DOI: 10.31557/EJHC.2022.2.50-55

Review Article

Demographic and clinical characteristics of COIVD-19 reinfection cases confirmed by genetic analysis: A Systematic review

Mohammad-Mahdi Salarabedi[1], Arefeh Tabashiri[1], Erfan Arabpour[1], Alireza Sardaripour[1], Amir Reza Pouladi[1], Zahra Nariman[1], Aliasghar Keramatinia[2,3], Ayad Bahadorimonfared[2], Ali Reza Mosavi Jarrahi[2,3]

[1]Student Research committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

[2] Department of Health & Community Medicine, Medical School, Shahid Beheshti University of Medical Sciences, Tehran, Iran

[3]Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Abstract

Background: Although infection with SARS-CoV-2 results in protective immune responses in recovered patients, reinfection with the virus is not impossible. Here we systematically reviewed literature-based-reported cases of reinfections in order to explore the virus-related, clinical, and demographic characteristics of re-infection in patients. **Methods:** This is a systematic review of all case reports of reinfection since the pandemic has begun. We searched through PubMed, Web of Science, Scopus, Google Scholar, and Embase databases and selected case reports and case series of reinfections by genetically confirmed COVID-19 virus strains. **Results:** Among 360 cases reported, just 39 cases met our criteria (genetically confirmed COVID-19 virus strains). The mean ± standard deviation of the age was 42 ± 17.4 (17.4 SD) with an equal proportion of males and females. The Second infection was asymptomatic or mild in most cases. The interval between the first and second infection was from 11 to 286 days. Nineteen patients had no underlying diseases, and four patients were immunodeficient due to immunosuppressive therapy. The First and second infection viruses were from different clades in 20 patients. Close to half of the reinfection occurred in health care workers. **Conclusion:** Evidence suggests that there is no guarantee that infection with SARS-CoV-2 protects from reinfection and that even immunocompetent patients are prone to be reinfected in the virus strain changes.

Key Words: COVID 19, Reinfection, Systematic Review.

East J Healthc, 2 (1), 50-55

Submission Date: 13/02/2022 Acceptance date:26/02/2022

1. INTRODUCTION

SARS-CoV-2, the virus responsible for COVID-19 disease is an RNA virus that belongs to the Coronaviridae family.The virus primarily attacks the respiratory system resulting in fever, dyspnea, cough, and respiratory failure, multiple organ failure, and death in the most severe cases .

Following infection with SARS-CoV-2, the virus induces the host's immune system to develop neutralizing antibodies, binding antibodies like IgG and IgM, CD4+ T cells, CD8+ T cells, and memory B cells all of which correlate with immunity to the virus. These immune responses support the idea that being infected with SARS-CoV-2 protects from subsequent infection. An animal study with rhesus macaques monkeys showed that infection with SARS-Cov-2 protects against reinfection with the same virus 14 days after the last negative RT-PCR test. However, several studies have reported patients who have become retest positive for SARS-CoV-2 RNA following recovery from the first infection . This could be due to false-negative RT-PCR test that was done as a criterion for discharge from isolation, persistence of shedding of the virus, and reinfection . The issue of reinfection has raised concern among healthcare professionals, reinfection could happen due to

Corresponding Author:
Ali Reza Mosavi Jarrahi
Department of Health & Community Medicine, Medical School, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
Email: rmosavi@yahoo.com

low antibody titer either because patients' immune system did not produce enough antibody during the first infection or antibody level has waned after recovery and emergence of new variants of the virus with higher infectivity and transmissibility and also the ability to escape from immune system the so-called Variants of Concern (VOC)[,].

Considering the fact that RNA viruses such as SARS-CoV-2 are highly mutable, new VOCs are expected to occur, thus increasing the risk of reinfection. We aimed to systematically review studies that have reported infection with a genetically distinct form of SARS-CoV-2 after recovery from the first COVID-19 infection. This paper describes the demographic and clinical characteristics of 39 confirmed reinfected patients reported in the literature.

2. METHODS

We conducted a systematic review of literature in May 2021; our study is in accordance with the Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.

2.1 Search strategy and information sources

The following databases were searched for relevant articles: PubMed, Web of Science, Scopus, Google Scholar, and Embase. Our search strategy includes (2019-nCoV OR COVID-19 OR SARS-CoV-2 OR novel coronavirus) AND (reinfection OR relapse OR recurrent OR reactivation OR re-detectable OR redetectable OR re-positive), we also applied Human studies and English article filters where possible in databases advanced search filters. Articles that were published until 15 May 2021 were retrieved.

2.2 Study selection and eligibility criteria

Duplicate articles were removed using Mendeley reference manager software Version 1.19.8. Two authors independently screened the title and abstract of articles to check for relevant ones; a third author was consulted in case of any discrepancy. We carefully reviewed the full-text of the remaining articles. Studies that had reported a case of reinfection with COVID-19 after recovery from the first episode of the disease in which reinfection was confirmed based on genetic analyses of the SARS-CoV-2 viruses causing the two episodes of infection were included in our study. Non-English articles, animal models and lab studies, and articles that their full-text or their original data was not available were excluded from the study.

2.3 Data collection and analysis

The following items were extracted and inserted into an excel sheet, Title, first authors name, country of origin, number of patients reported in each study, demographic characteristics of patients, infection severity during first and second infection, criteria for discharge from isolation after recovery from the first infection, the interval between last negative RT-PCR test and second infection, underlying diseases, presence of antibody in time of the second infection, clades and lineages of viruses responsible for the first and second infection. All statistical analyses were done using SPSS version 26.

2.4 Quality assessment

We used the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports to assess the quality of included studies.

3. RESULTS

We identified a total of 3331 articles through database searching. Of these, 1337 were duplicated. After removing duplicates, we screened the title and abstract of the remaining articles and selected 303 relevant articles for full-text screening. Of these 30 met our inclusion criteria mentioned in the method section and included in our study. (Figure 1)

Articles reviewed in this study are from 15 different countries, including 27 case reports and three case series reporting an overall of 39 patients with two episodes of SARS-CoV-2 infection caused by genetically distinct viruses. Patients data is 97.4% complete on sex, 87.2% for age, 100% for first infection severity, 94.9% for second infection severity, 67.7% for the criteria for discharge from isolation, 92.3% for the interval between two episodes of the disease, 79.4% for underlying diseases, 53.8% for antibody status of patients following the first infection, 56.4% for clades of viruses responsible for both episodes, and 12.8% for lineages of viruses causing the first and second episode of the disease. Patients with no reported underlying diseases were considered immunocompetent. Articles information is summarized in table1.

Our study's mean reported age of reviewed cases is 42(17.4(SD), ranging from 16 to 89 years old. Of reported patients, 18 (47.4%) were female, and 20 (52.6%) were male (one study has not reported the sex of the patient).

The Severity of the first infection was reported to be mild in most cases (74.4%). The Second episode of the disease was asymptomatic or mild in 75.7% of patients for whom the severity of the second infection was reported (Table 1 - Appendix). In 11 patients (29.7% of those data regarding second infection severity was available for them) second infection outcomes were more severe than the first infection.

Two negative RT-PCR tests was the most (76.9%) common criteria for discharge from isolation after

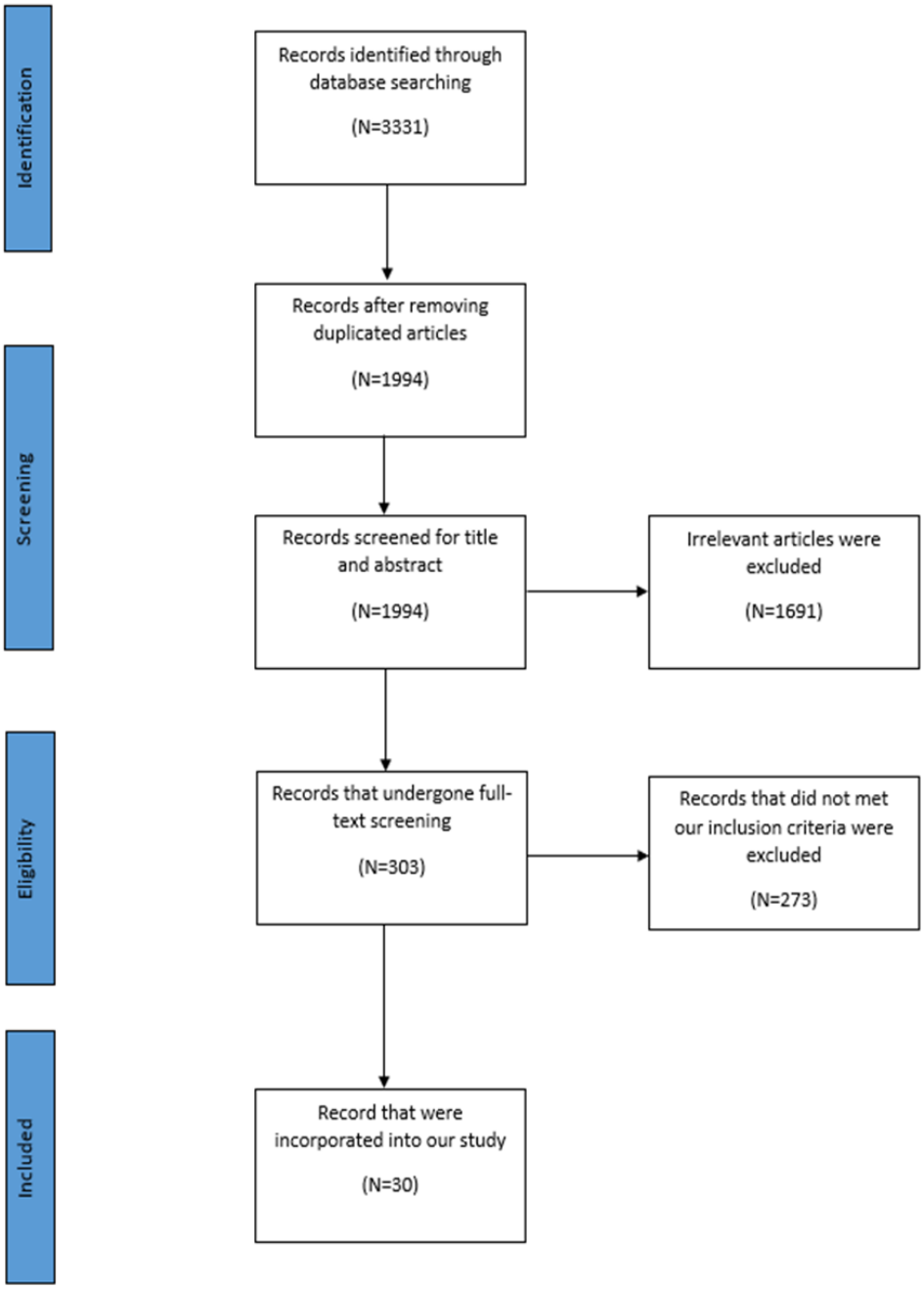

Figure 1: Flow diagram of search results and selection process

recovery from the first episode of the disease. Most of the patients for whom the data was available (61.2%) had no underlying diseases and only 4 patients have been treated with immunosuppressive drugs for their underlying diseases (Table 1 - Appendix).

Among cases with a reported interval between first and second infection, 58.3% were infected more than 90 days after the first infection with a range of 11 to 286 days (Table 1).

Virus clades responsible for the first and second infection were reported for 25 cases. The virus clade causing the first episode of the disease differed from the virus clade causing the second episode in 20 cases (Table1). Eight cases have been reinfected due to exposure to a VOC. There are two reports of reinfection with the same virus clade but from a different lineage and one report of reinfection with the same viral clade and the same virus lineage.

Antibody test was negative in 8 individuals (38%) at the time of reinfection and positive for anti-SARS-CoV-2 IgG following the first infection in 13 patients (61%).

Of reviewed cases in this study, 16 (41%) were among health care workers. All being infected more than 30 days after the first infection. There was only one case with underlying diseases among health care workers. Almost all (93.8%) health care workers were asymptomatic or experienced

mild symptoms in the second episode of the disease.

4. DISCUSSION

Here we reviewed demographic and clinical characteristics of 39 confirmed reinfected cases with SARS-CoV-2. The wide age distribution of reported patients (from 16 to 89) indicates that reinfection is not limited to a specific age group. 82.4 % of patients were younger than 60. The proportion of males and females were almost equal. In a cohort study conducted by Fan Wu et al., elderly patients had significantly higher levels of neutralizing antibodies than young patients; this could be a reason for the higher proportion of younger patients in our review. Fiona Tea et al. also found an association between antibody titer and older age, but they found no association between sex and antibody titer. Conversely, in a cohort of 126 convalescent patients, Sabra L.klein et al. indicated that higher titers of neutralizing antibodies are associated with the male gender.

According to our data, most reinfected patients do not develop severe disease during the second episode. A systematic review of 123 re-positive COVID-19 cases conducted by Szilárd Váncsa et al. revealed that 82.7% of patients developed the mild and moderate disease in the second episode, of note that the study, except for eight cases, lacked data to confirm that second episode was a reinfection and not reactivation of the previous infection. In a retrospective cohort study, 11.4% of suspected reinfection cases were hospitalized, but data regarding the severity of the second infection was not available, suspected reinfection is defined as being infected with SARS-CoV-2 for the second time a minimum of 90 days after the first infection [,]. Most of the mild cases during the first infection ended in mild or moderate reinfections. It is of note that all severe reinfections resulted from mild first infections reflecting the lower protective immunity of mild cases. According to a study, this could be due to the short-lasting antibodies in cases with mild SARS-CoV-2.

The interval between first and second infection varies widely among reported individuals suggesting that the immunity following infection with SARS-CoV-2 may differ from one person to another in terms of efficacy and duration and that there is no certainty about how long is the patient immune against the virus after being discharged from isolation. Luchsinger et al. found that 21 days after symptoms resolved, convalescent plasma had significantly lower neutralizing activity than a week earlier. Another study showed that Neutralizing activity of convalescent patients plasma showed a fivefold decrease 6.2 months after infection in comparison with 1.3 months post-infection.

Two negative RT-PCR test was reported for 20 patients before reinfection, which means that the virus has been cleared from the upper respiratory tract, thus decreasing the risk of the within-host mutation phenomenon. SARS-CoV-2 within-host mutations have been reported in an immunocompromised patient by Avanzato et al.

There were no reported comorbidities in 19 patients; this suggests that even patients who have no immunodeficiencies are at risk of reinfection. But a higher risk of reinfection in immunosuppressed patients was reported in the literature .

One study involved reinfection with a virus from the same clade and the same lineage of a 28-year-old male with no reported underlying conditions, but in the absence of IgG and IgM antibodies against the virus, authors suggested that the patient is a rare case of not developing immunity after the first infection. Conversely, a 21-year-old immunocompetent woman was reported to be reinfected with the virus from different clades despite having a protective titer of neutralizing antibodies against the virus of the first infection. Evidence suggests changes in the antigenicity of SARS-CoV-2, which affects the neutralizing potential of antibodies produced following infection with the unmutated virus. .

Working as a health care staff was common amongst the patients reported in the articles. Health care workers, especially those working in “patient-facing” roles, have an increased risk of exposure to the virus. Murillo-Zamora et al. indicated that health care workers are at higher risk of reinfection when compared with students and housewives; it is of note that reinfection criteria in their study was defined as a positive RT-PCR test after symptoms were resolved and at least 28 days following the first positive RT-PCR test 21.

Our study comes with strengths and limitations; one of its strengths is that we only included reports of patients with genetically confirmed reinfection. One of its limitations is that the presence and titer of antibodies in recovered individuals was reported at different time points, thus making it impossible to assess the role of antibodies in protecting from reinfection. Genome sequencing is not a procedure done routinely, so cases of confirmed reinfection may go unreported. It is of note that seven articles have not been peer-reviewed at the time of study selection.

5. CONCLUSION

There is no guarantee that one will be immune against subsequent infections once recovered from the COVID-19 disease. The immunity which is caused by a vaccine is longer lasting and is achieved at a lower cost as infection with SARS-CoV-2 may result in terrible outcomes. Also, while infection-induced immunity varies widely among individuals, vaccination results in

a strong immune response in most people. With these in mind, herd immunity is best achieved through vaccination rather than infection of a majority of the population.

6. ACKNOWLEDGEMENT

This study is related to project NO. 29728 From StudentResearch Committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran. We also appreciate the "Student Research Committee" and "Research & Technology Chancellor" in Shahid Beheshti University of Medical Sciences for their financial support of this study.

7. REFERENCES

1. Neerukonda SN, Katneni U. A Review on SARS-CoV-2 Virology, Pathophysiology, Animal Models, and Anti-Viral Interventions. Pathogens. 2020 May 29;9(6):426. doi: 10.3390/pathogens9060426. PMID: 32485970; PMCID: PMC7350325.

2. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clin Immunol. 2020 Jun;215:108427. doi: 10.1016/j.clim.2020.108427. Epub 2020 Apr 20. PMID: 32325252; PMCID: PMC7169933.

3. Cromer, D., Juno, J. A., Khoury, D., Reynaldi, A., Wheatley, A. K., Kent, S. J., & Davenport, M. P. (2021). Prospects for durable immune control of SARS-CoV-2 and prevention of reinfection. Nature reviews. Immunology, 21(6), 395–404. https://doi.org/10.1038/s41577-021-00550-x

4. Deng W, Bao L, Liu J, Xiao C, Liu J, Xue J, et al. Primary exposure to SARS-CoV-2 protects against reinfection in rhesus macaques. Science. 2020 Aug 14;369(6505):818-823. doi: 10.1126/science.abc5343. Epub 2020 Jul 2. PMID: 32616673; PMCID: PMC7402625.

5. Mattiuzzi C, Henry BM, Sanchis-Gomar F, Lippi G. SARS-CoV-2 recurrent RNA positivity after recovering from coronavirus disease 2019 (COVID-19): a meta-analysis. Acta Biomed. 2020 Sep 7;91(3):e2020014. doi: 10.23750/abm.v91i3.10303. PMID: 32921710; PMCID: PMC7717013.

6. Piri SM, Edalatfar M, Shool S, Jalalian MN, Tavakolpour S. A systematic review on the recurrence of SARS-CoV-2 virus: frequency, risk factors, and possible explanations. Infect Dis (Lond). 2021 May;53(5):315-324. doi: 10.1080/23744235.2020.1871066. Epub 2021 Jan 28. PMID: 33508989; PMCID: PMC7852280.

7. Jain VK, Iyengar K, Garg R, Vaishya R. Elucidating reasons of COVID-19 re-infection and its management strategies. Diabetes Metab Syndr. 2021 May-Jun;15(3):1001-1006. doi: 10.1016/j.dsx.2021.05.008. Epub 2021 May 7. PMID: 33989898; PMCID: PMC8102074.

8. Costa AOC, de Carvalho Aragão Neto H, Lopes Nunes AP, Dias de Castro R, Nóbrega de Almeida R. COVID-19: Is reinfection possible? EXCLI J. 2021 Mar 2;20:522-536. doi: 10.17179/excli2021-3383. PMID: 33883981; PMCID: PMC8056061

9. PRISMA. TRANSPARENT REPORTING of SYSTEMATIC REVIEWS and META-ANALYSES/PRISMA 2020 Checklist. Available from: http://www.prisma-statement.org/

10. Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P-F. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). JBI Manual for Evidence Synthesis. JBI, 2020. Available from https://synthesismanual.jbi.global

11. Wu F, Wang A, Liu M, Wang Q, Chen J, Xia S, et al. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. medRxiv [Preprint]. 2020;2020.03.30.20047365. Available from: https://www.medrxiv.org/content/medrxiv/early/2020/04/06/2020.03.30.20047365.full.pdf [Google Scholar]

12. Tea F, Ospina Stella A, Aggarwal A, Ross Darley D, Pilli D, et al. (2021) SARS-CoV-2 neutralizing antibodies: Longevity, breadth, and evasion by emerging viral variants. PLOS Medicine 18(7): e1003656. https://doi.org/10.1371/journal.pmed.1003656

13. Klein, S. L., Pekosz, A., Park, H. S., Ursin, R. L., Shapiro, J. R., Benner, S. E., Littlefield, K., Kumar, S., Naik, H. M., Betenbaugh, M. J., Shrestha, R., Wu, A. A., Hughes, R. M., Burgess, I., Caturegli, P., Laeyendecker, O., Quinn, T. C., Sullivan, D., Shoham, S., Redd, A. D., … Tobian, A. A. (2020). Sex, age, and hospitalization drive antibody responses in a COVID-19 convalescent plasma donor population. The Journal of clinical investigation, 130(11), 6141–6150. https://doi.org/10.1172/JCI142004

14. Váncsa S, Dembrovszky F, Farkas N, Szakó L, Teutsch B, Bunduc S, Nagy R, Párniczky A, Erőss B, Péterfi Z, Hegyi P. Repeated SARS-CoV-2 Positivity: Analysis of 123 Cases. Viruses. 2021 Mar 19;13(3):512. doi: 10.3390/v13030512. PMID: 33808867; PMCID: PMC8003803.

15. Slezak, J., Bruxvoort, K., Fischer, H., Broder, B., Ackerson, B., & Tartof, S. (2021). Rate and severity of suspected SARS-Cov2 reinfection in a cohort of PCR-positive COVID-19 patients. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases, S1198-743X(21)00422-5. Advance online publication. https://doi.org/10.1016/j.cmi.2021.07.030

16. Yahav, D., Yelin, D., Eckerle, I., Eberhardt, C. S., Wang, J., Cao, B., & Kaiser, L. (2021). Definitions for coronavirus disease 2019 reinfection, relapse and PCR re-positivity. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases, 27(3), 315–318. https://doi.org/10.1016/j.cmi.2020.11.028

17. Ibarrondo FJ, Fulcher JA, Goodman-Meza D, et al. Rapid Decay of Anti-SARS-CoV-2 Antibodies in Persons with Mild Covid-19 [published correction appears in N Engl J Med. 2020 Jul 23;:]. N Engl J Med. 2020;383(11):1085-1087. doi:10.1056/NEJMc2025179

18. Luchsinger, L. L., Ransegnola, B., Jin, D., Muecksch, F., Weisblum, Y., Bao, W., George, P. J., Rodriguez, M., Tricoche, N., Schmidt, F., Gao, C., Jawahar, S., Pal, M., Schnall, E., Zhang, H., Strauss, D., Yazdanbakhsh, K., Hillyer, C. D., Bieniasz, P. D., & Hatziioannou, T. (2020). Serological Assays Estimate Highly Variable SARS-CoV-2 Neutralizing Antibody Activity in Recovered COVID19 Patients. medRxiv : the preprint server for health sciences, 2020.06.08.20124792. https://doi.org/10.1101/2020.06.08.20124792

19. Gaebler, C., Wang, Z., Lorenzi, J., Muecksch, F., Finkin, S., Tokuyama, M., Cho, A., Jankovic, M., Schaefer-Babajew, D., Oliveira, T. Y., Cipolla, M., Viant, C., Barnes, C. O., Bram, Y., Breton, G., Hägglöf, T., Mendoza, P., Hurley, A., Turroja, M.,

Gordon, K., … Nussenzweig, M. C. (2021). Evolution of antibody immunity to SARS-CoV-2. Nature, 591(7851), 639–644. https://doi.org/10.1038/s41586-021-03207-w

20. Avanzato, V. A., Matson, M. J., Seifert, S. N., Pryce, R., Williamson, B. N., Anzick, S. L., Barbian, K., Judson, S. D., Fischer, E. R., Martens, C., Bowden, T. A., de Wit, E., Riedo, F. X., & Munster, V. J. (2020). Case Study: Prolonged Infectious SARS-CoV-2 Shedding from an Asymptomatic Immunocompromised Individual with Cancer. Cell, 183(7), 1901–1912.e9. https://doi.org/10.1016/j.cell.2020.10.049

21. Murillo-Zamora, E., Trujillo, X., Huerta, M. et al. Symptomatic SARS-COV-2 reinfection: healthcare workers and immunosuppressed individuals at high risk. BMC Infect Dis 21, 923 (2021). https://doi.org/10.1186/s12879-021-06643-1

22. Sevillano, G., Ortega-Paredes, D., Loaiza, K., Zurita-Salinas, C., & Zurita, J. (2021). Evidence of SARS-CoV-2 reinfection within the same clade in Ecuador: A case study. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases, 108, 53–56. https://doi.org/10.1016/j.ijid.2021.04.073

23. Soo Lee, So Yeon Kim, Taek Soo Kim, Ki Ho Hong, Nam-Hee Ryoo, Jaehyeon Lee, et al. Evidence of Severe Acute Respiratory Syndrome Coronavirus 2 Reinfection After Recovery from Mild Coronavirus Disease 2019, Clinical Infectious Diseases, 2020;, ciaa1421, https://doi.org/10.1093/cid/ciaa1421

24. Harvey, W.T., Carabelli, A.M., Jackson, B. et al. SARS-CoV-2 variants, spike mutations and immune escape. Nat Rev Microbiol 19, 409–424 (2021). https://doi.org/10.1038/s41579-021-00573-0

25. Razvi, S., Oliver, R., Moore, J., & Beeby, A. (2020). Exposure of hospital healthcare workers to the novel coronavirus (SARS-CoV-2). Clinical medicine (London, England), 20(6), e238–e240. https://doi.org/10.7861/clinmed.2020-0566

26. British society for immunology [Internet]. Connect on Coronavirus / Connect on Coronavirus: public engagement resources / COVID-19 immunity: Natural infection compared to vaccination. Available from: https://www.immunology.org/coronavirus/connect-coronavirus-public-engagement-resources/covid-immunity-natural-infection-vaccine

Appendix 1 – Literature review table

Number	Article title	First author	Article type	Country of Origin	Number of cases	Age	Sex	First infection severity	Second infection severity	Interval between first and second infection	First infection virus clade	First infection virus lineage	Second infection virus clade	Second infection virus lineage	Date of first positive RT-PCR during first infection	Date of first positive RT-PCR during second infection	Patient's Immunity status	Presence of antibody at the time of second infection	Occupational exposure
1	Reinfection with SARS-CoV-2 and Failure of Humoral Immunity: a case report	Jason D. Goldman	Case report	The US	1	NR*	NR	Severe	Moderate	101	19B (No mutation in spike protein compared to root)	NR	20A (the A23403G mutation, which confers the D614G amino acid change in spike protein)	NR	March, 2020	July, 2020	Immunocompetent	IgG, IgM	NR
2	Genomic Evidence of SARS-CoV-2 Reinfection Involving E484K Spike Mutation, Brazil	Carolina nonaka	Case report	Brazil	1	45.00	Female	Mild	Mild	147	Clade=20B, Spike mutation from root D614G	Pangolin lineage=B.1	Clade=20B, ()whereas the mutation S:E484K , D614G was observed in the second infection.	Pangolin lineage=P.2			Immunocompetent	NR	HCW**
3	Evidence of SARS-CoV-2 re-infection with a different genotype	Philippe Colson	Case report-A letter to the editor	France	1	70.00	Male	Moderate	Asymptomatic	105	Clade=20A	NR	Clade=B.1	Pangolin lineage:B.1.16			Immunocompetent	NR	NR
4	Severe Acute Respiratory Syndrome Coronavirus 2 P.2 Lineage Associated with Reinfection Case, Brazil, June-October 2020	Paola Cristina Resende	Case report	Brazil	1	37.00	Female	Mild	Mild	116	Clade=20B	Pangolin lineage=B.1.1.	Clade=20B, ()whereas the mutation S:E484K was observed in the second infection.	Pangolin lineage=P.2			Immunocompetent	NR	HCW
5	SARS-CoV-2 reinfection caused by the P.1 lineage in Araraquara city, Sao Paulo State, Brazil	Camila Malta Romano	Case report	Brazil	1	26.00	Female	Mild	Mild	128	not a VOC		Clade=P.1	Pangolin lineage=P.1			Immunocompetent (Rheumatoid arthritis, but had no history of drug administration)	NR	NR

6	Clinical characteristics of SARS-CoV-2 by re-infection vs. reactivation: a case series from Iran	Mostafa Salehi-Vaziri	Case series	Iran	2	32.00	Female	Mild	Mild	63	not reported		D614G mutation of S gene from the second isolate				Immunocompetent	IgG (presence of antibody at the time of second infection)	NR
						42.00	Male	Mild	Mild	111	not reported		D614G mutation of S gene from the second sample					IgG, IgM	NR
7	Symptomatic SARS-CoV-2 reinfection of a health care worker in a Belgian nosocomial outbreak despite primary neutralizing antibody response	Philippe Selhorst	Case report	Belgium	1	39.00	Female	Moderate	Mild	185	Clade: B.1		Clade: B				Immunocompetent	IgG (Neutralising activity after first infection although not exactly before reinfection)	HCW
8	Evidence of SARS-CoV-2 reinfection within the same clade in Ecuador: A case study	Gabriela Sevillano	Case report	Ecuador	1	28.00	Male	Mild	Mild	82	Clade=B.1.1, Pango lineage:B.1.1.29		Clade=B.1.1, Pango lineage:B.1.1.29 (re-infection with a very similar virus)				Immunocompetent	Antibody against SARS-CoV-2 was absent	NR
9	Clinical, Serological, Whole Genome Sequence Analyses to Confirm SARS-CoV-2 Reinfection in Patients From Mumbai, India	Jayanthi Shastri	Case series	India	3	27.00	Male	Mild	Mild	60	Pango lineage:B, Clade:B		Clade=B.1, Pango lineage=B.1.180				Immunocompetent	NR	HCW
						24.00	Female	Mild	Mild	48	Pango lineage:B.1, Clade:B.1		Clade=B.1.1, Pango lineage=B.1.1.32				Immunocompetent	IgG	HCW
						51.00	Female	Mild	Moderate	133	B.1.5		B.1				Immunocompetent	NR	HCW
10	Case series of four re-infections with a SARS-CoV-2 B.1.351 variant, Luxembourg, February 2021	Thérèse Staub	Case series	Luxembourg	4	NR	Male	Mild	Asymptomatic	278	not reported		B.1.351 (at the time of first infection B.1.351 was not circulating in the region)				Immunocompetent	NR	HCW

						NR	Female	Mild	Mild	278	not reported		B.1.351 (at the time of first infection B.1.351 was not circulating in the region)				Immunocompetent	NR	HCW
						NR	Female	Asymptomatic	Mild		not reported		B.1.351 (at the time of first infection B.1.351 was not circulating in the region)				Immunocompetent	NR	HCW
						NR	Female	Mild	Mild	33	not reported		B.1.351 (at the time of first infection B.1.351 was not circulating in the region)				Immunocompetent	NR	HCW
11	Asymptomatic reinfection in two healthcare workers from India with genetically distinct SARS-CoV-2	Vivek Gupta	Case report- A letter to the editor	India	2	25.00	Male	Asymptomatic	Asymptomatic	108	not reported exactly		not reported exactly				Immunocompetent	NR	HCW
						28.00	Female	Asymptomatic	Asymptomatic	111	not reported exactly		not reported exactly				Immunocompetent	NR	HCW
12	Confirmed Reinfection With Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV-2) Variant VOC-202012/01	David Harrington	Case report- A letter to the editor	The UK	1	78.00	Male	Mild	Critical	240	B.2		B.1.1.7				Immunocompetent	NR	NR
13	COVID-19 re-infection by a phylogenetically distinct SARS-CoV-2 variant, first confirmed event in South America.	Belén Prado-Vivar	Case report	Ecuador	1	46.00	Male	Mild	Moderate	28	B.2		B.1.79				Immunocompetent	NR	NR
14	Case Study: Longitudinal immune profiling of a SARS-CoV-2 reinfection in a solid organ transplant recipient	Jonathan Klein	Case report	The US	1	65.00	Male	Mild	Mild	209	B.1 (D614G)		B.1.280 (D614G)				Immunocompromised (Organ recipient)	IgG	NR

15	Clinical, virologic and immunologic features of a mild case of SARS CoV-2 reinfect	Pauline Vetter	Case report	Switzerland	1	36.00	Female	Mild	Mild	150	20A		20A (S477N)				Immunocompetent	Antibody against SARS-CoV-2 was absent	HCW
16	Reinfection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) B.1.1.7 variant in an immunocompromised adolescent	Lucila Marquez	Case report-A letter to the editor	The US	1	16.00	Female	Mild	Mild		B.1.2		B.1.1.7 (VOC)				Immunocompetent	IgM	NR
17	Reinfection of Severe Acute Respiratory Syndrome Coronavirus 2 in an Immunocompromised Patient: A Case Report	Marlies Mulder	Case report	Netherlands	1	89.00	Female	Mild	severe		not reported		not reported				Immunocompromised	Antibody against SARS-CoV-2 was absent	NR
18	sars-cov-2 reinfection by the new variant of concern (voc) p.1 in amazonas,brazil	Felipe Naveca	Case report	Brazil	1	29.00	Female	Mild	Mild	286	B.1		P.1 (S:K417T, S:E484K, and S:N501Y)				Immunocompetent	IgG	NR
19	SARS-CoV-2 B.1.1.7 reinfection after previous COVID-19 in two immunocompetent Italian patients	federica novazzi	Case report	Italy	2	56.00	Male	Severe		30	Wuhan-Hu-1		B.1.1.7				Immunocompetent	IgG present at the time of reinfection in both cases	NR
						58.00	Male	Severe		18	Wuhan-Hu-1		B.1.1.7				Immunocompetent	IgG present at the time of reinfection in both cases	NR
20	COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing	kelvin kai wang to	Case report	Hong kong	1	33.00	Male	Mild	Asymptomatic	142	B.2		B.1.79				Immunocompetent	Antibody against SARS-CoV-2 was absent	NR
21	SARS-CoV-2 Reinfection in a Liver Transplant Recipient	christopher h tomkins tinch	Case report	The US	1	61.00	Male	Mild	Moderate	63	not reported		not reported				Immunocompromised	Antibody against SARS-CoV-2 was absent	NR

22	Severe Reinfection With South African Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Variant 501Y.V2	Zucman, Noémie	Case report	France		58.00	Male	Mild	severe	129			and viral genome sequencing identified D80A, E484K and N501Y mutations in the spike region, characterizing the 501Y.V2 lineage B.1.351 variant.				Immunocompetent	IgG	NR
23	Symptomatic reinfection of SARS-CoV-2 with spike protein variant N440K associated with immune escape	Rani, Pallavali R	Case report-A letter to the editor	India	1	47.00	Male	Asymptomatic	Mild	38	B.1.36 (Spike: N440K)		B.1.36 (Spike: N440K)		25, July, 2020	2, August, 2020	Immunocompetent	NR	NR
24	Evidence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Reinfection Without Mutations in the Spike Protein	Onkar Kulkarni	Case report-A letter to the editor	India	2	61.00	Male	Asymptomatic	Mild	44	revealed that all of the 4 viral genomes belonged to the 20B clade, and carry the D614G mutation in spike. While						Immunocompetent	NR	HCW
						38.00	Male	Mild	Mild	18					4, Nov, 2020	22, Nov, 2020	Immunocompetent	NR	NR
25	SARS-CoV-2 Reinfection in a Healthcare Worker Despite the Presence of Detectable Neutralizing Antibodies	Brehm, Thomas Theo	Case report	Germany	1	27.00	Female	Mild	Mild	265			initial virus variant in March (HH-24.I) and the variant in December (HH-24.II) belonged to pangoline lineages B.3				Immunocompetent	IgG and neutralizing activity was present after first infection but did not protect from reinfection	HCW

													and B.1.177, respectively						
26	Serologic Responses in Healthy Adult with SARS-CoV-2 Reinfection, Hong Kong, August 2020	Paul K.S. Chan	Case report	Hong kong	1	33.00	Male	Mild	Asymptomatic	123					23,March, 2020	15, August, 2020	Immunocompetent	Antibody against SARS-CoV-2 was absent	NR
27	Symptomatic SARS-CoV-2 Reinfection in a Healthy Healthcare Worker in Italy Confirmed by Whole-Genome Sequencing	Daniela Loconsole	Case report	Italy	1	41.00	Female	Mild	Mild	270	B.1.1.74, S=D614G		B.1.177, S=A222V, D614G		21, March, 2020	11, January, 2021	Immunocompetent	NR	HCW
28	Evidence of Severe Acute Respiratory Syndrome Coronavirus 2 Reinfection After Recovery from Mild Coronavirus Disease 2019	Jee-Soo Lee	Case report	Korea	1	21.00	Female	Mild	Mild	11	Clade= V		Clade= G		11, March, 2020	6, April, 2020	Immunocompetent	IgG(protective neutralizing activity was reported)	NR
29	Early detection of SARS-CoV-2 P.1 variant in Southern Brazil and reinfection of the same patient by P.2	Mariana Soares da Silva	Case report	Brazil	1	39.00	Male	Mild	Death	87	P1(E484K)		P2(E484K)				Immunocompetent	NR	NR
30	Genomicevidence for reinfection with SARS-CoV-2: a case study	Richard L Tillett	Case report	The US	1	25.00	Male	Mild	severe	31	20C		20C				Immunocompetent	NR	NR

*Not reported

**Health care worker