

Duration of Infectious Virus Shedding by SARS-CoV-2 Omicron Variant–Infected Vaccinees

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To determine virus shedding duration, we examined clinical samples collected from the upper respiratory tracts of persons infected with severe acute respiratory syndrome coronavirus 2 Omicron variant in Japan during November 29–December 18, 2021. Vaccinees with mild or asymptomatic infection shed infectious virus 6–9 days after onset or diagnosis, even after symptom resolution.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant of concern belonging to the Pango lineage B.1.1.529, known as the Omicron variant, has spread rapidly worldwide (1,2). Several reports describe high infectivity and transmissibility of Omicron (3,4). The clinical course and the duration of virus shedding based on cycle quantification (C_q) values among 11 Omicron-infected patients has been reported (5). However, the relationship between duration of virus shedding and infectivity of Omicron is unknown. To help determine the criteria for patient isolation, we evaluated the duration of shedding of Omicron variant virus isolated from upper respiratory samples collected from the reported case-patients in Japan.

This study was approved by the ethics committee of the National Center for Global Health and Medicine (approval no. NCGM-G-003472-03) and the Medical Research Ethics Committee of the National Institute of Infectious Diseases (NIID) for the use of

human subjects (approval no. 1178). We obtained written informed consent to publish the article.

The Study

We conducted our retrospective study on leftover clinical samples collected from Omicron-infected patients in Japan during November 29–December 18, 2021. We sequenced the Omicron variant by using whole-genome sequencing as described (2) and uploaded the consensus sequences to GISAID (<https://www.gisaid.org>) (Table).

For cases detected by SARS-CoV-2 testing at airport quarantines, samples collected for diagnosis (saliva or nasopharyngeal) were transported to the NIID to confirm Omicron. We used the residual samples for this study. The date of sample collection of the first Omicron-positive sample for each patient was defined as the diagnosis date (day 0). Nasopharyngeal samples were collected serially during hospitalization, stored at –80°C, and transported to NIID.

We quantified SARS-CoV-2 RNA by using quantitative reverse transcription PCR (qRT-PCR) and virus isolation testing. We performed qRT-PCR as described previously (6). We measured C_q values (i.e., viral RNA levels) by using qRT-PCR targeting the SARS-CoV-2 nucleocapsid gene (Appendix Figure 1, <https://wwwnc.cdc.gov/EID/article/28/5/22-0197-App1.pdf>). We analyzed samples with C_q values that were reported as negative after 40 cycles by substituting a value of 45. We performed the virus isolation assay according to described procedure (7). All laboratory analyses were performed at the NIID.

To examine infectious virus shedding, we classified samples according to date of diagnosis, date of symptom onset, and date of symptom resolution.

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Table . Overview of 18 cases of SARS-CoV-2 infection caused by the Omicron variant, Japan, November 29–December 18, 2021*

Case no.	Patient age, y/sex	Disease severity	Vaccine, no. doses (type)	Duration of symptoms, d	Lowest Cq values (days after diagnosis, days after symptom onset)	Virus isolation, since diagnosis (days)†
1	39/M	Mild	2 (M, M)	5	21.6 (3, 3)	Positive (3)
2	30/M	Asymptomatic	2 (M, M)	NA	25.3 (5, NA)	Positive (5)
3	25/M	Mild	2 (P, P)	6	23.2 (4, 3)	Negative
4	46/M	Mild	3 (J, P, P)	11	24.7 (9, 11)	Positive (6)
5	50/M	Asymptomatic	2 (P, P)	NA	23.1 (5, NA)	Positive (5)
6	31/M	Mild	2 (P, P)	5	25.4 (0, 0)	Negative
7	47/M	Asymptomatic	2 (P, P)	NA	34.2 (9, NA)	Negative
8	33/F	Mild	2 (M, M)	12	32.4 (0, 1)	Negative
9	64/M	Mild	2 (P, P)	4	23.9 (0, -1)	Positive (0)
10	42/M	Mild	2 (M, M)	4	27.0 (0, -1)	Negative
11	49/M	Mild	2 (M, M)	5	26.5 (0, -1)	Positive (8)
12	31/M	Mild	2 (M, M)	4	25.4 (5, 4)	Positive (7)
13	50/M	Mild	2 (M, M)	6	24.7 (5, 7)	Positive (5)
14	30/F	Mild	2 (M, M)	11	30.0 (0, 2)	Negative
15	27/M	Mild	2 (P, P)	8	25.8 (6, 10)	Negative
16	23/M	Mild	2 (P, P)	5	18.7 (3, 4)	Positive (3)
17	47/M	Mild	2 (M, M)	6	24.2 (7, 7)	Positive (0)
18	38/M	Mild	2 (P, P)	6	29.0 (7, 8)	Negative

*The consensus sequences of the viral genome have been uploaded to GISAID (<https://www.gisaid.org>) (identification nos. EPI_ISL_6913953, EPI_ISL_6914908, EPI_ISL_7194610, EPI_ISL_7834392, EPI_ISL_7860184, EPI_ISL_7860185, EPI_ISL_7860188, EPI_ISL_7860189, EPI_ISL_7860190, EPI_ISL_7860193, EPI_ISL_7860197, EPI_ISL_7889642, EPI_ISL_7889643, EPI_ISL_8096984, EPI_ISL_8096995, EPI_ISL_8605240, EPI_ISL_8605241, EPI_ISL_8605242). Cq, quantification cycle; J, Johnson & Johnson; M, Moderna; NA, not available; P, Pfizer/BioNTech; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

For cases in which multiple samples were collected in each time segment, we used the sample with the highest amount of viral RNA (i.e., lowest Cq values) in each time segment for each case for comparison. For data analysis and visualization, we used GraphPad Prism version 8.4.3 (<https://www.graphpad.com>). To compare the Cq values, we used Mann-Whitney *t* and Friedman tests with Dunn multiple comparisons. Statistical significance was set at $p < 0.05$.

All 18 case-patients had been vaccinated >14 days before coronavirus disease (COVID-19) diagnosis (Table). The median (interquartile range [IQR]) duration between vaccination and diagnosis was 117

(71–131) days. Of the 18 case-patients, 15 were symptomatic and 3 were asymptomatic.

Among the 101 serially collected samples analyzed (85 nasopharyngeal and 16 saliva), we detected infectious virus in 10 (9.9%) from 10 patients (8 symptomatic and 2 asymptomatic) (Figure 1, panel A; Appendix Tables 1, 2). The viral RNA levels analyzed by using qRT-PCR were significantly higher in samples with the infectious virus than without ($p < 0.0001$) (Figure 1, panel A). Infectious virus was detected up to 9 days after diagnosis; the highest proportion of virus isolates (41.7%) was found in samples collected 2–5 days after diagnosis, and no isolates were detected

Figure 1. SARS-CoV-2 RNA level and infectious virus shedding in upper respiratory samples from symptomatic patients infected with the SARS-CoV-2 Omicron variant, Japan, November 29–December 18, 2021. A) SARS-CoV-2 RNA levels and presence of the infectious virus, by date of symptom onset. Each closed circle indicates case-patients from whom virus was isolated. Numbers above each plot indicate the proportion of case-patients from whom virus was isolated in each period. Black lines indicate median Cq values and error bars interquartile ranges; dotted lines indicate negative cutoff values.

*Before symptom onset. B) SARS-CoV-2 RNA levels and presence of

infectious virus, by date of symptom resolution. Closed circles indicate patients from whom virus was isolated. Numbers above each plot indicate the proportion of persons from whom virus was isolated in each period. Black lines indicate median Cq values and error bars interquartile ranges; dotted lines indicate cutoff values. †Before symptom resolution. Cq, quantification cycle; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

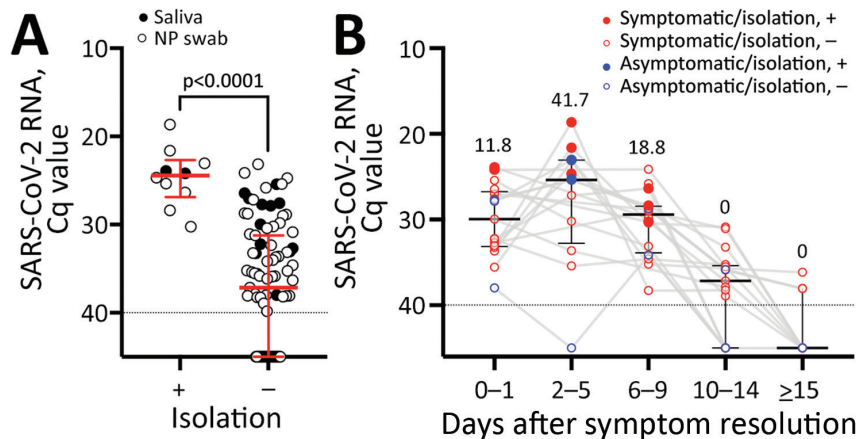
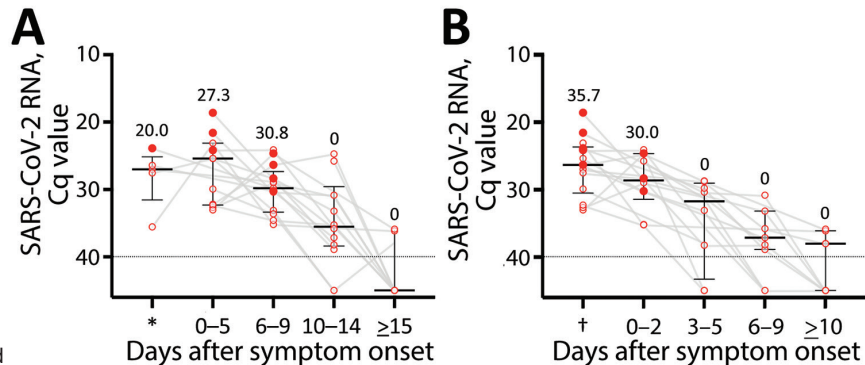


Figure 2. SARS-CoV-2 RNA level and infectious virus shedding in all upper respiratory samples from patients infected with the SARS-CoV-2 Omicron variant, Japan, November 29–December 18, 2021.

A) SARS-CoV-2 RNA levels in NP swab samples (open circles) and saliva (closed circles) with or without infectious virus. Red lines indicate median Cq values and error bars interquartile ranges; dotted lines indicate negative cutoff values. The Cq values between samples from which infectious virus was isolated and samples from which infectious virus was not isolated were compared by using the Mann-

Whitney test. B) SARS-CoV-2 RNA levels and presence of infectious virus organized by the days after diagnosis. Red circles indicate symptomatic case-patients; blue circles indicate asymptomatic case-patients; each closed circle indicates case-patients from whom virus was isolated. Numbers above each plot indicate the proportion of case-patients from whom virus was isolated in each period. Black lines indicate median Cq values and error bars interquartile ranges; dotted lines indicate negative cutoff values. Cq, quantification cycle; NP, nasopharyngeal; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; +, with infectious virus; -, without infectious virus.



10 days after diagnosis (Figure 1, panel B; Appendix Figure 3, panel A).

We detected infectious virus in the samples of 20%–30% symptomatic patients, ranging from before they were symptomatic to 9 days after symptom onset, but we detected no infectious virus beyond 10 days after symptom onset (Figure 2, panel A; Appendix Table 3, Figure 2, panel B, Figure 3, panel B). For ≈30% of case-patients, infectious virus shedding was detected up to 2 days after symptom resolution, but no virus was detected beyond 3 days after symptom resolution (Figure 2, panel B; Appendix Table 4, Figure 3, panel C). Many of the first samples collected were saliva samples. Of note, the results of only nasopharyngeal samples did not differ from samples including saliva after 2 days of diagnosis (Appendix Figure 4, panels A, B).

Conclusions

Omicron RNA detection was highest 2–5 days after diagnosis or after symptom onset and then decreased over time, markedly 10 days after diagnosis or symptom onset. In symptomatic case-patients with infectious virus detected on days 6–9 after symptom onset, infectious virus was also detected 0–2 days after symptom resolution. Although the sample size used in our study is small, these findings suggest the possibility of changes in the viral replication kinetics, unlike previous reports for ancestral (wild-type) strain (Wu01) strains (8,9). Cq values were frequently lower for the B.1.617.2 (Delta) variant than for the other variants (B.1.1.7 [Alpha]), and virus clearance was faster in vaccinated than in unvaccinated persons (10). Similar to findings for the Wu01 strain, the Alpha variant, and the Delta variant (11–13), RNA of the Omicron

variant was detectable 10 days after diagnosis or symptom onset, but no virus was isolated.

In the United States, the isolation period for COVID-19 patients is 5 days after symptom onset if the symptoms are improving (14). In Japan, based on the outbreak situation, the results of this study, and isolation criteria in other countries, the isolation criteria for Omicron patients were changed on January 6, 2022. Two consecutive negative test results 10 days after diagnosis or symptom onset are no longer required for patients who received 2 vaccine doses.

Our first study limitation is that we identified infectious virus by infection assays among only 18 patients. We do not know about the infectivity outside of this study. In addition, there are no epidemiologic data about whether secondary infections occurred from patients with these infectious viruses. Therefore, comparing these results with future epidemiologic studies of more samples is necessary. Our second study limitation is that the virus isolation and infectivity assay results depend on the sample collection method, storage period, and storage conditions. Therefore, negative results do not guarantee that there was no infectious virus in the sample at the time of collection. Last, for some case-patients, virus was not isolated in samples collected at the time of diagnosis. For these persons, the samples used for diagnosis were collected at the airport quarantine and were saliva, for which the quality may not be suitable for virus isolation. Although our results are insufficient to show a difference in efficiency of virus isolation between saliva and nasopharyngeal samples in Omicron-infected persons, this difference may have underestimated the presence of infectious virus at diagnosis. In conclusion, fully vaccinated COVID-19

case-patients with mild or asymptomatic infection shed infectious virus in their upper respiratory tract for 6–9 days after illness onset or diagnosis, even after symptom resolution, but not after day 10.

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Duration of Infectious Virus Shedding by SARS-CoV-2 Omicron Variant–Infected Vaccinees

Appendix

Appendix Table 1. SARS-CoV-2 RNA-positivity / viral isolation-positivity of SARS-CoV-2 Omicron variant-infected cases, organized by days post diagnosis (all cases)

Days post diagnosis	Positive for SARS-CoV-2 RNA	Cq value	SARS-CoV-2 virus isolation
0–1 days	17/17 (100)	30.0 (27.0-33.1)	2/17 (11.8)
2–5 days	11/12 (91.7)	25.4 (23.1-31.1)	5/12 (41.7)
6–9 days	16/16 (100)	29.4 (28.6-33.4)	3/16 (18.8)
10–14 days	12/17 (70.6)	37.2 (35.5-45.0)	0/17 (0)
After 15 days	3/10 (30.0)	45.0 (39.8-45.0)	0/10 (0)

*Unless otherwise stated, data are presented as n (%). Cq values are presented as the median (interquartile range). SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RNA, ribonucleic acid.

Appendix Table 2. SARS-CoV-2 RNA-positivity / viral isolation-positivity of SARS-CoV-2 Omicron variant-infected cases, organized by days post diagnosis (asymptomatic cases)*

Days post diagnosis	Positive for SARS-CoV-2 RNA	Cq value	SARS-CoV-2 virus isolation
0–1 days	3/3 (100)	27.7, 27.9, 38.0	0/3 (0)
2–5 days	2/3 (66.7)	23.1, 25.3	2/3 (66.7)
6–9 days	2/2 (100)	28.7, 34.2	0/2 (0)
10–14 days	1/3 (33.3)	35.8	0/3 (0)
After 15 days	0/1 (0)	NA	0/1 (0)

*Unless otherwise stated, data are presented as n (%). Cq values are presented as an actual number. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RNA, ribonucleic acid; NA, not available.

Appendix Table 3. SARS-CoV-2 RNA-positivity / viral isolation-positivity of SARS-CoV-2 Omicron variant-infected cases, organized by days post symptom onset (symptomatic cases only)*

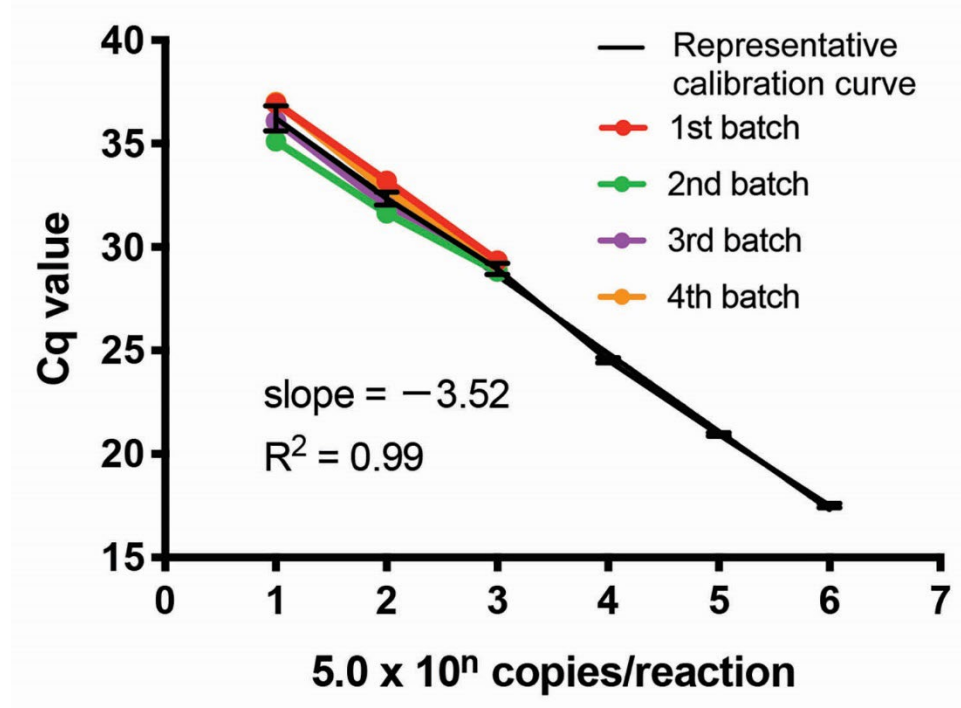
Days post diagnosis	Positive for SARS-CoV-2 RNA	Cq value	SARS-CoV-2 virus isolation
Presymptomatic	5/5 (100)	27.0 (26.5-27.6)	1/5 (20.0)
0–5 days	11/11 (100)	25.4 (23.7-32.3)	3/11 (27.3)
6–9 days	13/13 (100)	29.8 (28.4-33.1)	4/13 (30.8)
10–14 days	11/13 (84.6)	35.5 (31.1-38.2)	0/13 (0)
After 15 days	3/10 (30.0)	45.0 (39.7-45.0)	0/10 (0)

*Unless otherwise stated, data are presented as n (%). Cq values are presented as the median (interquartile range). SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RNA, ribonucleic acid.

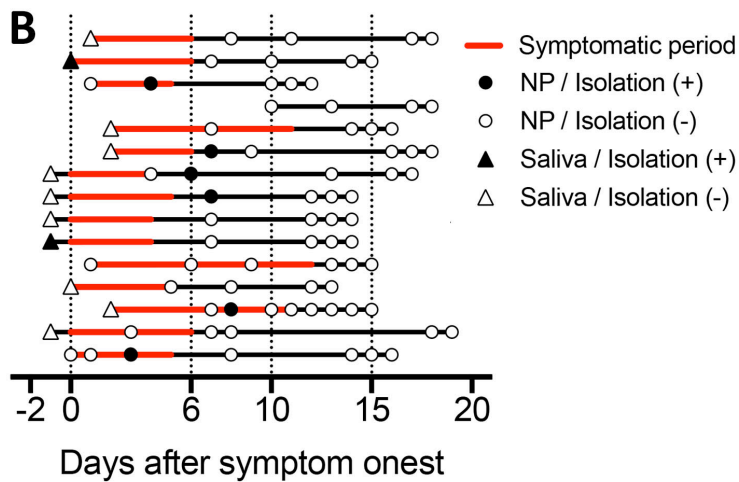
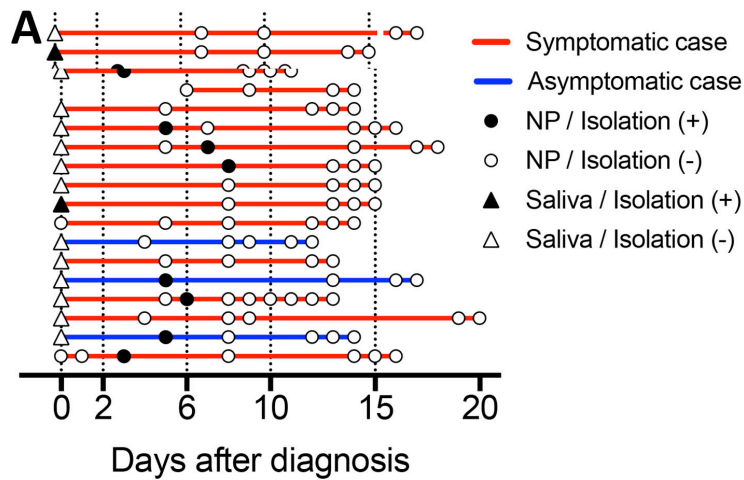
Appendix Table 4. SARS-CoV-2 RNA-positivity / viral isolation-positivity of SARS-CoV-2 Omicron variant-infected cases, organized by days post symptom resolution (symptomatic cases only)*

Days post symptom resolution	Positive for SARS-CoV-2		SARS-CoV-2 virus
	RNA	Cq value	isolation
Before	14/14 (100)	26.4 (24.0-29.4)	5/14 (35.7)
0–2 days	10/10 (100)	28.7 (25.0-30.2)	3/10 (30.0)
3–5 days	10/12 (83.3)	32.2 (30.3-38.0)	0/12 (0)
6–9 days	6/9 (66.7)	38.2 (35.8-45.0)	0/9 (0)
After 10 days	3/8 (37.5)	45.0 (37.6-45.0)	0/8 (0)

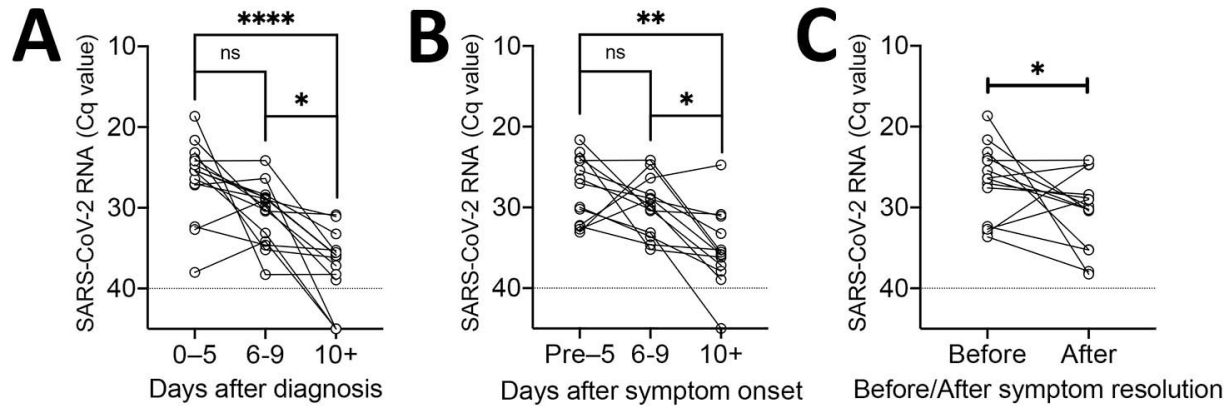
*Unless otherwise stated, data are presented as n (%). Cq values are presented as an actual number. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RNA, ribonucleic acid; NA, not available.



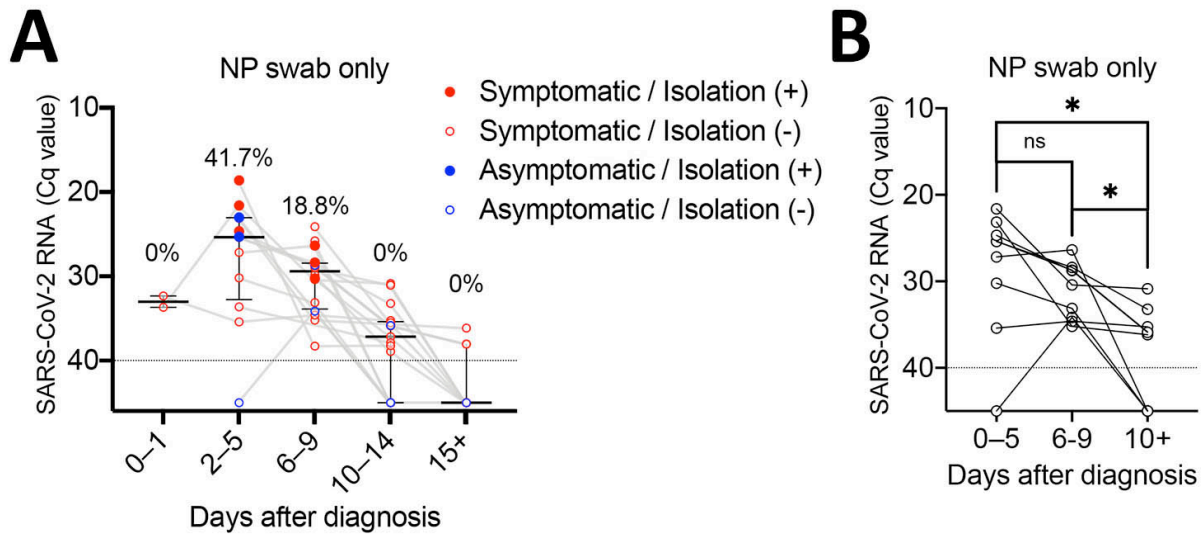
Appendix Figure 1. Performance characteristics of the SARS-CoV-2 RT-qPCR used in this study. All of the SARS-CoV-2 RT-qPCR assays in this study were performed at the NIID using One Step PrimeScript III RT-qPCR Mix (Takara Bio, Shiga, Japan), the N2 primer/probe set (NIID_2019-nCoV_N_F2 primer, NIID_2019-nCoV_N_R2 primer, and NIID_2019_nCoV_N_P2 probe), and a Roche LightCycler 96 (Roche, Basel, Switzerland). The Cq value of each sample in this study was acquired from four independently performed assays. For each assay, 50 copies, 500 copies, 5,000 copies of quantified in vitro transcribed RNA were included as control samples to ensure the integrity of the assay. The graph shows an overlay of a representative calibration curve for the assay with the quantified in vitro transcribed RNA samples and the Cq values of the control samples from each assay. The Cq values of the control samples in each assay fitted the representative calibration curve well, and the deviation of the Cq values of the control samples in each assay was minimal.



Appendix Figure 2. The timeline of upper respiratory samples collected from individuals infected with the SARS-CoV-2 Omicron variant (A and B) The timeline of collection of nasopharyngeal (NP) swabs (circles) and saliva (triangles) from individuals infected with the SARS-CoV-2 Omicron variant is indicated as horizontal line for each case. (A) The timeline starts from the day of diagnosis and extends to each sample collected from each case. Each symbol (circle for NP, or triangle for saliva) indicates that a sample was collected. Closed symbol: infectious virus (+); open symbol: infectious virus (-); red line: symptomatic case; blue line: asymptomatic case. (B) The timeline starts from the day of symptom onset and extends to each sample collected from each case. Each symbol (circle for NP, or triangle for saliva) indicates that a sample was collected. Closed symbol: infectious virus (+); open symbol: infectious virus (-). Red line: symptomatic period.



Appendix Figure 3. Comparison between Cq values and days after diagnosis, days after symptom onset, before/after symptom resolution (A) The levels of SARS-CoV-2 RNA at the time periods after diagnosis were compared. The Cq values among samples in each timepoint were compared using Friedman test with Dunn's multiple comparisons test; **** $p < 0.0001$, * $p < 0.05$, ns, not significant. (B) The levels of SARS-CoV-2 RNA at the time periods before or after symptom onset were compared. The Cq values among samples in each timepoint were compared using Friedman test with Dunn's multiple comparisons test; ** $p < 0.01$, * $p < 0.05$, ns, not significant. (C) The levels of SARS-CoV-2 RNA at the time periods before or after symptom resolution were compared. The Cq values among samples in each timepoint were compared using Mann Whitney test; * $p < 0.05$.



Appendix Figure 4. SARS-CoV-2 RNA level and infectious virus shedding in nasopharyngeal samples from patients infected with the SARS-CoV-2 Omicron variant (A) The SARS-CoV-2 RNA levels and presence of infectious virus in nasopharyngeal (NP) samples are shown organized by the days after diagnosis. Red circles and blue circles indicate symptomatic and asymptomatic cases, respectively. Each closed circle indicates the cases with positive viral isolation. The numbers above each plot indicate the proportion of positive-viral-isolation cases in each period. Black lines indicate median Cq values with interquartile range, and dotted lines indicate negative cutoff values. (B) The levels of SARS-CoV-2 RNA in nasopharyngeal samples at the time periods after diagnosis were compared. The Cq values among samples in each timepoint were compared using Friedman test with Dunn's multiple comparisons test; * $p < 0.05$, ns, not significant.