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An outbreak of SARS-CoV-2 reinfection in a long-term care facility in South Korea

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ABSTRACT

We report a cluster of 12 cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reinfection in a long-term care facility in South Korea. There were two outbreaks of SARS-CoV-2 infection in the facility at the beginning and end of October 2021, respectively. All residents in the facility were screened for SARS-CoV-2 infection using RT-PCR as part of the investigation of the second outbreak. Twelve residents, who had infection confirmed during the first outbreak, were found to be re-positive for RT-PCR test at the second outbreak. 8 Of 12 RT-PCR re-positive cases were confirmed as reinfections based on investigation through the whole genome sequencing, viral culture, and serological analysis, despite of the short interval between the first and second outbreaks (29–33 days) and a history of full vaccination for 7 of the 12 re-positive cases. This study suggests that decreased immunity and underlying health condition in older adults makes them susceptible to reinfection, highlighting the importance of prevention and control measures regardless of vaccination status in long-term care settings.

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus infection is presumed to reduce the risk of subsequent infection for at least 6 months [1]; however, when the antibody titer decreases and immunity wanes, SARS-CoV-2 reinfection is possible [2]. While cases of reinfection have been reported in several countries [3], it is challenging to distinguish between ongoing infection and reinfection [4]. Here, we present a cluster of cases of SARS-CoV-2 reinfection in a long-term care facility, detected 1 month after the initial infection, with reinfection confirmed by genetic sequencing.

Methods

From October 1 to 4, 2021, an outbreak of SARS-CoV-2 infected 39 people in a long-term care facility, including 9 healthcare workers and all inpatients on a floor. The outbreak lasted 3 days. The residents who tested positive for SARS-CoV-2 by reverse transcription polymerase chain reaction (RT-PCR) were transferred to other facilities for isolation and necessary treatment. The residents were released from at least 10 days of isolation on a clinical condition-based or test-based criteria in accordance with COVID-19 response guidelines (10–1st Edition) [5]. On October 26, 2 inpatients on another floor developed fevers and tested positive for SARS-CoV-2 by RT-PCR. Fourteen close contacts subsequently tested positive. This second outbreak led to facility-wide testing, leading to the detection of 12 re-positive cases on the floor where the first outbreak occurred.

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Between November 1 and 11, nasopharyngeal swab samples were collected from the 12 re-positive cases daily for the first 5 days and then every other day for 6 days (a further three times) to confirm RT-PCR re-positivity and to monitor changes in the cycle threshold (C_t) values. A substantial decrease in C_t value was observed in 5 cases, from an average of 33.64 in the first outbreak to 17.21 in the second outbreak.

In order to confirm reinfection, whole genome sequencing (WGS) was performed for the viral RNAs of specimens collected at two different time points during the first (2 out of 12 cases) and second (7 out of 12 cases) outbreaks. The sequences were aligned with MAFFT v7 [6], and maximum likelihood phylogenetic trees were inferred using FastTree v2.1.9 [7]. Viral culture was also conducted using nasopharyngeal specimens. On days 1 and 15 after the RT-PCR re-positivity, blood samples collected from the 12 re-positive cases were evaluated for the presence of SARS-CoV-2-specific IgM and neutralizing antibodies using ELISA and a plaque reduction neutralization test, respectively. WGS, viral culture, and serological assays were described in the Supplementary material.

Results

Outbreak investigation

Of the 12 re-positive patients, 6 were male and 6 were female, with a median age of 74.0 years (range: 48–90). At the time of the first outbreak, 2 out of 12 patients had been released from isolation based on negative PCR testing results, and the other 10 patients had been released without testing by meeting clinical condition-based criteria for asymptomatic patients. None of them were symptomatic at the time of the first retesting, based on an initial case investigation. A day after the test was re-positive, one of the 12 patients, an 86-year-old unvaccinated male, developed a fever and his condition subsequently deteriorated, and he died of respiratory failure 8 days after symptom onset, while the remaining 11 patients survived. Of the 12 patients, 7 were fully vaccinated, 2 had received 1 dose of vaccine, and 3 were unvaccinated. 6 out of 7 fully vaccinated patients received their first dose in March and their second dose in May 2021 at 11–12 weeks intervals, and the remaining 1 patient was vaccinated in June and August. The two outbreaks were distinct, as the sources of infection triggering each outbreak were different, without known epidemiological links. None of the 12 re-positive patients experienced specific COVID-19-related symptoms between the two outbreaks, although PCR testing was not performed on all patients between the outbreaks. The median interval between the onset of the primary infection and the second infection in the 12 patients was 31 days (range: 29–33) (Table 1).

Genomic analysis of the two outbreaks

WGS showed that the two outbreaks were due to the delta variant, but the lineage was different. The lineage AY.122 was confirmed in 2 out of 12 cases in the first outbreak, and these 2 cases of AY.122 were closely related to 3 additional cases that occurred in the same facility at the same time as the first outbreak. The lineage AY.69 was confirmed in 7 out of 12 cases in the second outbreak, and these 7 cases of AY.69 were also closely related to 3 additional cases from the second outbreak. Therefore, it was confirmed that each outbreak was caused by different lineages of viruses, indicating reinfection (Fig. 1).

Virus culture

Viruses were isolated in 1 case of the first outbreak and 5 cases of the second outbreak of 12 re-positive patients in those who showed considerable decreases in Ct values and observed the cytopathic

Table 1
Characteristics of 12 RT-PCR re-positive cases from the first and the second outbreaks.

Case	Age (y) sex	Negative PCR result between outbreaks	Interval (days)[a]	Culture, genetic sequencing, and C_t value						Serological assays				Vaccination status (Manufacturer)	Outcome	Reinfection
				1st outbreak			2nd outbreak			2nd outbreak						
				Culture	Virallineage	Ct	Culture	Virallineage	Ct	$PRNT_{50}$		IgM				
										1 day	15 days	1 day	15 days			
1	49 F	Not performed	30	–	NT	32.27	–	NT	33.37	3701	435	+	+	None	Survived	Presumed
2	52 F	Yes	31	–	NT	35.13	+	AY.69	17.42	796	1156	–	–	None	Survived	Confirmed
3	86 M	Not performed	30	–	NT	32.44	+	AY.69	15.57	496	NA	–	–	None	Died	Confirmed
4	84 M	Not performed	31	–	NT	31.27	–	AY.69	25.07	5424	11,838	–	+	1-dose (Pfizer)	Survived	Confirmed
5	81 F	Not performed	29	+	AY.122	15.72	–	NT	34.26	> 31,250	19,018	–	–	1-dose (Pfizer)	Survived	Presumed
6	60 M	Not performed	31	–	NT	33.24	+	AY.69	19.63	6250	11,265	–	–	Full (AstraZeneca)	Survived	Confirmed
7	48 M	Not performed	31	–	NT	34.61	+	AY.69	17.4	883	14,311	–	+	Full (AstraZeneca)	Survived	Confirmed
8	90 F	Not performed	31	–	NT	32.8	+	AY.69	16.05	704	7140	–	–	Full (AstraZeneca)	Survived	Confirmed
9	82 F	Yes	30	–	NT	31.21	–	NT	36.27	1738	987	–	–	Full (AstraZeneca)	Survived	Presumed
10	81 M	Not performed	31	–	NT	33.41	–	AY.69	28.91	18,747	> 31,250	+	+	Full (AstraZeneca)	Survived	Confirmed
11	62 F	Not performed	33	–	NT	34.45	–	NT	35.91	583	10,013	–	+	Full (AstraZeneca)	Survived	Confirmed
12	67 M	Not performed	33	–	AY.122	15.18	–	NT	33.96	9861	1911	–	–	Full (AstraZeneca)	Survived	Presumed

Abbreviations: +, positive; –, negative; Ct, cycle threshold; IgM, immunoglobulin M; NA, not available; NT, not tested; PRNT50, 50 % plaque reduction neutralization test; RT-PCR, reverse transcription polymerase chain reaction.
[a] Interval between the RT-PCT tests confirming the first and second infection in each patient.

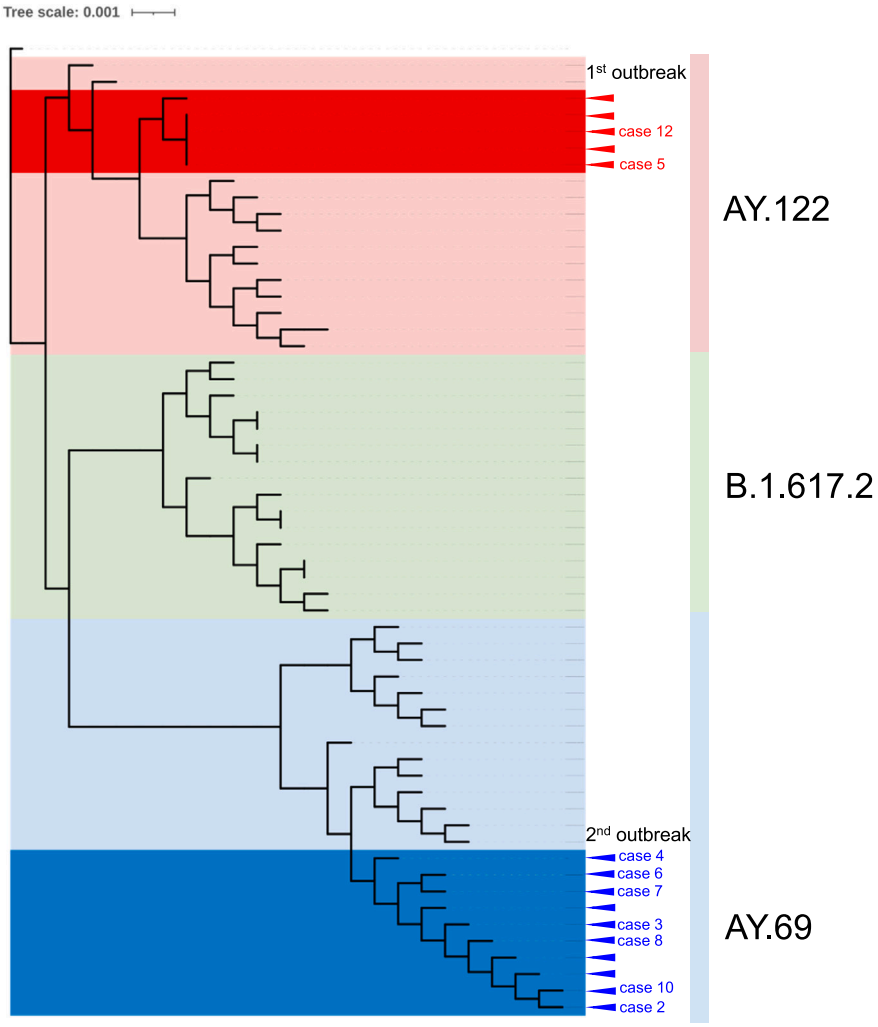

Fig. 1. Phylogenetic analysis of SARS-CoV-2 genome sequences of 9 cases from the first and second outbreaks. Two cases from the first outbreak (red) and 7 cases from the second outbreak (blue) were identified as lineages AY.122 and AY.69, respectively. Each outbreak formed a genetic cluster with the sequences of 3 additional cases confirmed in the same facility during the same period. The maximum likelihood phylogenetic tree was constructed using FastTree v2.1.9. The SARS-CoV-2 whole genome sequences were shared to the GISAID EpiCoV database (http://www.Gisaid.org/database).

effects of inoculated Vero E6 cell., suggesting reinfection (Table 1, Supplementary Fig. S1).

SARS-CoV-2 serological assays for the two outbreaks

SARS-CoV-2 IgM antibody was detected in the re-positive samples in 5 out of 11 cases (excluding the patient who died). Specifically, 3 patients who were IgM negative on the day 1 sample from the second outbreak were IgM positive on day 14. The neutralizing antibody titers against delta variant increased in 7 cases and decreased in 4 cases. The increased IgM and neutralizing antibody titers reflect a boost of immunity due to reinfection. Therefore, the serology results suggest that 7 out of 12 RT-PCR re-positive cases were due to reinfection (Table 1).

Discussion

Shedding of infectious SARS-CoV-2 usually ends within 10–20 days of symptom onset, but RT-PCR results may remain positive for more than 8 weeks [8–10]. In other words, since it is difficult to distinguish between reinfection and re-positivity in some cases, reinfection is proposed as positive PCR result after 90 days of first episode, and additional analysis such as WGS are required to confirm reinfection within 90 days [11]. In the reinfection cases confirmed between 4 and 9 weeks in South Korea, the United States and Ecuador, genetically different viruses were identified in each episode through WGS, and seroconversion of IgM and IgG or increased antibody levels were confirmed in the second infection [12–14].

In this study, based on the epidemiological, genomic and serological analyses, undetermined 12 RT-PCR re-positive cases were investigated and 8 cases were classified as confirmed reinfection and 4 cases as presumed reinfection, despite of the short interval between the first and second outbreaks (29–33 days) and a history of full vaccination in 7 of the 12 re-positive cases. To our knowledge, this is the first confirmed cluster of cases of reinfection to be reported in a long-term care facility, which is a setting where residents are at ongoing risk of infection given the closed environment and close contact between residents. Notably, a decline in the immune response with age and the presence of underlying health conditions can offset the protective effect generated by previous infection or vaccination when residents in long-term care facilities are exposed to a distinct lineage of SARS-CoV-2, even a short period after recovery, as clearly shown in this study.

This study suggests that a package of COVID 19 infection prevention and control measures are still of paramount importance when caring for older adults in long-term care, regardless of their vaccination status and previous infection history. In light of the emergence of SARS-CoV-2 variants and a growing body of evidence

of waning immunity following infection and vaccination, the current definition of reinfection needs to be reconsidered for case management and surveillance.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Korea Disease Control and Prevention Agency (2020-03-01-P-A) and designated as a service to public health during the outbreak.

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Data Availability

The SARS-CoV-2 whole genome sequences have been deposited to GISAID (Accession IDs: EPL-ISL_7792635 to EPL-ISL_7792648, and EPL_ISL_8327058).

Conflicts of interest

All authors declare that they have no competing interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2022.07.011.

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