REINFECTION AFTER SARS-COV2 INFECTION: A LOOMING CONCERN

Akshay Kumar¹*, Nimisha Shiwalkar²*, Juber Dastagir Shaikh³, Roopvir Kaur⁴, Ana Francesca Vommaro Leite⁵*, Purnadeo Persaud⁶*, Asim Kichloo⁷, Alfonso J Rodríguez-Morales⁸,⁹, Ranjit Sah.¹⁰*

¹Department of Cardiothoracic Surgery, Medanta Hospital, Gurugram 122001.
²Department of Anesthesiology, University of Texas Health Center, Houston, TX 77030
³Department of Neurology/Internal Medicine, Mahatma Gandhi Mission New Bombay Hospital, Vashi, Navi Mumbai 400703
⁴Department of Anesthesiology, Government Medical College, Amritsar, India 143001
⁵University of Minas Gerais, Passos, Brazil 37902-313
⁶Department of Internal Medicine, Kansas City University
⁷Department of Internal Medicine, Central Michigan University, Mt Pleasant, MI 48859
⁸Public Health and Infection Research Group, Faculty of Health Sciences, Universidad Tecnológica de Pereira, Pereira, Colombia,
⁹Grupo de Investigación Biomedicina, Faculty of Medicine, Fundación Universitaria Autónoma de las Américas, Pereira, Colombia
¹⁰Tribhuvan University Teaching Hospital, Institute of Medicine, Kathmandu, Nepal

Received – August 25, 2020; Revision – September 30, 2020; Accepted – October 20, 2020
Available Online October 25, 2020

DOI: http://dx.doi.org/10.18006/2020.8(Spl-1-SARS-CoV-2).S114.S118

ABSTRACT

Many unanswered questions remain about COVID-19 infection caused by SARS-CoV-2 coronavirus. One such looming concern is the possibility of reinfection of recovered cases. We conducted a literature review on various aspects of this possibility, including the case presentations of relapsed/re-infected patients, the immune response of production of neutralizing antibodies, immunity in response to coronavirus during SARS-CoV2 and MERS, possibility of false-positive results of real-time polymerase chain reaction. We concluded that further studies are required to establish whether relapse or reinfection is possible firmly. However, these possibilities point towards the needs of change in the protocol of isolation, quarantine, and discharge. It also undermines the role of the upcoming vaccine in disease prevention and treatment.

KEYWORDS

COVID-19
Reinfection
Relapse
Immune response

* Corresponding author
E-mail: ranjitsah57@gmail.com (Dr. Ranjit Sah); drakshay82@gmail.com (Dr. Akshay Kumar)

Peer review under responsibility of Journal of Experimental Biology and Agricultural Sciences.

All the articles published by Journal of Experimental Biology and Agricultural Sciences are licensed under a Creative Commons Attribution-NonCommercial 4.0 International License Based on a work at www.jebas.org.
1 Introduction

The first human case of COVID-19 was seen in Wuhan, China, in December 2019. The isolation of the genome has identified it as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Dhama et al., 2020). The World Health Organization declared the outbreak a Public Health Emergency of International Concern on Jan 30, 2020, and a pandemic on Mar 11 (WHO, 2020a; WHO, 2020b). As of October 20 2020, more than 40 million cases of COVID-19 have been reported from more than 217 countries across the world, resulting in more than 1,124,480 deaths.

The risk of reinfection is a significant threat to people worldwide. Along with this threat, there are other concerns which arise in the background of this possibility. Firstly, whether these cases are for real, reinfection or relapse or false-negative results, each of these has different implications. If it is reinfection, is there any protective immunity to COVID-19 in the very beginning? If not, convalescent plasma role is doubtful in the treatment of patients. If this is genuinely relapse of prior infection, will prospective vaccine succeed in providing long-term protective immunity to patients? Moreover, when the repeat cases are due to false-negative results, are the criteria used sufficiently to discharge patients and let them be out of isolation. Are we effectively terminating that chain of infection thus or not?

2 Current Status of COVID-19 reinfection

A hospital in Italy has reported two cases of possible reinfection aged 81 and 85 years old with new symptoms such as malaise and muscle pain approximately 2-5 days after a negative nasopharyngeal swab tested via a quantitative reverse transcriptase-polymerase chain reaction. Both patients had mild symptoms in the second wave and recovered spontaneously (Marco & Fiorpaolo, 2020). Wuhan has observed some cases of repeat fever and positive nucleic acid tests after discharge which was supposed to be due to reinfection (Zhou et al., 2020).

Another single centered cohort study has shown 69 (16.7%) out of a cohort of 414 patients to retest positive for COVID-19. 13 patients out of these also had two readmissions, and three patients had three readmissions (Huang et al., 2020). The median time from negative to positive test was 19 days with a range of 6-52 days. This study also suggests that there may be a correlation between transmissibility and retest positivity.

Thevarajan et al. published a case report of a 47-year-old woman who travelled from Wuhan to Australia and after that presented with coronavirus (Thevarajan et al., 2020). They studied the immune response of the patient with the timeline of clinical and laboratory symptoms. This patient did not have severe symptoms and had a complete clinical recovery by day 13 of the symptomatic disease. The patient had a robust immune response comprising of antibody-secreting cells, activated CD4 and CD8 cells and SARS-CoV-2 Ig-M and Ig-G antibodies (WHO, 2020a). This immune response can prevail upon disease recovery as well as possible protection from future infections.

There have also been reports of patients tested positive again after negative in China (Feng & Cheng, 2020). 111 people have been tested positive for the new coronavirus again, after they were tested negative and released from quarantine revealed by the Korea Centers for Disease Control and Prevention (KCDC, 2020).

In another study that investigated 11 cases of repeat symptoms, 4 were healthcare workers with a risk of re-exposure, and seven comorbid patients had repeat CT signs and required re-hospitalization. Three patients died during the second episode. Out of these 7, D21 serology showed 5 to be positive, one weakly positive and three negatives (Gousseff et al., 2020). Now, although the first group of health workers seems to be re-infected, the second group of patients appears to relapse due to inadequate immunological response and comorbid conditions.

2.1 Role of RT-PCR in reinfection cases

Real-time polymerase chain reaction (RT-PCR) is the most widely used test for COVID-19. In a study done to estimate the false results of RT-PCR, it was seen that 48/384 (12.5%) patients were found to convert from negative to positive in the first two tests (Alvarez-Moreno & Rodriguez-Morales, 2020). This can be an estimate of the false-negative report. In the initially confirmed cases which converted to negative after the treatment, one patient was found to be positive again after two consecutive negative results. The study showed that the results are quite variable (Li et al., 2020). This can be attributed to insufficient viral material in the specimen, restrictions on sample transportation, or laboratory error during sampling (Xi et al., 2020). There are other reported cases of false-negative reverse transcriptase-polymerase chain reaction. A case report in China has shown a 54-year-old man with negative PCR throat swab correlating with clinical recovery and then again, a positive test a few days later in isolation (Zhang et al., 2020). Another study showed that 15/70 patients with previous confirmed SARS-CoV-2 were later found to be positive after two consecutive negative results. These results were suspected to be found due to high false-negative rate of viral test and prolonged nucleic acid conversion time (Xiao et al., 2020). There also is a possibility that a positive result can come from dead viruses or fragments of viral genomes. The proportion was 9.1% (5/55) in another study (Yuan et al., 2020).

2.2 Immune response to SARS-Cov-2 viral infection

A recent study showing the seroconversion of SARS-CoV-2 suggests that neutralizing antibodies from around the end of week
2 of symptoms (Woelfel et al., 2020). Moreover, there is active virus shedding in earlier stages of the disease which decreases in later stages, thus, diminishing the infectivity. Another study of the immune response of SARS-CoV-2 evaluating the neutralizing antibodies showed that they are found at their peak levels on 10-15 days after the onset of symptoms and remain in a plateau phase after that. However, there is a variable immune response amongst individuals infected and recovered with a significant finding that in almost 30% of individuals, there are extremely low titers of neutralizing antibodies (Wu et al., 2020). This pool may be thus susceptible to reinfection. Current studies of SARS-CoV-2 show cross-reactivity only with SARS-CoV and not with any other previously known coronaviruses (Guo et al., 2020). This study also shows that the median response of neutralizing antibodies is found around five days for IgM and 14 days for IgG.

2.3 Risk factor for COVID-19 reinfection

To understand this risk of relapse or reinfection Bao et al. (2020) performed experimentation on Rhesus macaques' monkeys. They challenged these monkeys with SARS-CoV-2 intratraechally and observed the infection progression via symptoms such as weight loss and rectal temperature and checked the viral loads in respiratory and anal swabs. Specific antibody against SARS-CoV-2 was also found to be elevated at day 14, 21 and 28. When the monkeys reached a stage similar to clinical discharge criteria, some of them were re-challenged with repeat dose with the same strain to find the possibility of reinfection. There was seen a transient elevation of body temperature, but there were not any X-ray abnormalities or pathological or immunological findings corresponding to repeat infection. Thus, they concluded that adequate antibody response in primary infection protected these monkeys from subsequent infection with the same strain (Bao et al., 2020).

Another study regarding the immunological response in ferrets suggested that primary infection is followed by the innate immune response which is interferon-mediated and lead to an inflammatory reaction from SARS-CoV2 infection and in the later stages lead to neutralizing antibodies formation. If reinfection is there, there is no IFN response; only the neutralizing antibody response occurs, which may be protective (Cameron et al., 2012). There are uses of mathematical models to predict the reinfection as well. Alexander Victor Okheusein a method using Susceptible-Exposed-Infectious-Removed-Undetectable-Susceptible (SEIRUS) Model, tried to project the probability of reinfection in patients who are recovered from COVID-19. This model concluded that there are no chances of reinfection in patients who are already recovered (Okheuse, 2020).

There are various factors which interplay to increase the risk of reinfection. The most important being the virus should undergo steady mutation rate to escape the pre-existing immunity. The case fatality rate from COVID-19 varies from 0.3% to 15.6% amongst countries depending upon susceptible population and testing methods with a median of less than 5%. If a disease has low CFR, it tends to produce mutant genomes while transmission and thus can escape previous immunity (Biswa et al., 2020).

3 Lessons learnt from the past

Lessons from the previous infections of corona virus-like SARS-CoV, which occurred in 2003 suggest that there is a robust immune response against coronavirus rendering protection to individuals from reinfection (WHO, 2020a). Another study which followed the recovered patients from SARS-CoV for six years demonstrated that the protective Antibody and memory B cells disappear from the plasma of patients in due course of time which makes them susceptible to reinfection (Tang et al., 2011). Also, the data shows that the previous antibody response peaked around four months and declined after that. Other studies which followed up the patients of Middle East respiratory syndrome CoV (MERS-CoV) showed that the protective neutralizing antibodies in patients with severe infection were found even after 13 months of disease (Al-Abdallat et al., 2014). In contrast, for patients with mild or asymptomatic disease, the neutralizing antibodies were found to be produced at a low rate and were short-lived (Drosten et al, 2014). However, to what extent these results can be used to predict the immune response to SARS-CoV-2 is questionable.

Conclusion

SARS-CoV-2 is a new disease and has many unanswered questions as of now. Whether it is capable of causing reinfection in previously cured patients is still one of the questions. We will need more detailed studies to rule out the possibility of reinfection. Meanwhile, we should keep the false-negative results in mind and thus, modify the guidelines of discharge and isolation. The recovered patients should be considered susceptible to infection and use the relevant precautions until proven otherwise.

Abbreviations:

COVID-19: coronavirus disease 2019,
SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2,
MERS: Middle East respiratory syndrome.

Acknowledgements

Thankful to Dr Sanjit Sah for his support and help.

Conflict of Interest

Authors' declares no conflict of interest

Authors' declares no conflict of interest
Reinfection after Sars-CoV2 infection: A looming concern

Authors’ Contribution

All authors have contributed equally.

Funding

No funding received

Ethics Statement

Not applicable

References

Al-Abdallat MM, Payne DC, Alqsrawi S, Rha B, Tohme RA, Abedi GR, Al Nsour M, Ilhan I, Jarour N, Farag NH, Haddadin A, Al-Sanouri T, Tamin A, Harcourt JL, Kuhar DT, Swerdlow DL, Erdman DD, Pallansch MA, Haynes LM, Gerber SI; Jordan MERS-CoV Investigation Team (2014) Hospital-associated outbreak of Middle East respiratory syndrome coronavirus: a serologic, epidemiologic, and clinical description. Clinical Infectious Diseases 59:1225–3. DOI: 10.1093/cid/ciu359

Alvarez-Moreno CA, Rodriguez-Moraes AJ (2020) Testing Dilemmas: Post negative, positive SARS-CoV-2 RT-PCR - is it a reinfection? Travel Medicine and Infectious Disease 35:101743.

Bao L, Deng W, Gao H, Xiao C, Liu J, Xue J, Lv Q, Liu J, Yu P, Xu Y, Qi F, Qu Y, Li F, Xiang Z, Yu H, Gong S, Liu M, Wang G, Wang S, Song Z, Zhao W, Han Y, Zhao L, Liu X, Wei Q, Qin C (2020) Reinfection could not occur in SARS-CoV-2 infected rhesus macaques. Available on https://www.biorxiv.org/content/10.1101/2020.03.13.990226v1.

Biswas A, Bhattacharjee U, Chakrabarti AK, Tewari DN, Banu H, Dutta S (2020) Emergence of Novel Coronavirus and COVID-19: whether to stay or die out?. Critical reviews in Microbiology 46.2: 182-193. DOI: 10.1080/1040841X.2020.1739001.

Cameron MJ, Kelvin AA, Leon AJ, Cameron CM, Ran L, Xu L, Chu YK, Danesh A, Fang Y, Li Q, Anderson A, Couch RC, Paquette SG, Funakong NG, Kistner O, Lauchart M, Rowe T, Harrod KS, Jonsson CB, Kelvin DJ (2012) "Lack of Innate Interferon Responses during SARS Coronavirus Infection in a Vaccination and Reinfection Ferret Model." PLoS ONE, vol. 7, no. 9, p. e45842. doi: 10.1371/journal.pone.0045842.

Dhama K, Khan S, Tiwari R, Sircar S, Bhat S, Malik YS, Singh KP, Chaiumpa W, Bonilla-Aldana DK, Rodriguez-Moraes AJ (2020) Coronavirus Disease 2019-COVID-19. Clinical Microbiology Reviews 33(4):e00028-20.

Drosten C, Meyer B, Müller MA, Corman VM, Al-Masri M, Hossain R, Madani H, Sieberg A, Bosch BJ, Lattwein E, Alhakeem RF, Assiri AM, Hajomar W, Albarrak AM, Al-Tawfiq JA, Zamaa AI, Memish ZA (2014) Transmission of MERS-coronavirus in household contacts. The New England Journal of Medicine 371:828–35. DOI: 10.1056/NEJMoa1405858.

Gousseff M, Penot P, Gallay L, Batisse D, Benech N, Bouiller K, Collarino R, Conrad A, Slama D, Joseph C, Lemaigrene A, Lesecure FX, Levy B, Mahevas M, Pozetto B, Vignier N, Wyplosz B, Salmon D, Goehringer F, Botelho-Nevers E; in behalf of the COCOREC study group (2020) "Clinical recurrences of COVID-19 symptoms after recovery: viral relapse, reinfection or inflammatory rebound?" The Journal of Infection DOI:https://doi.org/10.1016/j.jinf.2020.06.073

Guo L, Ren L, Yang S, Xiao M, Chang D, Yang F, Dela Cruz CS, Wang Y, Wu C, Xiao Y, Zhang L, Han L, Dang S, Xu Y, Yang QW, Xu SY, Zhu HD, Xu YC, Jin Q, Sharma L, Wang L, Wang J (2020) Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19) [published online ahead of print, 2020 Mar 21]. Clinical Infectious Diseasesciaa310. DOI:10.1093/cid/ciaa310.

Huang J, Zheng L, Li Z, Hao S, Ye F, Chen J, Yao X, Liao J, Wang S, Zeng M, Qiu L, Cen F, Huang Y, Zhu T, Xu Z, Ye M, Yang Y, Wang G, Li J, Wang L, Qu J, Yuan J, Zheng W, Zhang Z, Li C, Whitin JC, Tian L, Chubb H, Hwa KY, Gans HA, Ceresnak SR, Zhang W, Lu Y, Maldonado YA, Cohen HI, McElhiney DB, Sylvester KG, He Q, Wang Z, Liu Y, Liu L, Ling X (2020) Recurrence of SARS-CoV-2 positive in COVID-19 patients: a single center experience and potential implications. medRxiv, 2020. DOI: https://doi.org/10.1101/2020.05.06.20089573.

Li Yafang, Yao L, Li J, Chen L, Song Y, Cai Z, Yang C (2020) "Stability issues of RT-PCR testing of SARS-CoV-2 for hospitalized patients clinically diagnosed with COVID-19." Journal of Medical Virology. DOI: 10.1002/jmv.25786

Marco B, Fiorpao B (2020) Reinfection by COVID-19: a real threat for the future management of pandemic? Infectious Diseases, 52(8),581–582. DOI:https://doi.org/10.1080/23744235.2020.1769177.

Okhuese AV (2020) A. Estimation of the Probability of Reinfection With COVID-19 by the Susceptible-Exposed-Infectious-Removed-Undetectable-Susceptible Model. JMIR Public Health and Surveillance 6(2):e19097. DOI:10.2196/19097.

Tang F, Quan Y, Xin ZT Wrammet J, Ma MJ, Lv H, Wang TB, Yang H, Richardsen JH, Wei Liu W, Cao WC(2011) Lack of peripheral memory B cell responses in recovered patients with severe acute respiratory syndrome: a six-year follow-up study. The Journal of Immunology 186(12):7264-7268. DOI:10.4049/jimmunol.0903490
Thevarajan I, Nguyen THO, Koutsakos-Druce MJ, Caly L, van de Sandt CE, Jia X, Nicholson S, Catton M, Cowie B, Tong SYC, Lewin SR, Kedzierska K (2020) Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. Nature Medicine26(4):453-455. DOI: 10.1038/s41591-020-0819.

Woelfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Mueller MA, Niemeyer D, Vollmar P, Rothe C, Hoelscher M, Bleicker T, Bruemink S, Schneider J, Ehmann R, Zwieglmaier K, Drosten C, Wendtner C (2020) "Clinical presentation and virological assessment of hospitalized cases of coronavirus disease 2019 in a travel-associated transmission cluster." MedRxiv. DOI: https://doi.org/10.1101/2020.03.05.20030502

Wu F, Wang A, Liu M, Wang Q, Chen J, Xia S, Ling Y, Zhang Y, Xun J, Lu L, Jiang S, Lu H, Wen Y, Huang J (2020) "Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications." DOI: https://dx.doi.org/10.2139/ssrn.3566211

XI M, WEI Q, QIHUA F, MING G (2020). Understanding the Influence Factors in Viral Nucleic Acid Test of 2019 novel Coronavirus (2019-nCoV). Chinese Journal of Laboratory Medicine (12): E002-E002, 2020.

Xiao AT, Tong YX, Zhang S (2020) "False-negative of RT-PCR and prolonged nucleic acid conversion in COVID-19: rather than recurrence." Journal of Medical Virology. DOI: https://doi.org/10.1002/jmv.25855

Yuan J, Kou, S, Liang Y, Zeng J, Pan Y, Liu L (2020) PCR Assays Turned Positive in 25 Discharged COVID-19 Patients. Clinical Infectious Diseases 2020. DOI: https://doi.org/10.1093/cid/ciaa398.

Zhang J, Yan K, Ye H, Lin J, Zheng J, Cai T (2020) SARS-CoV-2 turned positive in a discharged patient with COVID-19 arouses concern regarding the present standard for discharge. International Journal of Infectious Diseases 97: 212-214. DOI: https://doi.org/10.1016/j.ijid.2020.03.007.

Zhou L, Liu K, Liu HG (2020) Cause analysis and treatment strategies of "recurrence" with novel coronavirus pneumonia (COVID-19) patients after discharge from hospital. Zhonghua Jie He He Hu Xi ZaZhi. 43(4):281-284. DOI: 10.3760/cma.j.cn112147-20200229-00219

WHO (2020a) "Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV)". World Health Organization (WHO), Jan 30 2020.

WHO (2020b) "WHO Director-General's opening remarks at the media briefing on COVID-19—11 March 2020". World Health Organization, Mar 11 2020.

KCDC (2020) "Over 110 people retest positive for coronavirus: authorities. (Apr 12 2020). Available from: http://www.koreaherald.com/view.php?ud=20200412000213&np=3&mp=1. Accessed Jul 13 2020.

Feng E, Cheng A (2020) "Mystery in Wuhan: Recovered coronavirus patients test negative then positive. (Mar 27 2020). Available from: https://www.npr.org/sections/goatsandsoda/2020/03/27/822407626/mystery-in-wuhan-recovered-coronavirus-patients-test-negative-then-positive. Accessed Jul 1 2020