Discoveries Journals
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DISCOVERIES REPORTS 2021, 4: e21
DOI: 10.15190/drep.2021.6

REVIEW Article

A Systematic Review of COVID-19 Reinfections

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Submitted: Jan 1, 2021; *Revised*: April 5, 2021; *Accepted:* April 23, 2021; *Published:* June 30, 2021;
Citation: Haq AU, Bashir I, Ikhlaq A, Arshad AR, Ijaz F, Haq AU, Aftab RK. A Systematic Review of COVID-19 Reinfections. *Discoveries Reports,* 2021; 4: e21. DOI: 10.15190/drep.2021.6

ABSTRACT

In this review, we have summarized available data on SARS-CoV-2 reinfection and discussed the possible explanations for this phe-nomenon. A systematic review of literature was conducted concluding that although rare, COVID-19 reinfections are indeed possible, generally tend to occur in immunocompromised individuals and frequently involve a new variant strain of the SARS-CoV-2 virus. We suggest that this may be due to re-exposure, co-infections, or prolonged viral shedding due to a known or unknown etiology. We think that the criteria for classifying COVID-19 infection as a reinfection should be revised, such that either there is genomic evidence of infection with a different strain or there should be a 90 day 'indefinite period' time interval between the first and second COVID-19 infection, to avoid confusion with prolonged shedding of the virus.

Abbreviations

Coronavirus disease 2019 (COVID-19); Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); World Health Organization (WHO); reverse transcription polymerase chain reaction (RT-PCR tests); Centre of Disease Control (CDC); immunoglobulin A (IgA).

SUMMARY

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Keywords

Reinfection, COVID-19, re-exposure, IgA in COVID-19.

1. Introduction

More than a year has passed since the beginning of the Severe Acute Respiratory Coronavirus-2 (SARS-CoV-2) global pandemic. The disease caused by this virus is known as Coronavirus Disease of 2019 (COVID-19) and at the time of writing of this paper, has affected more than 164 million people with 3.39

million deaths[1]. Amidst the various uncertainties of the nature of the virus and its actions, one that is quickly gaining traction is reinfections, and its implications on acquired immunity and the efficacy of COVID-19 vaccines.

COVID-19 reinfection is defined as being clinically and virologically diagnosed with acute COVID-19 an 'indefinite period' after recovering from being clinically and virologically diagnosed with acute COVID-19, the recovery of which is confirmed by at least 2 consecutive negative reverse transcription polymerase chain reaction (RT-PCR) tests[2]. Many of the recovered patients were observed to be COVID-19 positive again within 82 days after the onset of symptoms of the initial infection[3]. However, epidemiological investigations revealed these patients did not transmit the disease to others and it was postulated that false positive RT- PCR tests were due to remnants of RNA of SARS-CoV-2[3]. Such relapses due to the persistence of the virus within the body has already been suggested to occur with other viruses[4-6]. Even the Centre of Disease Control (CDC) states that a positive RT-PCR test during a 90-day time frame suggests prolonged shedding of the virus rather than reinfection[7]. *Thus, we propose that the criteria for COVID-19 reinfection should be revised such that there should be a 90 day 'indefinite period' time interval between the first and second COVID-19 infection, or genomic evidence of an infection from a genetically different strain of SARS-CoV-2 to classify it as a COVID-19 reinfection.*

According to CDC, there were no confirmed reports of reinfection from COVID-19 within 3 months after first infection as of September 21, 2020. However, on September 21, 2020, CDC issued a report, citing several case reports and asking for a case definition[8]. Since then, there are several studies on reinfection providing various explanation to the phenomenon.

In this review, we summarize available data on COVID-19 reinfection and provide plausible hypotheses and explanations for its occurrence.

2. Review of the cases

Table 1 provides a review of 26 case reports regarding reinfection in COVID-19 patients.

Different patterns are seen in the case reports given in Table 1. There are cases in which the time period between first and second infection is less than 90 days. This so-called reinfection in these cases might be explained on the basis of the process of 'prolonged viral shedding', as discussed in the below section.

An obvious finding is that the otherwise healthy persons were all asymptomatic during the second infection. This supports the notion that infection with SARS-CoV-2 provides immunity in healthy individuals, a re-positivity might be due to a false positive result or a re-exposure which is noticed by chance during regular tests.

An infection for the second time in some of the cases might happen because there was limited antibody production after the first exposure, as in the cases 5,6, and 25.

Only the patients who were immunocompromised or had comorbidities were symptomatic for a second time. However, all individuals under 80 years of age recovered, which advocates that even in the immunocompromised individuals, the first exposure somehow prevents severity in a reinfection. The reinfection was fatal only in three cases (21, 22, and 23), which can be explained on the basis of their age; all of them were above 80 years of age and were severely immunocompromised.

Data regarding genetic makeup of the virus was available for the cases 3-8, which shows that a reinfection from a variant strain is possible and that antibodies against primary SARS-CoV-2 confer immunity at least against new variant strains too. Otherwise healthy patients were asymptomatic during the reinfection with the variant strains. Immunocompromised individuals were symptomatic second time and all of them recovered.

Another study[23] which has prospectively described the phenomenon of reinfection in 133,266 COVID-19 patients in Qatar is summarized in the Figure 1. All the reported cases of COVID-19 reinfection in this study were mild, with only 1 person requiring hospitalization, being discharged the following day. Whilst genetic evidence was available for only 12 reported cases of COVID-19 reinfection, only 4 were confirmed to be caused by the same strain of SARS-CoV-2. The risk of reinfection has been estimated to be 0.02% with 95% confidence interval.

Similarly, a prospective study involving 1081 COVID-19 patients in Italy[24] reported no COVID-19 reinfections in 804 patients discharged alive after the treatment. Moreover, it has been recently reported[25]

Table 1. Review of the case reports of COVID-19 patients with reinfections

	Country	Age/ Sex	General Health Status / Outcome	Interval between Episodes	1st episode severity	2nd episode severity	CT Value / antibody (1st episode)	CT Value / antibody (2nd episode)	Gene Sequencing
1	Israel[9]	20/F	Healthy / Recovered	80 days	Mild including fever, cough with no evidence of respiratory distress	Family got COVID positive, she was positive and asymptomatic	N/A / N/D	N/A / N/D	N/D
2	USA[10]	82/M	Parkinson's disease, T2DM, CKD, HTN / Recovered	10 days	Tachypneic, hypoxic to 89%, 1-week fever, shortness of breath, intubated in ICU for 28 days,	fever, hypoxia, tachypnea, hypotensive, tachycardia, **Superinfection with Corynebacte-rium**	N/A / N/D	N/A / N/D	N/D
3	USA[11]	25/M	Immunocompetent / Recovered	48 days	Mild, sore throat, cough, headache, diarrhea	Symptomatically more severe, sore throat, cough, headache, diarrhea	35.24 / N/D	35.31 / IgG positive	Both belonged to same clade 20C, but differed significantly
4	Belgium [12]	51/F	Daily inhaled corticosteroids / Recovered	93 days	headache, fever, myalgia, cough, chest pain, dyspnea; not hospitalized but some persistent symptoms for 5 weeks.	headache, cough, fatigue	25.6* / N/D	32.6* / IgG positive	First and second viral genomes belonged to different clades, differing by 11 nucleotides. 1st episode: Rambout lineage B.1.1. 2nd episode: Rambout lineage A
5	Hong Kong[13]	33/M	Immunocompetent / Recovered	142 days	fever, cough, headache	Asymptomatic	30.5 / IgG negative 10 days post symptom	32 / IgG reactive day 5 hospitalization	First and second viral genomes belonged to different clades/lineages, differing by 24 nucleotides. 1st episode: Nextstrain 19A/GISAID V/ Rambout lineage B.2 clusters with viruses from Hong Kong. 2nd episode Nextstrain 20A/GISAID G/Rambout B.1.79 Clusters with viruses from Spain.
6	Ecuador [14]	46/M	Immunocompetent / Recovered	63 days	headache, drowsiness.	fever, cough, shortness of breath, sore throat; more severe than 1st episode, hospitalization was not required	36.85 / IgG negative 4 days post symptom	N/A / IgG positive 30 days post symptom onset	First and second viral genomes belonged to different clades: 1st episode: Nextstrain 20A/GISAID B1.p9 lineage. 2nd episode: Nextstrain 19B/GISAID A.1.1 lineage

Table 1. Continued

	Country	Age/ Sex	General Health Status / Outcome	Interval between Episodes	1st episode severity	2nd episode severity	CT Value / antibody (1st episode)	CT Value / antibody (2nd episode)	Gene Sequencing
7	India[15]	25/ M	Immunocompetent* / Recovered	108 days	Asymptomatic	Asymptomatic	36 / N/A	16.6 / N/A	First and second episodes revealed 9 unique variant differences.
8	India[15]	28/F	Immunocom-petent* reported in personal communication of CDC, see reference 8 / Recovered	111 days	Asymptomatic	Asymptomatic	28.16 / N/A	16.92 / N/A	First and second episodes revealed 10 unique variant differences.
9	Pakistan [16]	58/ M	Healthy / Recovered	60 days	fatigue, headache, and sore throat several days after performing coronary artery bypass grafting on two patients, who were later diagnosed as SARS-CoV-2 positive.	a fever (>39°C), headache, and muscle aches after reexposure to patients with COVID-19 during cardiac surgery. Normal inflammatory and respiratory parameters	N/A / N/D	N/A / N/D	N/D
10	Bangeladesh[17]	54/ M	T2DM, HTN / Recovered	145 days	Asymptomatic	fever, anorexia, nonproductive cough for 10 days and shortness of breath for 4 days	N/A / N/D	N/A / N/D	N/D
11	Bangeladesh[17]	28/ M	Healthy / Recovered	96 days	Asymptomatic	fever, generalized weakness	N/A / N/D	N/A / N/D	N/D
12	Bangeladesh[17]	76/F	T2DM, HTN, IHD, Bronchial asthma, bullous pemphigoid, used oral Prednisone / Recovered	37 days	Mild symptoms, whole family was symptomatic	fever, cough, body ache and generalized weakness	N/A / N/D	N/A / N/D	N/D
13	France[18]	54/F	Healthy / Recovered	12 days	Severe	Asymptomatic	N/A / N/D	N/A / N/D	N/D
14	France[18]	72/F	Healthy / Recovered	13 days	Moderate	Asymptomatic	N/A / N/D	N/A / N/D	N/D
15	France[18]	60/F	Healthy / Recovered	9 days	Moderate	Asymptomatic	N/A / N/D	N/A / N/D	N/D
16	France[18]	65/F	Hypothyroidism / Recovered	12 days	Moderate	Asymptomatic	N/A / N/D	N/A / N/D	N/D
17	France[18]	58/ M	Tuberculosis / Recovered	16 days	Moderate	Asymptomatic	N/A / N/D	N/A / N/D	N/D

Table 1. Continued

	Country	Age/ Sex	General Health Status / Outcome	Interval between Episodes	1st episode severity	2nd episode severity	CT Value / antibody (1st episode)	CT Value / antibody (2nd episode)	Gene Sequencing
18	France[18]	64/ M	Healthy / Recovered	27 days	Severe	Asymptomatic	N/A / N/D	N/A / N/D	N/D
19	France[18]	36/F	Healthy / Recovered	27 days	Moderate	Asymptomatic	N/A / N/D	N/A / N/D	N/D
20	France[18]	26/ M	Healthy / Recovered	6 days	Moderate	Asymptomatic	N/A / N/D	N/A / N/D	N/D
21	France[19]	84/F	HTN, CHD, Cancer, COPD / Fatal	41 days	Cough, fever, and respiratory signs with oxygen desaturation at 79%.	hyperthermia and respiratory signs	31.4 / N/D	18.1 / N/D	N/D
22	France[19]	90/F	T2DM, HTN, CHD / Fatal	31 days	Cardiorespiratory decompensation with atrial fibrillation with fever	major dehydration with hypernatremia measured at 166 mmol/L, oxygen saturation at 93% under four liters of oxygen, melena and marked deterioration of her general condition.	21 / N/D	18.8 / N/D	N/D
23	France[19]	84/F	HTN, CHD, Immunosuppression / Fatal	37 days	Fever, asthenia, ageusia, and respiratory signs with dry cough, polypnea	80% desaturation requiring oxygen therapy, dry cough, and fever	Negative twice (probably false negative) / N/D	16.7 / N/D	N/D
24	China[20]	34/ M	T2DM / Recovered	59 days	Cough, sore throat, dizziness, and fatigue	Asymptomatic	N/D / N/D	N/A / N/D	N/D
25	Brazil[21]	24/F	Overweight, Headache / Recovered	38 days	Headache, malaise, adynamia, feverish sensation, sore throat, nasal congestion	malaise, myalgia, severe headache, fatigue, weakness, feverish sensation, sore throat, anosmia and dysgeusia, diarrhea,	N/A / Negative	N/A / N/D	N/D
26	USA[22]	70/ M	obesity, chronic low back pain, neuropathy, asthma, obstructive sleep apnea, and hypertension / Recovered	210 days	Worsening shortness of breath	shortness of breath and subjective fever	N/D / Negative	N/A / N/D	N/D

M/F= Male/Female; N/A= Not applicable; N/D = Not done.

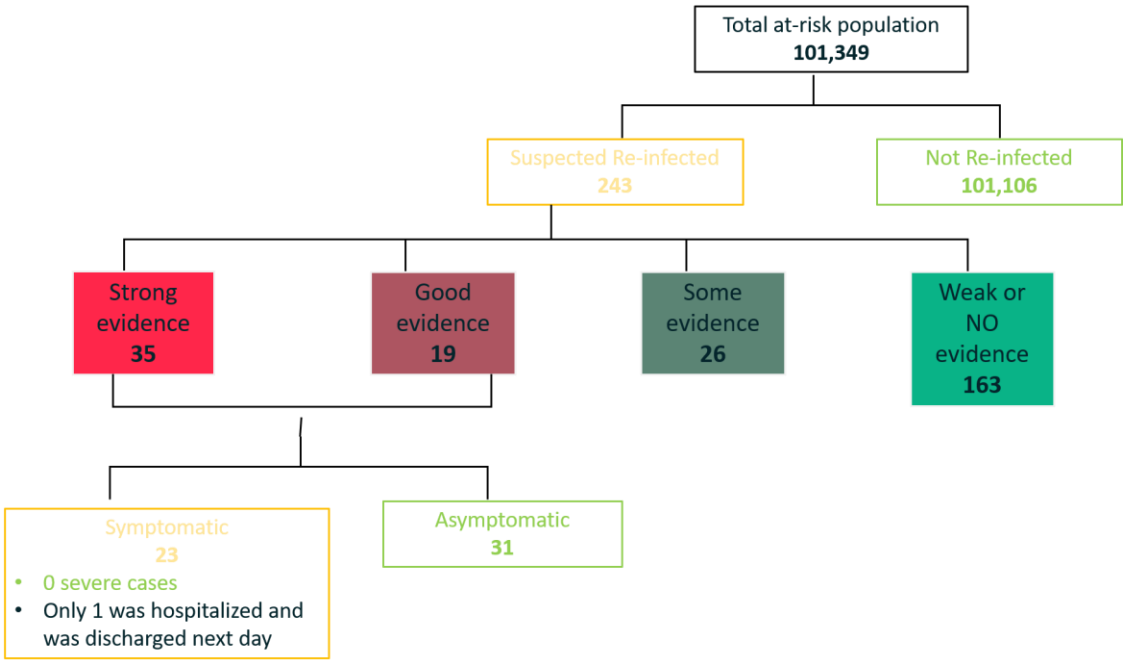

Figure 1. Reinfection in 133,266 COVID-19 patients in Qatar
Adapted with permission from reference[23]

that even during the seasonal coronavirus infections, immunity can last for at least a period of 6 months. Experimental trials on rhesus macaques[26] too revealed there to be no evidence of COVID-19 reinfection.

3. Analysis and Explanations

The current article reviews the reported cases of COVID-19 reinfection. Our analysis reveals that although rare, COVID-19 reinfections are indeed possible, generally tend to occur in immunocompromised individuals and frequently involve a variant strain of the SARS-CoV-2 virus. COVID-19 reinfections were also found to be considerably less severe than initial COVID-19 infections. We propose the following hypotheses and explanations for the observed phenomena.

3.1. Prolonged Viral Shedding

Fatma Eelrashdy et al.[27] have described the role of exosomes as possible causes of COVID-19 reinfection. As part of their 'Trojan horse' strategy, SARS-CoV-2 virus in their laden exosomes and other extracellular vesicles are released into the bloodstream after recovery. The reentry of the SARS-CoV-2 virus in the bloodstream is responsible for the COVID-19 reinfection. However, because it is essentially a reactivation/prolonged shedding of the virus, labelling it as a reinfection is not appropriate and such terminology needs to be updated. The 'Trojan Horse' strategy of exosome exit also explains the rather short duration between the primary infection and reinfection observed in many of the reported cases. Other viral shedding mechanisms may exist and are under investigation.

3.2. Compromised Immunity

Lasting immunity in COVID-19 was also a topic of speculation and discussion. Our review of literature reveals effective immunity in most of the COVID-19 reinfection cases. Neutralizing antibodies produced against SARS-CoV-2 protect the patient from reinfection[28]. The same phenomenon has also been described in rhesus macaques[26]. Our review reveals that the vast majority of patients who experienced COVID-19 reinfection were immunocompromised and/or had severe comorbidities. Immunosuppressed patients are likely to have impaired production of antibodies during the first COVID-19 infection, which was responsible for a second time infection from the same viral strain. Antibody data of the cases seem to confirm our hypothesis. Furthermore, the 3 reported deaths due to reinfection involved patients who were severely immunocompromised and had extensive comorbidities.

3.3. Viral infection from a different strain of the same virus

Antibodies are produced against a certain portion/epitope of the spike, making it difficult and less probable for the virus to escape the immune response. Furthermore, the antibodies undergo affinity maturation[29]. In the reported reinfections, some cases of reinfection are reported to be caused by a different strain of coronavirus. However, despite being immunocompromised, almost all the patients were able to launch an immune response when reinfected. Thus, it can be said that the COVID-19 caused by the mutant forms of the SARS-CoV-2 virus may in fact be less severe. We also postulate that immunity against a former SARS-CoV-2 virus might help coping with its second form. This puts a positive hope towards the effectivity of COVID-19 vaccine.

It has also been touted that COVID-19 reinfection causes waning of antibodies a few days after the infection[30]. However, this theory stands against the established concepts of immunology. Sterilizing immunity is not present in most of the cases. Antibody levels fall a few days after the infection as a normal body mechanism. However, memory T and B cells stay in the blood stream to maintain an escalated ability of the body to mount a response against a recurring infection from the same pathogen[31].

3.4. Superimposed bacterial/viral infections

A reported COVID-19 reinfection may be due to a false positive RT-PCR result. A false negative PCR showing the recovery of the patient might be a cause of mis-reported reinfection. One study reported a patient suffering from a superimposed infection of *Corynebacterium* who was falsely labelled as being COVID-19 positive RT-PCR[10]. We thus hypothesize that viral and bacterial co-infections can lead to false COVID-19 positive RT-PCR tests and hence recommend proper testing and diagnosis be done before labelling a case as a suspected COVID-19 reinfection case.

3.5. Reinfection or re-exposure? Role of IgA antibodies

It may also be possible for the people living in an environment with high SARS-CoV-2 exposure, to get a re-positive RT- PCR. Such people may even be asymptomatic but are labelled as asymptomatic cases of COVID-19 reinfections during routine COVID-19 surveys. We hypothesize that these virus particles in such flagrantly abundant SARS-CoV-2 environments easily enter the airways of people, causing them to be COVID-19 RT-PCR positive. However, people do not manifest symptoms of the condition as their immune responses are robust enough to tackle the virus due to their SARS-CoV-2 primary infection. This indeed explains the abundance of asymptomatic COVID-19 reinfections observed in our 'review of the cases' section.

It is imperative that we also discuss the role of IgA antibodies that mediate resistance to reinfection by clearing the infectious virus at the mucus membranes[32]. They have already been noted to prevent and/or decrease the severity of the COVID-19 infection[33]. Population-based differences in IgA can account for the disparity of COVID-19 reinfection severity observed in different populations of the world. Vaccines' efficiency in preventing reinfection is currently under investigation.

4. Conclusion

COVID-19 reinfections are indeed possible but rare. They tend to occur in immunocompromised individuals, and usually involve a different SARS-CoV-2 strain. We suggest that this may be due to re-exposure, co-infections or prolonged viral shedding due to a known or unknown etiology. Furthermore, current evidence suggests that immunity acquired during primary infection to SARS-CoV-2 is robust enough to prevent reinfection and mutant viral strains.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Acknowledgements

We acknowledge the support of our institution, CMH Lahore Medical College and Institute of Dentistry, Lahore.

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