

## Reinfection of COVID-19 in the Republic of Korea

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### Abstract

The aim of this study was to analyze the epidemiology and characteristics of presumed Coronavirus Disease-19 (COVID-19) reinfection cases. Since the first case of reinfection of COVID-19 in the Republic of Korea in April 2020 was identified, an additional four cases have been classified as reinfection cases. To conduct analysis, we performed whole-genome sequencing (WGS) of the viral RNA at the initial infection and at the reinfection of four presumed reinfection cases. The analysis of genome sequences indicated that there were two cases which showed distinct SARS-CoV-2 strain in reinfection when compared to that of the initial infection. Of the remaining two cases, the viral RNA of the initial infection was unobtainable for one case and a complete genome sequence of reinfection due to the high Ct value was unobtainable for the remaining case. Therefore, considering the epidemiological results, this study concluded that the two cases were reinfection cases. In an environment where concerns about reinfection are growing due to the ongoing COVID-19 pandemic and the emergence of variants, it is necessary to analyze cases through continuous monitoring.

Keywords: Coronavirus Disease-19 (COVID-19), Reinfection, Whole Genome Sequencing (WGS)

## Introduction

As of June 2021, the cumulative number of confirmed cases of coronavirus disease 2019 (COVID-19) infection has exceeded 170 million worldwide and the number has reached 140,000 in the Republic of Korea. As the pandemic continues, cases of reinfection have been reported worldwide. Since the first case of COVID-19 reinfection was reported in Hong Kong in August 2020, reinfection cases have continued to be reported in Belgium, the Netherlands, and the United States [1,2]. In particular, after the appearance of variants, some cases have occurred in which patients who were confirmed to have been infected with COVID-19 became re-infected with variants.

In December 2020, herd immunity was achieved in Manaus, Brazil, where three-quarters of the local population had been infected with COVID-19; however, there has been a recent surge in the number of COVID-19 cases, which is suspected of having occurred due to the P.1 variant [3]. With the increasing number of suspected reinfection cases, the Centers for Disease Control and Prevention (CDC) in the United States and the European Center for Disease Prevention and Control (ECDC) published criteria for the investigation of reinfection cases [4,5].

In the Republic of Korea, the first reinfection case was confirmed in April 2020 in a patient who had recovered after being infected with COVID-19 in March 2020: distinct viral strains were confirmed in the first and specimen from the

second infections [6]. Since then, the Korea Disease Control and Prevention Agency developed reinfection investigation criteria and has been conducting analyses of reinfection cases. Virological analyses were performed to ascertain reinfection based on laboratory evidence for five cases that had been epidemiologically classified as suspected reinfection cases.

## Result

Table 1 summarizes the five suspected reinfection cases identified in the Republic of Korea. Case 1 was the first reinfection case in the Republic of Korea: reinfection was ascertained by a disparity in the genotype (V→G) between the first and specimen from the second infections [6]. The remaining cases (cases 2 to 5) were epidemiologically classified as suspected reinfection, as exposure to new COVID-19 variants was confirmed after collection of a specimen from the second infection 90 days or more after the infection.

Other than the confirmed reinfection case (case 1), the four suspected reinfection cases underwent whole-genome sequencing (the scope of analysis may be limited depending on whether

specimens were secured): the specimens from the first infection and the specimens from the second infection (four specimens) were analyzed for case 4 and case 5, and the specimens from the second infection (two specimens) were analyzed for case 2 and case 3. Whole-genome sequencing was performed on the six specimens available for analysis to investigate clades and lineages [7]. The results of the analysis are presented in Table 2.

Whole-genome sequencing was completed for five of the six specimens, with the exception of the specimen from the second infection obtained from case 5, as genetic analysis was not possible due to a low viral load. In case 5, although reinfection could not be ascertained through laboratory examinations, it was classified as a presumed reinfection case based on epidemiological data (e.g., contact history with a confirmed case). In case 4, whole-genome sequencing revealed that the specimen from the first infection belonged to clade GH and lineage B.1.497, whereas the specimen from the second specimen was in clade GH but lineage B.1.429 [7], which led to the confirmation of the epsilon variant ( $\epsilon$ , California variant). Therefore, as the virus strains of the specimen from the first infection and the specimen from the second infection were different, the case was confirmed as reinfection. In case 3, the whole-genome sequencing analysis

Table 1. Epidemiological and clinical characteristics of presumed reinfection cases

Case	Gender	Age	Confirmed date and symptom		Periods of time after infection	Reference
			Initial infection	Reinfection		
1	Female	20-29	▶ March 2020 ▶ Cough, sore throat, expectoration	▶ April 2020 ▶ Cough, phlegm	26 days	Reference [6]
2	Male	20-29	▶ June 2020 ▶ Cough, phlegm, loss of smell	▶ Feb. 2021 ▶ Sore throat	241 days	
3	Female	20-29	▶ March 2020 ▶ Phlegm, muscle pain, dizziness	▶ April 2021 ▶ Asymptomatic	404 days	
4	Male	10-19	▶ Dec. 2020 ▶ Asymptomatic	▶ May 2021 ▶ Asymptomatic	133 days	
5	Male	10-19	▶ Dec. 2020 ▶ Muscle pain, loss of smell, snot	▶ May 2021 ▶ Asymptomatic	134 days	

Table 2. Epidemiological and biological results of presumed reinfection cases

	Case 2		Case 3		Case 4		Case 5	
	Initial*	Reinfection	Initial*	Reinfection	Initial	Reinfection	Initial	Reinfection
Clade	–	GH	V (presumed)	GH	GH	GH	GH	ND <sup>†</sup>
Lineage	–	B.1.497	–	B.1.429	B.1.497	B.1.429	B.1.497	–
Type of variant	–	No variant	No variant	ε	No variant	ε	No variant	–
Result	Presumed reinfection		Reinfection		Reinfection		Presumed reinfection	

\* No specimen of initial infection

† Low quality of data due to low viral load

of the specimen from the second infection revealed clade GH, corresponding to the epsilon variant (ε, California variant). Considering that the epsilon variant was first detected in the Republic of Korea in December 2020 [8] and had not been identified at the time of the first infection of case 3 (June 2020), this case was confirmed as reinfection. In case 2, whole-genome sequencing of the second collected specimen confirmed that it belonged to clade GH and lineage B.1.497 and showed a high similarity with a domestic outbreak (a heater factory in Asan, Cheonan). Although a specimen from the first infection was not obtained from case 2, considering that the case was confirmed during the quarantine process (entry from Bangladesh), it was classified as a suspected reinfection case.

than the first infection and recovery is faster [10], and there are differences in the level of immunity against reinfection according to age [11]. Although cases of reinfection continue to be reported worldwide, no results have been published from analyses of possible reinfection cases in the Republic of Korea. Therefore, in consideration of the increased likelihood of reinfection due to the prevalence of variants and prolongation of the pandemic, ongoing monitoring of reinfection cases should be carried out for effective quarantine responses in order to prevent further spread caused by reinfection. Specifically, analyses should investigate the occurrence of additional infections due to reinfection cases, the severity of reinfection, the risk of reinfection by age, and the effect of vaccination on reinfection.

## Conclusion

Due to the prolonged COVID-19 pandemic and the emergence of variants, the number of reinfection cases is increasing worldwide. In the Republic of Korea, since the first reinfection case was reported in April 2020, four suspected reinfection cases have been identified, two of which were confirmed based on epidemiological and virological data. According to data published abroad, cases of reinfection are often milder

**① What was known?**

After the first case of reinfection was confirmed in Hong Kong in August 2020, reinfection cases have been reported all over the world. The first case of reinfection was identified in the Republic of Korea in April 2020. With the emergence of variants, concerns about reinfection with variants are growing.

**② What is newly learned?**

So far, there have been a total of five suspected cases of reinfection in the Republic of Korea. With the exception of one case, which was the first confirmed case of reinfection, four cases underwent whole-genome sequencing. Based on epidemiological data and whole-genome sequencing results, two cases were confirmed as involving reinfection due to exposure to variants, and the other two cases were classified as suspected reinfection cases based on epidemiological information (e.g., history of contact with confirmed cases).

**③ What are the implications?**

Whole-genome sequencing analysis of the suspected reinfection cases led to confirmation of reinfection based on genetic discordances between the first and specimens from the second infection. Accordingly, it is necessary to examine whether additional quarantine measures for reinfection cases are required through ongoing monitoring of suspected reinfection cases.

This article has been translated from the Public Health Weekly Report (PHWR) volume 14, Number 25, 2021.

**Acknowledgment****Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

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**Submitted:** June 10, 2021; **Revised:** June 14, 2021; **Accepted:** June 15, 2021

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