		60	
Explanatory variable	Estimated coefficient	*p*-value	Estimated coefficient	*p*-value	Estimated coefficient	*p*-value
Temperature	-0. 0303246	0.000	-0. 0145604	0.030	-0. 0033899	0.580
Humidity	-0.0000878	0. 971	0. 0027978	0. 28	0.0047061	0. 026
Mobility	0.0307465	0.000	0. 0252805	0.000	0. 0235421	0.000
SCVEC	0.7325365	0.000	0. 8908076	0.000	0. 9750906	0.000
1st State of emergency	-0. 1238115	0. 568	-0. 0695034	0. 737	-0. 1467767	0. 437
GTTC	-0. 724785	0.000	-0. 7185415	0.000	-0. 7454243	0.000
2nd State of emergency	-0. 778941	0.000	-0.6734057	0.000	-0. 578201	0.000
3rd State of emergency	-0. 4231518	0. 0043	-1. 231362	0.000	-1.408352	0.000
4th State of emergency	-0.3580662	0. 055	0. 746005	0.000	2.220661	0.000

Olympic Games	0.7266174	0. 007	1.014697	0.000	0.9851499	0.000
Vaccine coverage of the second dose(%)	0.0123796	0.024	-0. 1175103	0.000	-0. 1114389	0.000
Vaccine coverage of the second dose with lag (%)			0. 1408391	0.000	0. 1592314	0.000
Vaccine coverage of the third dose(%)	-0.0317324	0.000	-0.0843318	0. 000	-0.1180785	0.000
Vaccine coverage of the third dose with lag (%)			0.0442899	0.000	0.0620513	0.000

Vaccine coverage of the fourth dose(%)	126.8032	0.145	41.57505	0.615	-14.53239	0.849
Share of alpha variant strain (%)	-0.0030941	0. 203	0.0094856	0.000	0..0113863	0.000
Share of delta variant strain (%)	-0.0099752	0. 019	-0.0062878	0.134	-0.0058684	0. 159
Share of omicron variant strain (%)	-0.0108279	0. 020	-0.0147271	0.001	-0.030859	0.000
Share of omicron BA.2 variant strain (%)	-0.0076355	0. 023	-0.0046706	0.140	-0.0026523	0. 360
Constant	-1.261945	0.011	-1.123301	0.020	-1.240827	0.005

Adjusted R^2	0. 3217	0. 3995	0. 4979
Number of observations		844	

Notes: The dependent variable was R(*t*); GTTC stands for “Go To Travel Campaign”; SCVEC denotes school closure and voluntary event cancellation. Mobility was defined as Apple data predicted by Google data. The sample period was February 1, 2021 through June 6, 2022, as of the end of June, 2022.

Table 1 (cont.)

Lag for waning	90		120		150	
Explanatory variable	Estimated coefficient	*p*-value	Estimated coefficient	*p*-value	Estimated coefficient	*p*-value
Temperature	-0. 0056926 0.361	0.000361	-0. 0030279	0.607	-0. 00338990062426	0. 309
Humidity	0.0038949	0. 071	0. 004137	0. 042	0. 003148	0. 139
Mobility	0.0264746	0.000	0. 0285312	0.000	0. 0328003	0.000
SCVEC	0. 9050146	0.000	0. 9109198	0.000	0. 8793941	0.000
1st State of emergency	-0.080091	0. 676	-0. 0084205	0. 963	0. .164968	0. 385
GTTC	-0. 7942484	0.000	-0. 81830225	0.000	-0. 8219579	0.000
2nd State of emergency	-0. 5942834	0.000	-0. 5439592	0.000	-0. 5286844	0.000
3rd State of emergency	-0. 8680561	0. 000	-0. 6611971	0.000	-0. 4950076	0.007
4th State of emergency	1.71583	0. 000	1.387647	0.000	0.6409293	0.001

Olympic Games	0. 5383749	0. 024	0.286946	0.205	0. 3993745	0.094
Vaccine coverage of the second dose(%)	-0.0405291	0.000	-0. 0203969	0.001	-0. 0034443	0.636
Vaccine coverage of the second dose with lag (%)	0.1077188	0.000	0. 1131753	0.000	0. 1198189	0.000
Vaccine coverage of the third dose(%)	-0. 1455608	0.000	-0. 1902187	0. 000	-0. 216008	0.000
Vaccine coverage of the third dose with lag (%)	0.20675	0.000	2.008724	0.000	9.653778	0.000

Vaccine coverage of the fourth dose(%)	-268.4982	0. 007	-790.4347	0. 000	-210.66	0. 040
Share of alpha variant strain (%)	0.0024963	0. 249	-0.0007962	0.694	-0.0029345	0.166
Share of delta variant strain (%)	-0. 0155261	0. 003	-0. 0163545	0. 000	-0. 0152194	0. 005
Share of omicron variant strain (%)	-0. 042507	0. 000	-0. 0501403	0.000	-0.0521724	0.000
Share of omicron BA.2 variant strain (%)	-0. 0020237	0. 494	-0. 0023288	0.405	-0.0036775	0. 210
Constant	-1.441512	0.001	-1.733853	0.000	-2.110194	0.000

Adjusted R^2	0.4780	0.5321	0.4853
Number of observations		844	