

# Recurrence of COVID-19: Treading the Fine Line Between Relapse and Re-infection

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The etiological agent for the ongoing pandemic of COVID-19 is a novel coronavirus, known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The most common symptoms of COVID-19 include fever, dry cough, sore throat, and headache.<sup>1</sup> Severe disease can progress to the highly morbid outcome of Acute Respiratory Distress Syndrome (ARDS).<sup>2</sup> The number of infected individuals during this pandemic is high while the worldwide mortality rate remain slow.<sup>3</sup> According to World Health Organization (WHO) guidelines, the infected patient should be discharged from hospital after containment period of 14 days along with two consecutive negative Quantitative Reverse Transcription Polymerase Chain Reaction (RT-qPCR) results of respiratory specimens at least 24 hours apart.<sup>4</sup> During January 28 to March 13, COVID-19 relapse cases have been documented in Shangqiu, Henan province and later in Korea.<sup>5,6</sup> Pathogenesis of these relapse cases needs further exploration as they hold important links towards the development of a second wave of the pandemic. Here in this article, we propose the following hypotheses on how COVID-19 relapse can play a significant role in disease burden and further horizontal transmission based on available evidence.

## Relapse vs. Reinfection: Immunological Perspective

The second wave of infection among COVID-19 patients has dazed the scientific world, but it has to be decided whether the second wave of infection is due to reinfection or relapse. According to recent documentation from China<sup>5</sup> and Korea,<sup>6</sup> there have been recovered patients testing positive after one or two consecutive negative results. Various methods for the diagnosis of the infection are used. These include RT-qPCR, high-throughput sequencing, CT scan, and immunological detection kits.<sup>7</sup> Furthermore, improper sampling procedure, different source of swab samples, and variable specificity/sensitivity of nucleic acid tests can lead to the false negative RT-qPCR results implying the persistence of infection rather than recurrence or relapse.<sup>7,8</sup> This particular limitation of antibody testing method should be carefully considered before declaration of reinfection or relapse. The durability of the infected patient's immune response plays a significant role to determine the reinfection. The presence of CD4+ T cells and memory CD8+ T cells are found to be protective in case of Coronavirus mediated infection by producing effector cytokines and IFN-gamma.<sup>9</sup> It is also noted that immunoglobulins alone are not sufficient to provide long-term immunity.<sup>10</sup> Accumulating evidence have shown that virus specific CD8+ T cells were persistent up to 6 years after Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV-1) infection, but memory B cells and accompanying antibodies were undetectable at that time.<sup>11</sup> A similar scenario may result from SARS-

CoV-2 infection as it shows phylogenetic similarity with SARS-CoV-1.<sup>12</sup> A recent study performed by Zhang and colleagues investigated monocyte expression of Angiotensin Converting Enzyme 2 (ACE2), the endogenous entry receptor of SARS-CoV-2. They came to the conclusion that monocytes of COVID-19 patients express a lower concentration of ACE2 in comparison to healthy individuals.<sup>13</sup> Therefore, it can be interpreted that SARS-CoV-2 might exist in human Peripheral Blood Mononuclear Cells (PBMCs) (monocytes mainly) and cause relapse after negative PCR on samples from the respiratory tract.<sup>14</sup> Considering the aforementioned facts, further research work is required for fine delineation between relapse and reinfection.

## Probable Association of Phylogenetic Perspective with Relapse

Distinct viral clades of SARS-CoV-2 (e.g., A2a, B1) appears to result in variation of virulence.<sup>15</sup> Considering this fact, there is a possibility that duration between primary infection and relapse may vary across different clades. Furthermore, there is a possibility that the nature and affinity of protective neutralizing antibodies (NABs) may vary for different strains as well. Hence, it can be hypothesized that NABs of primary infection may be unable to protect re-infection by other strains. It also remains to be seen whether, in the case of relapse, there is an insufficient increase in NABs during the second course of infection.

## Viral Reactivation in SARS-CoV-2 Relapse

Viral latency period might be considered as a potential factor in order to determine relapse or reactivation. Reports have suggested disparity amongst proposed viral latency period with a maximum duration of 24 days.<sup>16</sup> According to an article by Ye *et al*, the reported reactivation among 5 patients was a maximum time period of 17 days, but proper clinical characteristics to distinguish reactivation with relapse was not properly demarcated.<sup>17</sup> It might be suggested that the virus causes latent infection of cells, while later on the genome gets transcribed and translated into viral proteins. Hence, it could be inferred that the virus gets reactivated from a latent stage to a lytic stage where manifestation of symptoms might be observed as similar phenomenon were already observed for many other viruses.<sup>18</sup> Additionally, SARS-CoV-2 can survive and replicate in neuronal cell lines.<sup>19</sup> Therefore, another indication towards viral latency through neuro-invasion of virus and reactivation at a later stage is suggested. Considering the abovementioned fact, an important question can be raised: Can an asymptomatic individual with a latent infection spread the virus without being detected? Proper clinical investigation into the potential reactivation of this virus requires immediate further study.

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Editor: Francisco J. Bonilla-Escobar

Reviewers: Mihnea-Alexandru Gaman,

Paul MacDaragh Ryan

Copyeditor: Sohaib Haseeb

Proofreader: Leah Komer

Layout Editor: Annora A. Kumar

Submission: Sep 3, 2020

Revisions required: Sep 28;

Nov 24, 2020

Received in revised form: Sep 30; Nov

30, 2020

Acceptance: Dec 1, 2020

Publication: Dec 9, 2020

Process: Peer-reviewed

### Consideration of Viral Shedding to Determine Relapse or Reinfection

Another undermined and potentially influential factor might be the viral shedding which may cause transmission from an apparently recovered individual or asymptomatic individual to a healthy individual.<sup>20</sup> The viral shedding may begin 2-3 days before the appearance of symptoms with viral loads decreasing monotonically after onset of symptoms.<sup>21</sup> The virus has been detected in patients at a median of 20 days and up to 37 days post-infection.<sup>22</sup> The viral transmission not only comes through droplet or aerosol route but also through the fecal-oral route.<sup>23,24</sup> The participation of tears and conjunctival secretions in viral shedding has also been speculated.<sup>25</sup> All of these non-classical or non-respiratory tract routes of virus shedding might go unrecognized during discharge of patients who are tested negative through nasopharyngeal swab RT-qPCR alone. It is possible that viral titers are still relatively high in various non-classical transmission sites of recovered patients, indicating that they are not only able to spread the infection but also may relapse themselves.

### Conclusion

In conclusion, the ongoing public health emergency should look after protocols regarding both molecular testing and antibody testing to

contain the pandemic. The infected individuals should strictly be discharged only after two proper consecutive RT-PCR negative results of swab samples from various sources so that it can reduce clinically recovered individuals with apparently hidden viral source. Even after that, the convalescent patients should be monitored by the health system during the post-discharge domiciliary quarantine period of 14 days, and on completion of this period they should be tested again. This should thereby avoid increment in numbers of asymptomatic individuals with reactivation or relapse. Moreover, antibody testing should not be authorized at the time of discharge as its variation of sensitivity/specificity has potential to provide unfounded confidence. That said, there remain a few unanswered questions at this point in time - Does the virus really clear out from the system after the primary infection?; Is it safe to assume that the fragments of virus residing inside the body cannot infect someone after the first course of infection?; Have patients acquired immunity against the diseases for rest of their life?

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**Acknowledgments**

None.

**Conflict of Interest Statement & Funding**

The Authors have no funding, financial relationships or conflicts of interest to disclose.

**Author Contributions**

Conceptualization: RM, SD, DL and GS. Data Curation: SD and GS. Formal Analysis: RM and SD. Investigation: SD and GS. Methodology: RM and SD. Project Administration: DL and GS. Resources: SD and GS. Software: RM and DL. Supervision: GS and DL. Validation: GS and SD. Visualization: RM and SD. Writing – Original Draft: GS, RM and SD. Writing – Review & Editing: RM, SD, DL and GS.

**Cite as:**

Mondal R, Deb S, Lahiri D, Shome G. Recurrence of COVID-19: Treading the Fine Line Between Relapse and Re-infection. Int J Med Students. 2020 Sep-Dec;8(3):311-3.

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ISSN 2076-6327

This journal is published by the [University Library System, University of Pittsburgh](#) as part of the [Digital Publishing Program](#) and is co-sponsored by the [University of Pittsburgh Press](#).

