

**UNDERSTANDING IMMUNE DYNAMICS IN SARS-COV-2 RE-  
INFECTION AND VIRAL REACTIVATION****Hernandez, Luis Fernando Castillo**

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**Abstract**

Coronavirus Disease 2019 (COVID-19), caused by the novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), emerged in late 2019 in Wuhan, China, and rapidly evolved into a global public health crisis. SARS-CoV-2 belongs to the beta-coronavirus family and shares genetic and structural similarities with earlier zoonotic coronaviruses, including SARS-CoV (2002) and Middle East Respiratory Syndrome (MERS) (2012). Despite these similarities, SARS-CoV-2 exhibits distinct biological and immunological characteristics, underscoring its classification as a novel human pathogen.

The virus is believed to have originated from bat-derived coronaviruses, with evidence suggesting a possible intermediate host, such as the pangolin, facilitating cross-species transmission to humans. A key mechanism of infection involves the viral spike (S) glycoprotein, which binds with high affinity to the angiotensin-converting enzyme 2 (ACE2) receptor on host cells, particularly in type II alveolar epithelial cells of the lungs. This interaction enables viral entry, replication, and subsequent host immune activation.

The host immune response to SARS-CoV-2 plays a critical role in disease progression and outcome. While an effective immune response can eliminate the virus, dysregulated immune activity may lead to severe complications, including acute respiratory distress syndrome (ARDS). Variations in immune response among individuals have been linked to factors such as age, sex, and underlying health conditions. For instance, differences in ACE2 expression and lifestyle factors, including smoking prevalence, may contribute to observed disparities in disease severity between males and females.

Furthermore, emerging evidence suggests the possibility of SARS-CoV-2 re-infection or viral persistence, raising important questions regarding long-term immunity and viral reactivation. These concerns highlight the need for continuous research into immune memory, antibody durability, and the mechanisms underlying recurrent infection. Understanding these dynamics is essential for improving preventive strategies, vaccine development, and therapeutic interventions.

In conclusion, SARS-CoV-2 represents a complex and evolving viral pathogen with significant implications for global health. A comprehensive understanding of its origin, transmission, and interaction with the human immune system is crucial for controlling the spread of COVID-19 and mitigating future outbreaks.

**Keywords:** COVID-19; SARS-CoV-2; Immune Response; Viral Reactivation; ACE2 Receptor

**I. INTRODUCTION**

COVID-19 is contract form of corona virus disease in 2019, where is CO=Corona, VI=Virus, D=Disease and 19=2019. This disease in the first time recognized in Wuhan city of China in late 2019. There are many Corona viruses that infects animal as well as human, but this virus seen in human first in 2019. This virus unlike common cold, but it is similar to zoonotic Sever Acute Respiratory Syndrome Corona Virus (SARS-COV) from 2002 and Meddle East Respiratory Syndrome (MERS) from 2012 [1].

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There is similarity between SARS-COV from 2002 and this new virus that causes COVID-19 diseases and because of that named SARS-COV-2 (Sever Acute Respiratory Syndrome Corona Virus-2). This virus named by the WHO and International Committee on Taxonomy of Viruses. This virus is a new human-infecting Beta coronavirus that, based on its genetic proximity to 2 bat-derived SARS-like coronaviruses, likely originated in chrysanthemum bats. The virus uses a densely glycosylated spike (S) protein to enter host cells and binds with high affinity to the angiotensin-converting enzyme2 (ACE2) receptor in humans in a manner similar to SARS-COV from 2002. However, monoclonal antibodies against the receptor-binding domain of SARS-COV do not exhibit much binding to SARS-COV-2, confirming that this is a new virus. The ACE2 enzyme is expressed in type II alveolar cells, and some unconfirmed data suggest that Asian males have a large number of ACE2-expressing cells in the lung, which may partially explain the male predominance of COVID-19. However, other factors such as a higher prevalence of smoking among men in China may explain the difference in the sex distribution of the disease. There is likely an intermediate host between bats and humans, and preliminary data suggest it is the pangolin (a scaly anteater), an endangered and commonly trafficked Mammal in which recombination of the bat and pangolin coronaviruses could have occurred [2].

Common symptoms of COVID-19 includes fever, cough, myalgia, and fatigue. Patients may initially present with diarrhea and nausea a few days before developing a fever, which suggests that fever is dominant but not the premier symptom of infection. A small number of patients can have headache or hemoptysis and be relatively asymptomatic. Affected older men with comorbidities are more likely to have respiratory failure due to severe alveolar damage. Disease onset may show rapid progression to organ dysfunction (e.g. shock, acute respiratory distress syndrome, acute cardiac injury, and acute kidney injury) and even death in severe cases. Meanwhile, patients might have normal or lower white blood cell counts, lymphopenia, or thrombocytopenia, with extended activated thromboplastin time and increased Creactive protein level. In short, COVID-19 should be suspected in a patient with fever and upper respiratory tract symptoms with lymphopenia or leukopenia [3].

There are many tests for COVID-19 disease but main tests are: Fever test, RT-PCR test and Antibody test. Fever test: fever test is the first symptom of COVID-19 and above 37°C may show COVID-19 disease but it will not show exact disease just shows possibility of COVID-19. RT-PCR or (Real Time Polymerase Chain Reaction also calling Reverse Transcriptase PCR) test: this test will do by nasal swab or any other swab, by this method isolation of RNA will occurs then from RNA by RT-PCR the DNA will produce after that by probe the exact gene of virus will identify, but this test also unreliable, because so many possibilities will be there for exact disease conformation. Antibody test: this test will occur by taking serum from patient and then we can check the amount of IgM antibody and IgG antibody, this test with RT-PCR will show COVID-19 disease [4].

**II. LITERATURE REVIEW**

Zhongrui et al. in (2020) wrote their observation on 45 years old that he travels to Wuhan and he had COVID-19 before and after primary infection he recover and in (2020) when he did again test of RT-PC his test was positive and they told he may re-infected [5].

Ziyue Zu, Mengg Di Jiany et al. did radiography on characteristic image chest also in same time RT-PCR to control COVID-19 diseases and also finding out reinfection of SARS-COV-2 [6].

Sayak Roy in (2020) did test on the neutralizing of viral antibody with RT-PCR in some recover patient and found out there was no any RNA replication on swab testing and there was no any evidence to shows reinfection [7].

Bao et al. in (2020) did experiment on rhesus macaques. Four monkeys were infected with COVID-19 two of these monkeys re-infected after recover, means they showed some symptom of COVID-19 again, but when they took nasal swab and did RT-PCR there was no any sign of COVID-19 [8].

Lan Lan et al. in (2020), four patients with COVID-19 had RT-PCR positive result 5 to 13 days after recovered in China but they do not have any symptoms of COVID-19 and no one of their family were infected by them [9].

Robert D et al. in (2020) did experiment on some patient with COVID-19 on antibody responses to SARS-COV-2 and related coronavirus and they found out the recovery from COVID-19 might confer immunity against reinfection at least temporarily [10].

Sung-II Cho, professor of epidemiology at Seoul National University Graduate School of Public Health in South Korea in (2020), told those people that shows positive RT-PCR when the antibody neutralization will do those patients that they re-infected they will show high a neutralizing antibody during reinfection and this test procedure will recognize difference between redetection and reinfection [11].

Egor Malkov in (2020) by the experimental scenario and possibility calculation find out reinfection possibility will be so less. When one-time infection occurs by this calculation and also observation of experiment the second time infection will not occur [12].

Sarah Ee Fang Yong and colleagues<sup>4</sup> report three clusters of COVID-19 cases identified in Singapore in early 2020 by active case-finding and contact tracing and confirmed with RT-PCR. One of them confirmed before and conduct with two of remaining cluster then serological test they finding out they early infection and post infection and also they told by serological test we can know many things: early infection and those who infected later, responses of immune system rapidly or slowly, false RT-PCR test or true test, infection and reinfection, activation and reactivation, to identify individuals who mounted a strong immunological response to the virus and whose antibody isolates can be used to treat patients via plasma therapy, to control disease from spread infection and also to control in same patient [13].

Tongqiang Zhang et al. in February to 17 February 2020 in Tianjin of China collected three children cases diagnosed with COVID-19. The clinical characteristics of these children were analyzed and reported, all the three

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cases exhibited familial aggregation and experienced a history of close contact with their adult relatives who were diagnosed with COVID-19. All of them were male, aged 9, 6, and 8 years, respectively. Throat swab samples were collected on 1 to 14 days after onset of disease and the results of SARS-COV-2 nucleic acid tests were positive. All the patients were classified as common type. Cases 1 and 3 had fever, nasal obstruction, runny nose, and digestive tract symptoms. Case 2 had mild clinical manifestations included cough, expectoration, and wheezing. As Case 1 combined with supportive tonsillitis, ceftriaxone anti-infection was used. Case 2 was given ribavirin antivirus treatment. All three cases were given interferon atomization, vitamin C, and oral Chinese medicine treatment. After the treatment, three patients obtained the negative throat swab nucleic acid in 14, 11, and 7 days, and were discharged from hospital with two times of negative results in 16, 13, and 9 days, respectively. Follow-up of isolation point after discharge: no positive result was found in either of the two times of throat swab nucleic acid tests, but the stool SARS-COV-2 nucleic acid tests were positive after 10 days [14].

Enrico Bentivegnaw et al. in (2020) published their experiment and observation on 69 years old woman that she had type 2 diabetes mellitus and recently diagnosed urinary tract neoplasm arrived in the emergency room with mild fever and cough. Nasopharyngeal swab RNA test for SARS-COV-2 resulted positive high-resolution computer tomography (HRCT) revealed bilateral parenchymal consolidations and ground glass areas. Hydroxychloroquine and lopinavir/ritonavir were initiated. After symptoms resolution and two negative RT-PCR tests, the patient was discharged. 20 days later she came back for urinary tract infection and again the nasal swab taken from her and the RT-PCR was negative, also in same time they test the serological test also the IgM, IgG and IgA antibody concentration was normal, the leucocyte count also was normal. The patient during recovery again tested because she had contact with new infected patient with SARS-COV-2 and her sera test showed high IgM concentration and also IgG, IgA antibodies with RT-PCR positive, but patient was asymptomatic, means there was no evidence to shows the patient again infected [15].

Kirkcaldy, A on article in (2020) told that those people that had positive RT-PCR test, the sample that taken may be not deeply or the result may be false because the RT-PCR test always not giving insurance results [16].

Anees Mohammad in (2020) collected so many data from different article and reference and reviewed all of them and then told this review highlights the recurrence of COVID-19 infection in recovered patients. In the light of this review, it is unclear that the relapse of COVID-19 infection in recovered patients occurred due to re-infection, false-negative reported at discharge, the false-positive result after discharge or patients discharged without full recovery. The relapse of COVID-19 in recovered is considered a more complicated problem as cases of re infections are also high. Non-human studies revealed recurrence of COVID-19 are not occurred but human trials are yet to determined. It is necessary to avoid false negative and false positive results by performing the coronavirus antibody tests [17].

Ye et al in. (2020) found evidence for COVID-19 reactivation in a small group of cases with no specific clinical characteristics to distinguish them. With recurrence of symptoms and positive PCR-testing after clinical remission and negative nasopharyngeal swab in the presented two cases, reactivation of SARS-CoV-2 must be assumed, but they did not confirm the first test that they did it was in correct method or not and also the patient completely became healthy or not [18].

Anming Luo in (2020) present the report describes a woman with COVID-19 who was discharged from the hospital after treatment because she met the discharge standards but obtained positive results on a nucleic acid test 22 days later, then in result told: In this patient with COVID-19, whether this occurred because of recurrence of the disease, re-infection by the virus, or a false-positive result at discharge is worth further discussion [19].

### III. REINFECTION, REACTIVATION AND REDETECTION

**Reinfection:** It is a process that same person will again infects by same type of parasite, for e.g. When same person again infects by SARS-COV-2 virus and cause COVID-19 disease.

**Re-activation:** If the same parasite causes any diseases and then the symptom and sign of that disease removes and after some days the symptom again appears to the patient, this type of disease calling re-activation.

**Redetection:** If the same result (positive result) seen two times after some times or same times calling re-detection.

#### A. Overview on SARS-COV-2 Re-infection, Re-activation and Re-detection

In all of the above article that I studied and reviewed there was no any exact evidence to re-infection and re-activation was done. For example, Lan Lan et al. told there was four patient that showed positive RT-PCR after recovering but in discussion they told the patients have not spread the virus to any their family members. In other article Bao et al. did an experiment on four that infects by COVID-19 but after collection of result found there was no any re-infection. In other article they told there is re-infection with positive RT-PCR in south Korea but when they did the antibody test there was no evidence of re-infection. In some article the serology of COVID-19 was done and they found there was IgM antibody for primary infection and also there was IgG antibody against this virus. There is no exact report or any evidence to shows re-activation of this virus was done. And we all know when virus entering to human body first IgM antibody will produce and this antibody will be active for 1-3 month and also in same time the IgG antibody also will produce by plasma cell, hence the re-activation of COVID-19 also impossible. Detection of COVID-19 is possible, because when the nasal swab or any swab taking the RT-PCR may shows first false positive result or false negative result and when again the swab was testing it may show positive result again, means there will be any reliable test.

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### IV. RESULTS AND DISCUSSION

In all of these above articles there is no any evidence of re-infection and re-activation but why in some cases the RT-PCR test is positive and the symptom also will be in patient? The answer is because of these below possibilities:

1. When first they did RT-PCR test (negative RT-PCR test) after recovery and that test may be wrong.
2. The kit for test in second time may be sensitive (good quality) than previous (primary) one.
3. In some times the host cells will keep viral RNA for weak (one weak) without any replication or in other word the viral RNA will stay in human cell without any replication.
4. The virus may still present on nose.
5. First swab may not be taken correctly.
6. The second swab that taken may not be taken correctly.
7. They show symptoms because first result for confirmed recovery may be false.
8. They will be recovered but the virus will be present still in some part of patient body and because of that they may still shed virus and this reason also suggest doubt of re-infection.

All of these possibilities suggest that the re-infection and re-activation by SARS-COV-2 impossible, in some article says the mutation of this virus in short time is not possible. Re-activation of this virus also not possible because the IgM antibody will be alive for 1-3 month and IgG antibody after activation of plasma cell also will produce and it will be alive at least for one year. Studies on SARS-COV-1 shows that the re-infection has not happened in same person after recovery by this (SARS-COV-1) virus during of 3-years, hence we can say the re-infection will not take place in same person by same stain of virus at least for one year.

### V. CONCLUSION

In summary we can say re-infection and re-activation of SARS-COV-2 will not occur in same person with same strain at least for one year, because of IgM, IgG and IgA antibody. In those patients that showed positive RT-PCR and some symptoms that is because of false test or any other reasons. By studying on immunological memory of SARS-COV-1 in human immunity responses the IgG antibody for SARS-COV-2 will be alive for 1-3 year. In some articles evidence shows the mutation in this virus will not take place in short time. So, the re-infection and re-activation will not take place in same person by same strain of virus at least for one year.

### REFERENCES

- K. J. Clerkin, J. A. Fried, J. Raikhelkar, G. Sayer, J. M. Griffin, A. Masoumi, S. S. Jain, D. Burkhoff, D. Kumaraiah and L. Rabbani, "COVID-19 and cardiovascular disease," *Circulation*, vol. 141, no. 20, pp. 1648--1655, 5 2020.

# Pharmacology, Alternative Medicine, and Healthcare Journal

## Research Article

- C. Del Rio and P. N. Malani, "COVID-19—New Insights on a Rapidly Changing Epidemic," *Jama*, vol. 323, no. 14, pp. 1339--1340, 14 4 2020.
- Z. Y. Zu, M. D. Jiang, P. P. Xu, Chen, W. Q. Q. Ni, G. M. Lu and L. J. Zhang, "Coronavirus disease 2019 (COVID19): a perspective from China," *Radiology*, p. 200490, 21 2 2020.
- N. J. Beeching, T. E. Fletcher and M. B. Beadsworth, "Covid-19: testing times," *BMJ*, vol. 369, no. 1403, pp. 1-2, 7 4 2020.
- Z.-R. Ruan, P. Gong, W. Han, M.-Q. Huang and M. Han, "A case of 2019 novel coronavirus infected pneumonia with twice negative 2019-nCoV nucleic acid testing within 8 days," *Chines Medical Journal*, 4 2 2020.
- Z. Y. Zu, M. D. Jiang, P. P. Xu, W. Chen, Q. Q. Ni, G. M. Lu and L. J. Zhang, "Coronavirus Disease 2019 (COVID19): A Perspective from China," *Radiology*, p. 200490, 12 2 2020.
- S. Roy, "COVID-19 Reinfection: Myth or Truth?" *SN Comprehensive Clinical Medicine*, pp. 710-713, 22 5 2020.
- L. Malle, M. Ota and M. D. Park, "Will we see protection or reinfection in COVID-19?" *Nature Reviews*, p. 351, 6 2020.
- L. Lan, D. Xu, G. Ye, C. Xia, S. Wang, Y. Li and. H. Xu, "Positive RT-PCR test results in patients recovered from COVID-19," *Jama*, vol. 323, no. 15, pp. 1502--1503, 15 4 2020.
- R. Kirkcaldy, B. King and J. T. Brooks, "COVID-19 and Postinfection Immunity Limited Evidence, Many Remaining Questions," *Jama*, vol. 323, no. 22, p. 2245, 9 4 2020.
- E. Mahase, "Covid-19: who and South Korea investigate reconfirmed cases," *BMJ: British Medical Journal*, vol. 369, no. 1498, pp. 1-2, 15 4 2020.
- E. Malkov, "Simulation of Coronavirus Disease 2019 (COVID-19) Scenarios with Possibility of Reinfection," *Available at SSRN 3569097*, 13 4 2020.
- A. K. Winter and S. T. Hegde, "The important role of serology for COVID-19 control," *The Lancet. Infectious Diseases*, vol. 20, p. 809, 2020.

# Pharmacology, Alternative Medicine, and Healthcare Journal

## Research Article

- T. Zhang, X. Cui, X. Zhao, J. Wang, J. Zheng, G. Zheng, W. Guo, C. Cai, S. He and Y. Xu, "Detectable SARS-CoV2 viral RNA in feces of three children during recovery period of COVID-19 pneumonia," *Journal of medical virology*, vol. 92, pp. 909-911, 23 3 2020.
- E. Bentivegna, A. Sentimentale, M. Luciani, M. L. Speranza, L. Guerritore and P. Martelletti, "New IgM seroconversion and positive RT-PCR test after exposure to the virus in recovered COVID-19 patient," *Journal of medical virology*, 2020.
- A. Kirkcaldy, "REFLEXIONS ON POSSIBLE COVID-19 REINFECTIONS," 2020.
- A. Mohammad, "RECURRENT COVID-19 INFECTION IN RECOVERED PATIENTS (A CRITICAL REVIEW)," *Pakistan Heart Journal*, vol. 53, no. 1, pp. 24-26, 29 4 2020.
- S. Ravioli, H. Ochsner and G. Lindner, "Reactivation of COVID-19 pneumonia: A report of two cases," *The Journal of Infection*, vol. 5, no. 8, 23 4 2020.
- A. Luo, "Positive SARS-Cov-2 test in a woman with COVID-19 at 22 days after hospital discharge: A case report," *Journal of Traditional Chinese Medical Sciences*, pp. 1-5, 28 3 2020.