

Epidemiological and clinical characteristics of SARS-CoV-2 reinfections in a Spanish region

SAGE Open Medicine

Volume 10: 1–6

© The Author(s) 2022

Article reuse guidelines:

sagepub.com/journals-permissions

DOI: 10.1177/20503121221108556

journals.sagepub.com/home/smo



Oriol Yuguero^{1,2} , Maria Companys¹, Marianela Guzmán¹, Rita Maciel¹, Cecília Llobet¹, Aurora López¹, Rebeca Olles¹, Violant Pujol¹, Maria José Ruiz¹, Mireia Saura¹, Carmel Vidal¹ and Pere Godoy^{2,3}

Abstract

Objective: We aimed to assess the prevalence and clinical characteristics of SARS-CoV-2 reinfections in a Spanish region.

Methods: This is a retrospective observational study in all patients with SARS-CoV-2 infections in the Lleida health region from 1 March to 30 November 2020. Reinfections were classified as patients with positive SARS-CoV-2 PCR tests separated by at least 90 days plus a negative test result between both infection episodes. Primary and secondary outcomes: The primary outcome was the percentage of SARS-CoV-2 reinfections among all SARS-CoV-2 infections detected during our study period. Secondary outcomes were the clinical and sociodemographic characteristics of patients with SARS-CoV-2 reinfections.

Results: Of the 27,758 patients diagnosed with SARS-CoV-2 infection in the study period, 14 were identified as coronavirus reinfection (0.050%). Of the reinfected sample, 12 patients (85.7%) were women. The median age was 41.5 years. Two patients died in the second coronavirus episode.

Conclusion: The reinfection rate of SARS-CoV-2 in the Spanish region Lleida was relatively low during the observational period in 2020 (less than 1%). These data are in line with the notion that previous SARS-CoV-2 infections may offer a significant protection by so called natural immunity.

Keywords

SARS-CoV-2, reinfection, emergency department

Date received: 21 October 2021; accepted: 4 June 2022

Introduction

The SARS-CoV-2 pandemic has changed all health and social priorities around the world, and special emphasis has been given to the strengths of the different health systems and policy decisions. During the first wave in March and April 2020, the majority of the patients attended to by the Emergency Departments of European and Spanish hospitals was due to SARS-CoV-2 infection and its clinical consequences.¹ Then, we did not know what would happen once people had had the infection and what real likelihood of reinfection could be expected. Some months later, we have greater knowledge about different therapeutic options and types of diagnostic tests, and in January 2021 vaccination campaigns began throughout Europe.

After 2 years of the pandemic, more than 10 different variants of coronavirus have been detected with different impacts on the waves of the disease in different countries. The relaxation of restrictive measures has favoured citizens' travel movements and hence the propagation of the various strains. The most relevant have been Delta and more recently the appearance of Omicron. A recent study conducted in

¹ER LAB, Biomedical Research Institute of Lleida (IRBLleida), Lleida, Spain

²Faculty of Medicine, University of Lleida, Lleida, Spain

³CIBER of Epidemiology and Public Health (CIBERESP), Madrid, Spain

Corresponding author:

Oriol Yuguero, Biomedical Research Institute of Lleida (IRBLleida), Av. Rovira Roure 80, Lleida 25198, Spain.

Email: oriol.yuguero@udl.cat



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons

Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

Barcelona in 2021² showed multiple lineages were co-circulating under a neutral selection evolution until massive vaccination campaigns started, but a different predominant lineage was observed in each pandemic wave, suggesting acquired genetic advantages over other previous circulating variants.

Genome sequencing is essential to distinguish viral reinfection from viral reactivation.³ However, the rapid evolution of the pandemic and the lack of protocolized genome sequencing of positive cases not only limits health monitoring but also the definition and detection of cases of reinfection.⁴

Between June and December 2020, different labs and research institutes were trying to find out whether patients previously infected with SARS-CoV-2 could be reinfected or not, and if not, how long their immunity would last. Since the appearance of the first cases of reinfection,⁵ after the first wave, evidence of reinfection has increased. In the United Kingdom, a research study detected eight reinfections (0.075%),⁶ and various articles have reported reinfection around the world. Initially, researchers believed that reinfection was due to viruses with immune escape mutations.⁷

In our region of Lleida, in north-eastern Spain, we have the particularity that we have suffered an extra wave of the pandemic compared to the rest of Spain. In addition to the waves of March and November 2020, we also faced a severe wave in July 2020 as a result of an accumulation of seasonal harvest and agricultural workers. This wave severely strained the health system because a huge number of new cases were detected, and control and quarantine measures were in some cases difficult to follow. Due to the above reasons, our region has experienced a high incidence of SARS-CoV-2 infection.

The CDC⁸ argues that patients can be reinfected 90 days after prior infection, or sooner in the case of subjects with some immune defects, or professionals who are greatly exposed to the virus, such as healthcare workers. During all these months, the criteria and options for considering a case as being a reinfection have changed. Today, we know that the result of a polymerase chain reaction (PCR) can remain positive many weeks after the first episode.⁹ A recent review¹⁰ outlined how in previous studies, some cases have been declared reinfections due to a PCR test being positive more than 6 weeks after the first symptoms.¹¹ Another review casts doubts as to the real possibility of reinfection.¹²

The duration of natural immunity in terms of protection against reinfections and related morbidity and mortality may be key for the SARS-CoV-2 pandemic. It seems that more than one-third and possibly more than half of the global population may have already been infected (at least once) with SARS-CoV-2 by the beginning of 2022, with the majority of cases not being officially detected and reported.¹³ In fact, in our country, patients have been described to have been reinfected by the Omicron strain having already been infected by the Delta strain.¹⁴

Due to insufficient evidence on the real possibilities of reinfection, we have conducted this study with the aim of detecting whether there have indeed been cases of reinfection and describe their clinical characteristics.

Methods

Retrospective observational study of all patients with SARS-CoV-2 treated in the Lleida health region between 1 March and 30 November 2020.

Patients were treated in primary care centres in our region and at the Arnau de Vilanova University Hospital. This healthcare region serves 300,000 people.

Data source

Data were taken from two different information systems. On the one hand, patients registered with the public system who consulted their general practitioner or an emergency service by means of the Electronic clinical workstation (SAP® and Electronic-Centre d'Atenció Primària (ECAP) for its acronym in Spain¹⁵) programmes. On the other hand, all cases of SARS-CoV-2 notified to our region's public health authorities. Thus, we managed to detect almost all cases, even those displaying few symptoms or who self-diagnosed by using an antigen test.

Data from the databases were crossed, and cases that were registered twice were eliminated. Of all the patients we obtained, we finally collected those who had contacted the healthcare system and diagnosed with SARS-CoV-2 on two separate occasions in 90 days.

Inclusion criteria

We included all patients attended in the Lleida Health Region due to SARS-CoV-2 disease between March and November 2020.

Exclusion criteria

We only excluded patients who did not consent to participate.

Variables

Definition of reinfection. Reinfection refers to patients whose nasopharyngeal swab (PCR) test yields a positive result separated by at least 90 days, according to the current CDC recommendations.¹⁶ Moreover, such patients must have a negative PCR between episodes or negative antibody levels (immunoglobulin G) at the onset of the second episode. We have taken into account PCR conducted by health personnel at certified laboratories in our region.

Following to the Spanish Ministry of Health recommendations, despite being asymptomatic, patients testing positive 90 days after the initial symptoms underwent serology to

detect the presence of high levels of immunoglobulin M and the existence of any new active infection.

Clinical variables. We evaluated risk factors for SARS-CoV-2 disease like previous lung disease, diabetes, hypertension and smoking habits.

We reported different clinical variables such as duration of symptoms, hospitalization requirements, the need for taking sick leave and the treatment received. The same clinical variables were evaluated for the second episode.

Other variables. We recorded the sociodemographic variables of all cases of reinfection and whether they were people working in the healthcare environment.

Statistical analysis

The descriptive analysis includes absolute and relative frequencies for the qualitative variables and median and interquartile range for the quantitative variables. R software¹⁷ was used for data analysis.

Ethical statement

Neither the patients nor the public were involved in the design, development, reporting or dissemination plans of our research.

The study was approved by the Research Ethics Committee of the Regional Catalan Health System with ID 2020/2350. Verbal informed consent was obtained from all reinfected subjects before the study. Informed consent was verbal in accordance with the Research Ethics Committee of our centre.

The Ethics Committee exempted us from obtaining informed consent of all the patients we reviewed prior to obtain the final sample, since it was a retrospective study.

Results

In our health region, 358,998 people live in Lleida. Of the 27,758 patients diagnosed with SARS-CoV-2 infection in the study period, 20,534 patients had a positive PCR. Of this group of patients, 972 performed a consultation related to the infection separated by at least 90 days (Figure 1).

Of this group of patients, 14 were identified as cases of SARS-CoV-2 reinfection (0.068%). These reinfected patients had a positive PCR test, followed by a negative PCR test and a second PCR test 90 days after the initial symptoms. The sample selection is described in Figure 1. Of the reinfected sample, 85.7% were women, mainly young (median 41.5 years). None of the patients were smokers or diabetic. Only two patients had previously suffered lung disease. Two health professionals were reinfected during the study period.

The mean duration of symptoms was 8.5 days, and none of the 14 patients required hospitalization. Most of them did not receive treatment (Table 1). A negative PCR was obtained after the first episode by 12 of the 14 patients. In the other

two, it was not performed. The average number of days between a negative result and the second episode was 91.5 days [12–176]. The number of days between the initial symptoms of the first episode and the second episode was 112 days [72–188].

In the second episode, the duration of symptoms was shorter (at 6 days). Of the 14 patients, three required hospitalization and two died (14.28% of the sample). Both patients who died were women with no respiratory comorbidities. Five patients (35.7%) were asymptomatic in the first episode, whereas three cases (21.4%) were asymptomatic in the second.

Discussion

This is the one of the first study in our country on SARS-CoV-2-reinfected patients. However, in Europe, other projects have studied the reinfected patients. For example in Denmark, Hansen et al.¹⁸ found that reinfection was seen in certain population groups, especially in older people.

In Austria, Pilz et al.¹⁹ found that the reinfection rate after SARS-CoV-2 infection was low. In Qatar, Abu-Raddad et al.²⁰ warned that reinfections were rare, but could increase with the introduction of new variants of the virus.²¹

Up until today, our healthcare area is the only region in Spanish that has suffered seven waves, and the patients evaluated have been diagnosed during the three waves we have undergone in 9 months. During the first weeks after the first wave, many researchers tried to find out whether infected patients can be reinfected.²² The reinfection rate prior to the vaccination campaigns was under 1%. One study²³ has detected a higher reinfection rate, but those reinfections have been always lower than 1% of cases. Other research conducted in China²⁴ described some cases of reinfection but with less than 90 days between episodes.

In our sample, the majority of reinfected patients were women, especially young women, as the study by Breathnach⁶ reports. We think this is particularly interesting because the available evidence shows that men usually present with severe disease.²⁵ However, other studies have shown greater reinfection among women.^{26,27} This is interesting and prompts the possibility of considering new lines of research. Our sample did not include any pregnant or immunosuppressed patients. We were unaware of the professions of the reinfected patients, but we knew that 2 of the 14 reinfected patients were health workers. It would make sense that women who generally play a greater role as caregivers (of both children and the elderly) may be more vulnerable to reinfection, as could occur with health professionals.

All of the patients included had a mild first episode of infection (none of them required hospitalization), and the second episode was shorter in duration. None of the patients had respiratory distress. It could be that patients with a mild initial episode developed low immunity, thus facilitating reinfection. Indeed, a study conducted in France²⁸ revealed a correlation between levels of antibodies and the severity of

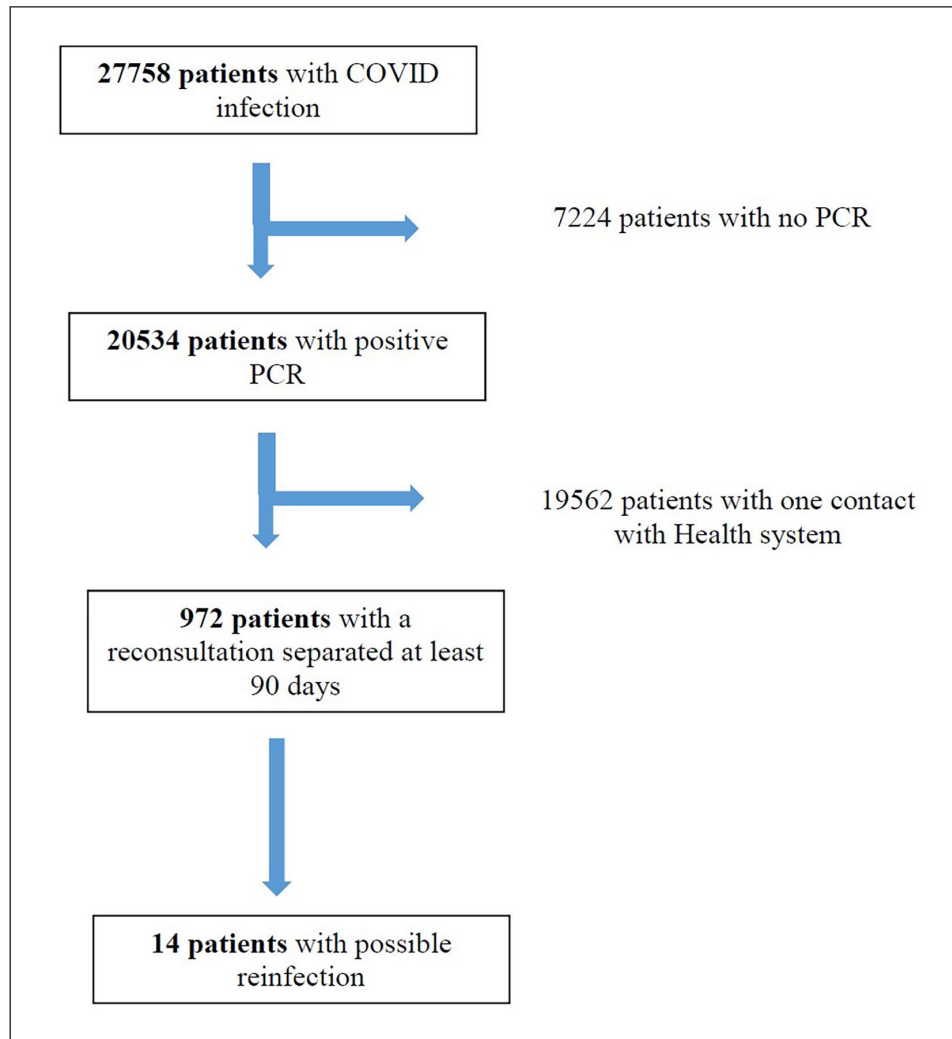


Figure 1. Flowchart of patients included.

infection by SARS-CoV-2. However, further studies will be needed to verify this.

Our study is mainly based on patients who, apart from having a repeat positive PCR, have no symptoms, which until now questioned whether patients actually could be reinfected. However, three of the reinfected patients had clinical complications, and two of them died. The main characteristic of the deceased patients was that both were over 85 years of age, with no previous lung disease.

The main challenge that remains for us is to assess whether patients can be reinfected by a different strain of the virus or whether the virus that has caused the first episode can be reactivated, as previously mentioned.²⁹ However, in our study, we spaced the two episodes over 90 days, corresponding to the longest-persisting positive PCR described.

Strengths and limitations of this study

The main strength of our study is that our sample is very broad and includes patients who have been diagnosed in one of the

three waves we suffered in our region between March and November 2020. However, one of our main limitations is that we were not able to perform genetic sequencing of the virus because in the first wave the samples of many swabs were not kept. As we have explained, given the appearance of different strains, sample sequencing is of utmost importance. Moreover, we did not calculate power analysis because all patients were included consecutively as they attended. In addition, one of the limitations is that at the moment there are new variants that can change the evolution of the different waves of SARS-CoV-2 infection.

Conclusion

Our main finding is that the rate of SARS-CoV-2 reinfection is very low and is often associated with mild symptoms, but it may cause complications in elderly patients. Probably because there were few patients at risk of reinfection, and new variants of the virus had not yet spread. Moreover, nowadays we have more tools to detect and to evaluate SARS-CoV-2 infections.

Table 1. Reinfected patients sample description.

	N (%)
Age (median)	41.5 [13.0; 103]
Women	12 (85.7%)
Risk factors	
Diabetes mellitus	0 (0%)
Diagnosed obesity	3 (21.4%)
Hypertension	5 (35.7%)
Smoker	0 (0%)
Previous respiratory disease	2 (14.3%)
Healthcare professionals	2 (14.3%)
First episode clinical variables	
Symptoms duration	8.50 [0.00; 21.0]
Radiology pathology	0
Requires hospitalization	0 (0%)
Received hydroxychloroquine	1 (7.14%)
Received enoxaparin	4 (28.6%)
Received dexamethasone	1 (7.14%)
Negative PCR at the end of episode	12 (85.7%)
Sick leave prescription	7 (50%)
Serology performed	4 (28.6%)
Second episode clinical variables	
Symptoms duration	6.00 [0.00; 21.0]
Positive PCR	14 (100%)
Requires hospitalization	3 (21.4%)
Complications	3 (21.4%)
Death	2 (66.7%)
Received enoxaparin	6 (42.9%)
Received dexamethasone	2 (14.3%)

We conclude that men are more likely to suffer severe infection with SARS-CoV-2, but women are more likely to be reinfected. Although to date reinfection with the Delta variant seems to be rather exceptional, in all of the series referred to, the new Omicron variant has also been seen to avoid the natural immunity gained from having been previously infected by the disease. Further research should be conducted to confirm our results.

Acknowledgements

We wish to thank all the professionals in our service who cared for SARS-CoV-2 patients in the first wave amid the uncertainty and the fear of the unknown.

Author contributions

OY and CV developed the study and reviewed the manuscript. MC, AL, CL and MJR created the database and reviewed all the data. MG, RO and MS performed the statistical analysis. RM and VP analysed the results and wrote the manuscript draft. PG reviewed the manuscript after revision.

Data sharing statement

Data are available upon reasonable request.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval for this study was obtained from the Research Ethics Committee of Regional Catalan Health System with ID 2020/2350.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Informed consent

Verbal informed consent was obtained from all subjects before the study. Informed consent was verbal in accordance with the Research Ethics Committee of our centre. Consent was recorded in the clinical history of the patients.

ORCID iD

Oriol Yuguero  <https://orcid.org/0000-0002-3433-8005>

References

1. Nuñez JH, Sallent A, Lakhani K, et al. Impact of the COVID-19 pandemic on an emergency traumatology service: experience at a tertiary trauma centre in Spain. *Injury* 2020; 51(7): 1414–1418.
2. Andrés C, Piñana M, Borràs-Bermejo B, et al. A year living with SARS-CoV-2: an epidemiological overview of viral lineage circulation by whole-genome sequencing in Barcelona city (Catalonia, Spain). *Emerg Microbes Infect* 2022; 11(1): 172–181.
3. To KK, Hung IF, Ip JD, et al. COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing. *Clin Infect Dis* 2021; 73(9): e2946–e2951
4. Tillett RL, Sevinsky JR, Hartley PD, et al. Genomic evidence for reinfection with SARS-CoV-2: a case study. *Lancet Infect Dis* 2021; 21(1): 52–58.
5. Parry J. COVID-19: Hong Kong scientists report first confirmed case of reinfection. *BMJ* 2020; 370: m3340.
6. Breathnach AS, Riley PA, Cotter MP, et al. Prior COVID-19 significantly reduces the risk of subsequent infection, but reinfections are seen after eight months. *J Infect* 2021; 82(4): e11–e12.
7. Colson P, Finaud M, Levy N, et al. Evidence of SARS-CoV-2 re-infection with a different genotype. *J Infect* 2021; 82(4): 84–123
8. European CDC. 2020. Threat assessment brief: reinfection with SARS-CoV-2: considerations for public health response, <https://www.ecdc.europa.eu/sites/default/files/documents/Re-infection-and-viral-shedding-threat-assessment-brief.pdf>
9. Pollán M, Pérez-Gómez B, Pastor-Barriuso R, et al. Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study. *Lancet* 2020; 396(10250): 535–544.

10. SeyedAlinaghi S, Oliaei S, Kianzad S, et al. Reinfection risk of novel coronavirus (COVID-19): a systematic review of current evidence. *J Virol* 2020; 9(5): 79–90.
11. Iwasaki A. What reinfections mean for COVID-19. *Lancet Infect Dis* 2021; 21(1): 3–5.
12. Arafkas M, Khosrawipour T, Kocbach P, et al. Current meta-analysis does not support the possibility of COVID-19 reinfections. *J Med Virol* 2021; 93(3): 1599–1604.
13. Pilz S, Theiler-Schwetz V, Trummer C, et al. SARS-CoV-2 reinfections: Overview of efficacy and duration of natural and hybrid immunity. *Environ Res* 2022; 209: 112911.
14. Sánchez-Varela N, Cinza-Sanjurjo S and Portela-Romero M. Reinfección por variante Ómicron en pacientes previamente infectados con la variante Delta del coronavirus SARS-CoV-2: una realidad cada vez más frecuente en atención primaria [Reinfection by the Omicron variant in patients previously infected with the Delta variant of the SARS-CoV-2 coronavirus: an increasingly frequent reality in primary care]. *Semergen* 2022; 22: S1138–S3593.
15. Pons-Mesquida MA, Oms-Arias M, Diogène-Fadini E, et al. Safer prescription of drugs: impact of the PREFASEG system to aid clinical decision-making in primary care in Catalonia. *BMC Med Inform Decis Mak* 2021; 21(1): 349.
16. Center for Disease Control and Prevention (CDC). Duration of isolation and precautions for adults with COVID-19, https://nil.org.pl/uploaded_files/art_1598432568_duration-of-isolation-and-precautions-for-adults-with-covid-19-cdc.pdf (2020).
17. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing, 2021, <https://www.R-project.org/>
18. Hansen CH, Michlmayr D, Gubbels SM, et al. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. *Lancet* 2021; 397(10280): 1204–1212.
19. Pilz S, Chakeri A, Ioannidis JP, et al. SARS-CoV-2 re-infection risk in Austria. *Eur J Clin Invest* 2021; 51(4): e13520.
20. Abu-Raddad LJ, Chemaitelly H, Coyle P, et al. SARS-CoV-2 antibody-positivity protects against reinfection for at least seven months with 95% efficacy. *EClinicalMedicine* 2021; 35: 100861.
21. Abu-Raddad LJ, Chemaitelly H, Ayoub HH, et al. Introduction and expansion of the SARS-CoV-2 B.1.1.7 variant and reinfections in Qatar: a nationally representative cohort study. *PLoS Med* 2021; 18(12): e1003879.
22. Roy S. COVID-19 reinfection: myth or truth? *SN Compr Clin Med* 2020; 2(6): 710–713.
23. Hall V, Foulkes S, Charlett A, et al. Do antibody positive healthcare workers have lower SARS-CoV-2 infection rates than antibody negative healthcare workers? Large multi-centre prospective cohort study (the SIREN study), England: June to November 2020. *medRxiv*.
24. Yahav D, Yelin D, Eckerle I, et al. Definitions for coronavirus disease 2019 reinfection, relapse and PCR re-positivity. *Clin Microbiol Infect* 2021; 27(3): 315–318.
25. Gebhard C, Regitz-Zagrosek V, Neuhauser HK, et al. Impact of sex and gender on COVID-19 outcomes in Europe. *Biol Sex Differ* 2020; 11(1): 29.
26. CDC COVID-19 Vaccine Breakthrough Case Investigations Team. COVID-19 vaccine breakthrough infections reported to CDC—United States, January 1–April 30, 2021. *MMWR Morb Mortal Wkly Rep* 2021; 70(21): 792–793.
27. Lawandi A, Warner S, Sun J, et al. Suspected SARS-CoV-2 reinfections: incidence, predictors, and healthcare use among patients at 238 U.S. healthcare facilities, June 1, 2020–February 28, 2021. *Clin Infect Dis* 2022; 74(8): 1489–1492.
28. Legros V, Denolly S, Vogrig M, et al. A longitudinal study of SARS-CoV-2-infected patients reveals a high correlation between neutralizing antibodies and COVID-19 severity. *Cell Mol Immunol* 2021; 18(2): 318–327.
29. Kang H, Wang Y, Tong Z, et al. Retest positive for SARS-CoV-2 RNA of “recovered” patients with COVID-19: persistence, sampling issues, or re-infection? *J Med Virol* 2020; 92(11): 2263–2265.