COVID-19 reinfection: a rapid systematic review of case reports and case series

Jingzhou Wang,[1] Christopher Kaperak,[1] Toshiro Sato,[2,3] Atsushi Sakuraba [4]

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[1]Department of Medicine, University of Chicago, Chicago, Illinois, USA
[2]Department of Organoid Medicine, Keio University School of Medicine, Tokyo, Japan
[3]Coronavirus Task Force, Keio Univeristy, Tokyo, Japan
[4]Section of Gastroenterology, Hepatology and Nutrition, Department of Medicine, University of Chicago, Chicago, Illinois, USA

Correspondence to
Dr Atsushi Sakuraba, Section of Gastroenterology, Hepatology and Nutrition, Department of Medicine, University of Chicago, Chicago, IL 60637, USA; asakurab@medicine.bsd.uchicago.edu

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ABSTRACT

The COVID-19 pandemic has infected millions of people worldwide and many countries have been suffering from a large number of deaths. Acknowledging the ability of SARS-CoV-2 to mutate into distinct strains as an RNA virus and investigating its potential to cause reinfection is important for future health policy guidelines. It was thought that individuals who recovered from COVID-19 generate a robust immune response and develop protective immunity; however, since the first case of documented reinfection of COVID-19 in August 2020, there have been a number of cases with reinfection. Many cases are lacking genomic data of the two infections, and it remains unclear whether they were caused by different strains. In the present study, we undertook a rapid systematic review to identify cases infected with different genetic strains of SARS-CoV-2 confirmed by PCR and viral genome sequencing. A total of 17 cases of genetically confirmed COVID-19 reinfection were found. One immunocompromised patient had mild symptoms with the first infection but developed severe symptoms resulting in death with the second infection. Overall, 68.8% (11/16) had similar severity; 18.8% (3/16) had worse symptoms; and 12.5% (2/16) had milder symptoms with the second episode. Our case series shows that reinfection with different strains is possible, and some cases may experience more severe infections with the second episode. The findings also suggest that COVID-19 may continue to circulate even after achieving herd immunity through natural infection or vaccination, suggesting the need for longer-term transmission mitigation efforts.

COVID-19 has infected over 38 million individuals and claimed at least one million lives across the globe since it originated in Wuhan, China, in late 2019.[1] As an RNA virus that is prone to mutations, SARS-CoV-2 has been reported to have heterogeneous genetic composition in different geographical locations.[2] Since August 2020, several cases of COVID-19 reinfections have been reported. The current study aimed to summarize these cases to facilitate our understanding on the degree of protective immunity.

Electronic databases (PubMed, MedRxiv, and Social Science Research Network) were searched from January 1, 2020, to October 12, 2020, using terms "SARS-CoV-2," "CoV2," "COVID-19," and "reinfection". COVID-19 reinfection was defined as individuals infected with different genetic strains of SARS-CoV-2 confirmed by PCR. Only studies with viral genome sequencing available for both infectious events were included in this report to distinguish true reinfection and prolonged viral shedding, as research has shown that a certain proportion of patients may continue to carry the virus despite resolution of symptoms and prior negative PCR tests.[3] For this reason, six peer-reviewed articles and two news articles from the stated date range describing either individual or small groups of additional possible COVID-19 reinfections (totaling 31 individuals) were excluded.

A total of 17 cases of genetically confirmed COVID-19 reinfection have been reported in the literature to date, which are summarized in table 1. Reinfection has been reported in Asia, Europe, and North and South America. Ages of reinfected individuals ranged between 24 and 89 years old. Mean interval between the first and the second infections averaged 76 days (range 19–142). Only one reinfected patient was immunocompromised (1/17, 5.8%). This patient was a woman in her 80s undergoing chemotherapy for a hematological malignancy who had mild symptoms with her first infection but developed severe symptoms, resulting in death with her second infection.[4] Among the remaining 16 patients, the proportion of patients having mild/asymptomatic infections were the same for the first and second episodes (93.8%). Overall, 68.8% (11/16) had similar severity; 18.8% (3/16) had worse symptoms; and 12.5% (2/16) had milder symptoms with the second episode.

Individuals who recovered from COVID-19 were generally thought to generate a robust immune response to clear the virus. However, it remains to be determined whether the initial infection confers a protective immunity to subsequent infections. Recent research has suggested that positive COVID-19 antibody from initial infection may provide protection against reinfection in a majority of study subjects, but reinfection is still possible in certain individuals.[5] Reinfection with other human coronaviruses is common, despite the presence of antibodies.[6] The current case series indicate that COVID-19 reinfection is possible, and the second infection may result in worse

Table 1 Summary of COVID-19 reinfection cases with confirmed genomic differences

Patient	Date reported	Age/ sex	Immuno compromised	Interval (days)	Symptom severity* (first episode)	Symptom severity (second episode)	Negative PCR test in between infections	Seroconversion after initial infection	Seroconversion after second infection	Viral clade (first episode)	Viral clade (second episode)	Recovered	Country	References†
1	May 20	42/M	No	51	Mild	Mild	Not performed	Not performed	Not performed	B.1.26	B.1.26 but with several mutations	Yes	USA	Larson *et al*, 2020
2	June 20	25/M	No	48	Mild	Moderate‡	Yes	Not performed	Yes	20C	20C with 11 SNP mutations	Yes	USA	Tillett *et al*, 2020
3	June 20	51/F	No	120	Mild	Mild	Not performed	Not performed	Not performed	B.1.1	A	Yes	Belgium	Van Elslande *et al*, 2020
4	July 20	60/M	No	140	Moderate	Mild	Yes	Not performed	Yes	19B	20A	Yes	USA	Goldman *et al*, 2020
5	July 20	33/M	No	142	Mild	Asymptomatic	Yes	Yes	Yes	D614 (V/19A;B.2)	G614 (G20A, B.1)	Yes	China	To *et al*[12]
6	July 20	46/M	No	68	Mild	Mild	Yes	Not performed	Yes	B1.p9	A.1.1	Yes	Ecuador	Prado *et al*, 2020
7	July 20	89/F	Yes	59	Mild	Severe‡	Not performed	Not performed	No	N/A	10 SNP mutations	No	The Netherlands	Mulder *et al*[4]
8	July 20	27/M	No	66	Mild	Mild	Yes	Not performed	No	B.1	B, 8 SNP mutations	Yes	India	Shastri *et al*, 2020
9	July 20	31/M	No	65	Asymptomatic	Mild‡	Yes	Not performed	No	B.1.1	B.1.1, 9 SNP mutations	Yes	India	Shastri *et al*, 2020
10	July 20	27/M	No	19	Asymptomatic	Mild‡	Yes	Not performed	Not performed	B.1.1	B.1.1, 9 SNP mutation	Yes	India	Shastri *et al*, 2020
11	July 20	24/F	No	55	Mild	Mild	Not performed	Not performed	No	B.1.1	B.1.1, 12 SNP mutations	Yes	India	Shastri *et al*, 2020
12	August 20	47/F§	N/A	88	Mild	Mild	Not performed	Not performed	No	D614	G614	Yes	Qatar	Abu-Raddad *et al*, 2020
13	August 20	27/M§	N/A	46	Mild	Mild	Not performed	Not performed	Not performed	D614	G614	Yes	Qatar	Abu-Raddad *et al*, 2020
14	August 20	42/M§	N/A	71	Mild	Mild	Not performed	Not performed	Not performed	D614	G614	Yes	Qatar	Abu-Raddad *et al*, 2020
15	August 20	27/M§	N/A	55	Mild	Mild	Not performed	Not performed	Not performed	D614	G614	Yes	Qatar	Abu-Raddad *et al*, 2020
16	August 20	25/M	No	106	Asymptomatic	Asymptomatic	Yes	Not performed	Not performed	N/A	9 SNP mutations	Yes	India	Gupta *et al*, 2020
17	September 20	28/F	No	107	Asymptomatic	Asymptomatic	Yes	Not performed	Not performed	N/A	10 SNP mutations	Yes	India	Gupta *et al*, 2020

*Symptom severity was classified as follows: severe: intensive care unit admission; moderate: supplemental oxygen with nasal cannula; mild; no oxygen support but other COVID-19 symptoms (which may include cough, rhinorrhea, sore throat, shortness of breath, change in taste or smell, headache, nausea, vomiting, diarrhea, fever, chills, fatigue, and myalgias).
†See full citations in the online supplemental file.
‡Worse symptoms at second infection compared with the first infection.
§Only age range was reported in this study, so an average number is taken, that is, 47 for range 45–49 years.
F, female; M, male; N/A, not applicable; SNP, single-nucleotide polymorphism.

symptoms in nearly 20% of patients and serious complications in those who are elderly and immunocompromised. This raises concern because previous reports from SARS, MERS-CoV, and dengue viruses documented that pre-existing, non-neutralizing or poorly neutralizing antibodies that developed as a result of infection or vaccine enhanced subsequent infection (antibody-dependent enhancement (ADE)) and a similar phenomenon may be occurring with SARS-CoV-2.[7] Our data also suggest that reinfection is not specific to any particular strain, and multiple strains with a different genetic sequence have been shown to cause reinfection. Due to the emergence of the recently described spike deletion variants from UK and South Africa, it is of interest whether second infections can occur in people who have had COVID-19 during the 'first wave' before these variants were prevalent.

Given the potential reporting bias and the current report including only studies with genomic data, there are likely many more reinfection cases than have been currently described. However, the true prevalence of COVID-19 reinfection may be difficult to estimate, considering that complete genomic data are not available in most COVID-19 infections and many patients with milder symptoms were not tested in the early phase of this pandemic. Additionally, people with asymptomatic reinfections are less likely to be identified, so identifying true prevalence of COVID-19 reinfection is difficult without population-based studies, which is a possible area for future research. Studies included in our analysis reported certain key nucleotide differences between the sequenced viruses, but more recently, new variants have also been detected in areas of the UK where cases are rising.[8] Some primary literature cited in our study did not contain data on seroconversion, so it is difficult to comment on the connection between immunity and presence of antibody, but one patient developed reinfection despite prior positive antibody test (patient 5). Considering that the two strains belong to the same clade in some reported cases, the possibility of accelerated mutation of the original strain or simultaneous infection with more than one strain, in addition to waning immunity, should be also considered. It is also difficult to differentiate between COVID-19 reinfection, relapse and PCR repositivity in some cases, and Yahav *et al*[9] proposed reinfection as >90 days apart, but we restricted our inclusion criteria to only patients with confirmed infection with different genetic strains. Two meta-analyses undertaken early in the pandemic reported that reinfection or repositivity were rare but lacked cases with genomic data.[10 11]

Our case series indicate that previous COVID-19 exposure does not confer total immunity and that a second infection is possible. Therefore, individuals, regardless of history of prior infection, should continue to participate in mitigating the spread of infection by practicing social distancing and mask wearing. The findings also suggest that COVID-19 may continue to circulate in humans,[12] even after achieving herd immunity through natural infection or vaccination.

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ORCID iD

Atsushi Sakuraba http://orcid.org/0000-0003-2519-6129

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