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Review Article

Reinfection in COVID-19: A scoping review

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ABSTRACT

Reinfections in COVID-19 are being reported all around the world and are a cause for concern, considering that a lot of our assumptions and modeling (including vaccination) related to the disease have relied on long-term immunity. We were one of the first groups to report a series of 4 healthcare workers to have been reinfected. This review article reports a scoping review of the available literature on reinfections, with a discussion of the implications of reinfections.

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Introduction

In December 2019, there was an outbreak of a novel coronavirus in Wuhan, China. This virus was subsequently named SARS-CoV-2 and the disease caused by it COVID-19. In March 2020, the World Health Organization declared a pandemic of COVID-19.¹ Millions of people have since been infected with SARS-CoV-2.

Till recently, it was assumed that an infection with the virus was likely to provide an individual with long-standing immunity. However, recently, reinfections have been reported across the world. A healthcare worker at our institution was reinfected with SARS-CoV-2 and we collaboratively published a series of four such reinfections.²

This article is a summary of the current knowledge about reinfections and their potential implications.

Methods

We searched Medline, EMBASE and medRxiv on 28 October 2020 using the keywords “COVID-19”, “SARS-COV-2” and “reinfection”. Two researchers (LP and VN) then reviewed the titles and abstracts for relevance, and reviewed full texts of the relevant articles.

Results

The results of our search are summarized in Fig. 1. We identified 27 reported cases of reinfection with SARS-CoV-2, of which 13 were confirmed cases, with whole genome sequencing (WGS) of the strains used for confirmation. Details of these 13 cases are summarized in Table 1. Nine published reports were identified with 13 reported cases that met our inclusion

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criteria. Of these 13 patients, 9 were males. The median age was 31 years (interquartile range [IQR] 27–46 years). The median duration between the first and second episodes was 60 days (IQR 51–108 days). Eight of the 13 patients had the second episode, which was of a greater severity than the first. **To the best of our knowledge, there was no infection among contacts of the patients whom we reported. However, a detailed contact tracing exercise was not undertaken, and we cannot be sure of the same. None of the other studies report contact tracing information as well (See Table 2).**

COVID-19 and immunity

Reinfection with endemic human coronaviruses is not very uncommon.³ Short-lasting protective immunity postinfection followed by reinfection with genetically disparate forms of the viral strain has been reported for endemic coronaviruses causing milder respiratory illness.⁴

In patients recovering from the novel coronavirus infection, anti-SARS-CoV-2 antibodies detected in the blood are known to decline rapidly, with a mean half-life of 36 days.⁵ This is especially true among individuals who have had mild symptoms or have an asymptomatic infection.⁶ This is in contrast to SARS-CoV infections, in which IgG antibodies were found to persist in high titres for up to 2 years.⁷ Whether these declining antibody levels render individuals susceptible to reinfection is presently not known.

Studies indicate that SARS-CoV-2 infection induces both a neutralizing antibody response⁸ and a cellular response with virus-specific T cells.⁹ Individuals who recover from COVID-19 appear to have memory B and T cells.¹⁰ However, not all individuals seroconvert, and in mild infections, antibody tiers may decline with time.¹¹

For SARS-CoV, despite waning antibody levels, the presence of cell-mediated immunity has been demonstrated for over a decade after initial infection.¹² A recent study from France has demonstrated the presence of a similar cell-mediated immunity in family contacts of individuals with mild COVID-19 despite having no antibodies.¹³ Whether SARS-CoV-2 will universally induce a similar response and whether such a cell-mediated immune response is protective are unknown.

An individual who tests positive for the second time after recovery could have a reinfection, could be persistent positive or could be a relapse/recurrence of the same infection.

A) Reinfection

An infection with a new strain of SARS-CoV-2, in an individual who has recovered from an episode of COVID-19, is termed as “reinfection”.

To confirm a reinfection, it is necessary to demonstrate a new strain on WGS. It is also ideal that a negative swab is documented between the episodes.² A “reinfection” was defined as one in which paired specimens underwent WGS and were compared and found to be different. We also collected data for “possible reinfections” in which a reinfection was postulated, but not confirmed. At our institute, all tested samples are stored at –70 °C, and they are processed for WGS if a reinfection is suspected.

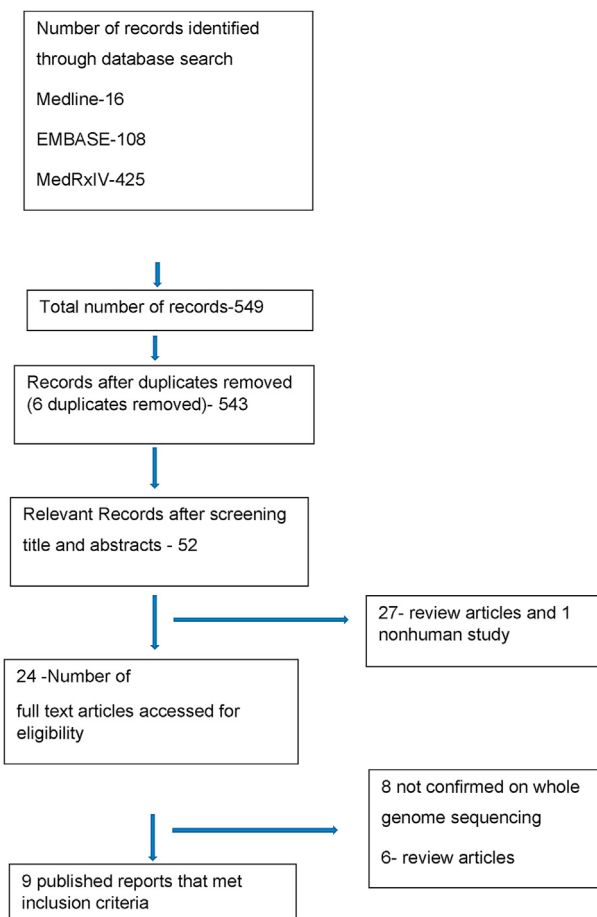


Fig. 1 – Flowchart of the studies included in the scoping review.

B) Persistent positivity

Some individuals are known to demonstrate presence of viral RNA in the nasopharyngeal swabs for a prolonged period after infection. However, studies suggest that such “shedders” are unlikely to harbour live virus and such RNA possibly represents a non-viable virus.¹⁴

An epidemiological study from the Korean CDC over a period of 1 month found that in 447 re-positive cases, with an average of 44.9 days (range 8–82 days) from initial symptom onset date to testing positive after discharge. This was surveillance data, and only 37.5% of these individuals had symptoms. Of the subset of 285 patients who were investigated, none of the 790 contacts appear to have been infected, suggesting that these re-positive patients were likely to not harbour live virus or have been reinfected.¹⁵

Subgenomic messenger RNA, found in actively replicating virus, can be detected by RT-PCR, and maybe a more useful test for viable virus.¹⁶

C) Relapse/recurrence

There is a hypothesis that a reservoir of infection in the body could reactivate after apparent recovery causing

Table 1 – The cases of reinfection reported.

Paper/Case number	Age/sex/demographics	Severity of COVID-19 during the first episode	Severity of COVID-19 during the second episode	Time between the first and second episode
1-K, Hung I, et al. ²³	33/male/no comorbidities	Mild infection	Asymptomatic second infection	142 days
2-Tillett R, Sevinsky J, et al. ²⁴	25/male/no comorbidities	Mild infection	Increased clinical severity during the second episode	42 days
3-Jayanthi Shastri, et al. ^{2,25}	Series of 4 patients: <u>Patient 1</u> —27/male/no comorbidities <u>Patient 2</u> —31/male/no comorbidities <u>Patient 3</u> —27/male/no comorbidities <u>Patient 4</u> —24/female/no comorbidities	All 4 patients had mild infection	All 4 patients had increased clinical severity during the second episode	Between 19 and 65 days
4-Van Elslande, et al. ²⁶	51/female /asthmatic	Mild infection	Similar symptoms but milder in the second episode	60 days
5-Prado-Vivar, et al. ²⁷	46/male/no comorbidities	Mild symptoms	Increased clinical severity during the second episode	30 days
5-Larson D, et al. ²⁸	42/male/no comorbidities	Mild symptoms	Increased clinical severity during the second episode	51 days
7-Mulder M, et al. ²⁹	89/female/ immunocompromized-known case of Waldenström's macroglobulinemia	Mild symptoms	Severe illness during the second episode	59 days
8-Goldman j, et al. ³⁰	60–69/male/known case of severe emphysema on home oxygen	Moderate illness	Mild illness	140 days
9-Gupta V, et al. ³¹	Series of two healthcare workers: <u>Patient 1</u> —25/male/ no comorbidities <u>Patient 2</u> —28/female/no comorbidities	Both patients were asymptomatic	Both patients were asymptomatic during the second episode	108–111 days

9 of the 12 cases reported suggest that the second infection was more severe than the first episode. This may be similar to what is described for other viral infections such as dengue.³²

Table 2 – Cases of reinfection not confirmed by whole genome sequencing (supplementary appendix).

Name of the paper	Patients' demographics and comorbidities	Severity of the first infection	Severity of the second infection	Duration between the two infections	Any antibodies formed.
1-Bongiovanni, M, et al ³⁷	48/female/healthcare worker	Mild symptoms	asymptomatic	90 days	Yes
2-Duggan, N.M, et al. ³⁸	82/female/CKD/Parkinson's disease/HTN/DM	Severe illness	Moderate illness	10 days	No
3-Lafaie L, et al. ³⁹	Geriatric case report of 3 patients	Severe illness	Severe illness	Almost 60 days	No
4-Luo, A. ⁴⁰	58/female/no comorbidities	Mild to moderate illness	Mild illness	22 days	Yes
5-Nachmias, et al. ⁴¹	20/male/no co-morbidities	Mild illness	Mild illness	120 days	Yes
6-Livia pimento	24/female/no comorbidities/healthcare worker/overweight	Mild illness	Mild illness	Almost 30 days	Yes
Bonifacio, et al. ⁴²	Series of 6 healthcare workers/5 were females and 3 had co-morbidities	Mild illness with only one reporting hypoxia.	Mild illness	53–70 days	No
7-Fernandes Valente Takeda, et al ⁴³					
8-Alanoud AlFehaidi, et al ⁴⁴	46/female/healthcare worker/asthmatic	Mild illness	Mild illness	66 days	No

relapses.¹⁷ The COCOREC study (Collaborative study Covid Recurrences) conducted across multiple centres in France identified 11 patients between 6 April 2020 and 14 May 2020 who had possible reinfections. However, the investigators acknowledged that the short median symptom-free interval (9 days for four healthcare workers with mild symptoms, 11 days for moderately affected) made the possibility of “viral reactivation from sanctuaries” feasible.¹⁷

How do we confirm a reinfection?

The clinical context of a reinfection would be that of an individual having two separate clinical presentations consistent with COVID-19, the swab becoming positive in both the instances and a negative swab after the first episode during recovery. The confirmatory test would be a WGS.

A) WGS

In WGS, the RNA from nasopharyngeal and oropharyngeal swab is subjected to whole genome sequencing and comparative genome and protein-based functional analyses are performed on the nucleotide and amino acid sequences. Paired-end sequencing, the recommended mode of WGS, allows users to sequence both ends of a fragment and generate high-quality, alignable sequence data, and facilitates detection of genomic rearrangements and repetitive sequence elements, as well as gene fusions and novel transcripts. It improves the ability to identify the relative positions of various reads in the genome, making it much more effective than single-end reading in resolving structural rearrangements such as gene insertions, deletions, or inversions. It can also improve the assembly of repetitive regions¹⁸. Genomic variations observed through whole genome sequencing are then correlated with clinical presentation and can be confirmed a reinfection of SARS-CoV-2.²

To improve the accuracy of WGS, certain quality criteria need to be adhered to, to improve specificity. “Genome coverage” alludes to the average number of sequenced bases that align to, or “cover”, known reference bases. For example, a whole genome sequenced at 30× coverage means that, on average, each base in the genome was sequenced 30 times. At higher levels of coverage, each base is covered by a greater number of aligned sequences reads, so base calls can be made with a higher degree of confidence. A quality score, “Q score”, is a metric that predicts or estimates the probability of an error in base calling. It serves as a compact way to communicate very small error probabilities. A high Q-score implies that a base call is more reliable and less likely to be incorrect. Higher the Q-score, lower the probability of error.¹⁹

When the genome is sequenced, the read pairs found are phylogenetically analyzed to classify the sequence as belonging to a particular clade (being monophyletic, or having a common ancestor) based on single nucleotide variants (SNVs), mutations that are characteristic for a clade. Clusters of two or more SNVs are called multinucleotide variants (MNVs).

As viruses multiply and propagate, SNVs and MNVs accumulate. For SARS-CoV-2, the observed extrapolated rate of

SNV and MNV accumulation of 22.78 has been presently reported, and a rate significantly greater than this in paired samples has been used to classify episodes of infections caused by these strains as being reinfections.²⁰

In addition to whole genome sequencing, culturing the virus in the second episode and demonstrating its cytopathic effects is recommended, but not routinely feasible because of the biosafety standards that such culturing necessitates.

B) Cycle threshold (Ct value)

Ct is defined as the cycle number when the sample fluorescence exceeds a chosen threshold above the calculated background fluorescence.²¹

For the RT-PCR test performed, the cycle threshold (Ct) is suggestive of the quantum of viral RNA present in the specimen collected. A cycle threshold (Ct) value of less than 37 is defined as a positive test, whereas a Ct value of more than 40 is defined as a negative test.²²

One expects the Ct value to increase as an individual recovers from COVID-19.

If, however, the Ct value decreases, especially with the passage of a few weeks, this could point towards a reinfection if the clinical context is consistent. The disadvantages of the Ct value are as follows: (1) there is no absolute Ct cut-off value; and (2) Ct cut-off values are different for each diagnostic reagent even for the same gene.² Ct value cannot be a tool to confirm reinfection, but can be useful in cases of persistent positivity as an indication of a possible reinfection that would need confirmation by whole genome sequencing.

We conducted a scoping review of the available literature about the reinfection cases.

Implications of a reinfection

A) Herd immunity

When a sufficiently large proportion of immune individuals are present in a given population, it provides indirect protection from the infection to the susceptible individuals and this is what is referred to as herd immunity.³³

There are possible ways in which widespread SARS-CoV-2 immunity may develop by a mass vaccination campaign or if natural immunization of global populations with the infection over time. If reinfections are more prevalent, this would interfere with the development of herd immunity by natural immunization.

B) The preliminary findings from the first large seroprevalence study from Mumbai were reported on 29 July 2020.³⁴ Fifty-seven percent individuals sampled from slums and 16 percent individuals sampled from buildings were found to have antibodies. This has led to optimism that the city may soon be able to achieve herd immunity. However, a follow-up seroprevalence study from Mumbai reported that the presence of COVID-19 antibodies in the samples from the slum areas in the city have decreased by 12%, and seroprevalence of COVID-19 was decreased to 45% compared with 57% in

the first survey.³⁵ This suggests a likely antibody decay. If such decay is associated with susceptibility to reinfection, we might witness more reinfections being reported in future

C) The idea of “immunity passports” was based on the same assumption that reinfections are unlikely.³⁶ Reinfections suggest that we may have to understand the immunology of COVID-19 disease better before such assumptions can be held to be true.

D) If vaccine-induced immune response is likely to decay akin to natural immune response, the likelihood of vaccine failure and the need for booster immunization will need to be re-evaluated.

Limitations

Our search of the literature resulted in the above summary of cases with reinfections (confirmed as well as probable). However, these are not representative of any sample, and hence, making demographic or causal inferences would not be appropriate, as these are likely to suffer from various confounders and biases.*

Conclusion

Clinicians should consider COVID reinfection as one of the differential diagnoses even if a patient had a history of past COVID-19 infection. If those who recover from mild COVID-19 have a short-term immunity, reinfections may become more common in the future and recovered individuals need to take all the same universal precautions (masking, distancing, sanitizing hands) recommended to susceptible individuals. Vaccination strategies will need to take into account the likelihood of antibody decay and possible susceptibility to reinfection. Surveillance to detect such reinfections, and studies aimed at understanding the immunological predictors of such reinfections would be crucial in preventing them and avoiding future waves of the pandemic.

Disclosure of conflicting interest

The authors have none to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mjafi.2021.02.010>.

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