Review Article

iMedPub Journals
www.imedpub.com

Medical Case Reports
ISSN 2471-8041

2022
Vol.8 No.5:228

Re-Detectable Sars-CoV-2-An Emerging Problem in Recovered Sars-CoV-2 Patients in COVID Pandemic

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Received date: March 14, 2022, Manuscript No. IPMCRS-22-12294; **Editor assigned date:** March 17, 2022, PreQC No. IPMCRS-22-12294 (PQ); **Reviewed date:** March 31, 2022, QC No. IPMCRS-22-12294**; Revised date:** May 11, 2022, Manuscript No. IPMCRS-22-12294 (R); **Published date:** May 18, 2022, DOI: 10.36648/2471 8041/22. 8. 5.228

Citation: Agarwal J, Garg J (2022) Re-Detectable Sars-CoV-2-An Emerging Problem in Recovered Sars-CoV-2 Patients in COVID Pandemic. Med Case Rep Vol:8 No:5:228

Abstract

Re-positive or Re-detectable SARS-CoV-2 (RD SARS-CoV-2) in recovered COVID-19 patients is a major issue in containment of COVID pandemic at present. This can be classified as Real-Time Reverse Transcription-PCR (RT-PCR) interpretation fault (false-negative or false-positive RT-PCR tests), re-activation or relapse of dormant virus or re-infection with SARS-CoV-2 either same or different variant. Though the literature has many documented cases on RD SARS-CoV-2 but the true epidemiology, etiology, clinico-demography, pathophysiology, and outcome of these cases are yet to be elucidated.

To define RD SARS-CoV-2 it's important to understand the standard discharge criteria for SARS-CoV-2 patients which include both the test based and the symptom based strategy. Currently, the WHO criteria and CDC criteria for releasing COVID-19 patients from isolation without requiring re-testing specify, 10days of period after a positive test for SARS-CoV-2 in asymptomatic patients; while in symptomatic cases, patient should have at least three additional symptom-free days.

Keywords: COVID-19 Re-infection; COVID-19 Re-activation; COVID-19 RT-PCR; COVID-19 Re-positive

Introduction

However the test based strategy includes two negative RT-PCR results of consecutive respiratory specimen collected more than 24 hours apartin asymptomatic cases; while in symptomatic cases, resolution of fever without the use of fever-reducing medications and improvement of symptoms are essential criteria along with 2 consecutive negative RT-PCR reports as above [1].

In spite of following strict clinical and laboratory criteria for discharge, re-positivity is seen in terms of laboratory test results and clinical manifestations. Hence CDC has released a guidance protocol to identify Re-detectable SARS-CoV-2 in terms of suspected SARS-CoV-2 re-infection. Investigative criteria include a positive RT-PCR test more than 90 days after the initial test [with CT (Cycle threshold) of <33] or a positive RT-PCR test more than 45 days after the initial test [with CT of <33] that is accompanied by compatible symptoms or epidemiological exposure. Though the re-infection is considered confirmed when the viruses from the first and second infections are different enough to belong to different clades or lineages or when they differ by more than 2 substitutions per month, which is the general population-level viral substitution rate as assessed by multiple studies [2-4]. According to European CDC, re-infection is defined as 'laboratory confirmation of two infections by two different strains (minimum distance to be determined or supported by phylogenetic and epidemiological data) with timely separated illness/infection episodes [5].

As above criteria needs Genome sequencing and bio banking of strains; hence to strengthen surveillance, a retrospective survey on magnitude of re-infection was conducted in India, based on epidemiological case definition ofSARS-CoV-2 re-infection. Here re-infection with SARS-CoV-2 was defined as two positive tests at an interval of at least 102 days with one interim negative test [6].

Literature Review

Epidemiology of Re-detectable SARS-CoV-2

Many studies have shown that Re-detectable SARS-CoV-2 by RT-PCR in recovered COVID-19 patients are very common, varying from 2.4 to 69.2%. Re-positivity lasted from 1 to 38 days after discharge, depending on population size, age of patients, and type of specimens in various studies [7]. Age of re-positive patients after discharge ranged from 0 to 91 years old. Males accounted for 26.7–73.3% of patients. The majority of patients who tested re-positive was asymptomatic or had mild symptoms, but for some patients, illness progressed critically and had fatal outcome [8].

Re-detectable SARS-CoV-2 in COVID pathophysiology is a broad terminology. Most of the studies are based on re-infection and were identified *via* defined criteria discussed previously.

The first case of re-infection of SARS-CoV-2 was reported on 25th August 2020 from Hong kong [9]. Soon more than 300 cases of COVID-19 re-infectionwere reported from United States, Ecuador, Hong Kong and Belgium [10-12]. Recently identified 63 cases of re-infection among 9119 patients previously infected with SARS-CoV-2 infection (0.7%, 95% confidence interval 0.5–0.9%) [13]. Till now studies from all around the world showed re-infection in up to 2% cases only [14].

Patients infected with SARS COV-2 within age group of 21 to 40 years are most commonly affected (nearly 40%).Gender predilection has not been seen in these studies as females accounted for 45.8% and males for 54.2% cases. The main risk groups were healthcare workers (2.3%) and patients with co-morbidities (35%). However in India a retrospective study records re-infection in 4.5% as per epidemiological case definition [6].

The documented Re-detectable SARS-CoV-2 (range 2 to 69.2%) are much higher than true re-infection cases (up to 4.5%). This can be explained as re-positivity is a broad definition which includes not only re-infection but also reactivated cases/ relapse, false positive and false negative RT-PCR results and rare cases from contaminated surfaces.

True epidemiology of re-positive cases is missing. Underreporting of re-infection has been seen as investigative criteria do not apply to immuno-compromised individuals, who can have prolonged virus replication [15]. Also cutoff CT of less than 33 may miss cases in which partial immune protection leads to lower viral loads during re-infection. Further laboratory confirmed criteria has many lacunae as complete genomic data are not available in most COVID-19 infections since many patients with mild symptoms were not tested in the early phase of this pandemic and people with asymptomatic re-infections are less likely to be tested/screened and identified [16].

Clinical presentation and outcome of Re-detectable SARS-CoV-2

Clinically re-infection cases can present as either mild or severe. Many re-infection cases were less severe than primary infection and suggest partial protection from disease [17]. Also studies from Hong Kong, Belgium and Netherlands patients suggest that second time symptoms are generally reduced which shows immune system is responding [12]. A review article concluded that only 35.3% cases of re-infection were severe, with death only in 5.3% in patients with associated neoplastic/ immune system diseases/transplant or other important co-morbidities and also with age >80 years [14]. We have also presented first case report of Recurrent COVID-19 from India. This was a young health care worker who reported re-positive after a gap of almost two months. Patient's Anti SARS-CoV-2 IgG assay was negative and he presented with mild symptoms during both the episodes [18].

Above literature shows favorable data in terms of clinical presentation of RD positive cases, however cases from Nevada and Ecuador consistently presented with more severe symptoms during the second COVID-19 attack. This suggests that in these subjects, immune system made matters worse due to either re-infection by high dose of virus or more virulent variant of the virus, or due to antibody-dependent enhancement where specific Fc-bearing immune cells become infected with virus by binding to specific antibodies [10].

Immune cells that are induced in primary infection may respond disproportionately the second time or antibodies themselves facilitate the virus during a second infection rather than fight it [19-25]. These mechanisms were proposed by researchers while working on vaccine production for severe acute respiratory syndrome and Middle East respiratory syndrome 0 and subsequently for SARS-CoV-2 [26-30].

Outcome of re-infection was assessed in study from Qatar which experienced consecutive COVID waves. The risk of severe disease (leading to acute care hospitalization), critical disease (leading to hospitalization in an Intensive Care Unit (ICU)), and fatal disease caused by re-infection were analyzed in National cohort of persons between February 28, 2020, and April 28, 2021; after exclusion of 87,547 persons with vaccination record.

Re-infections had 90% lower odds of resulting in hospitalization or death than primary infections. Hence a person who has already had a primary infection, the risk of having a severe re-infection is only approximately 1% of the risk of a previously uninfected person having a severe primary infection. The odds of the composite outcome of severe, critical, or fatal disease at re-infection were 0.10 times (95% CI, 0.03 to 0.25) than at primary infection [31].

Etiologies of Re-detectable SARS-CoV-2: RT-PCR misinterpretation, Re-activation and Re-infection

RT-PCR misinterpretation

Re-positive results in cases of primary infection can be due to false positive or false negative results seen with molecular tests. RT-PCR tests can give false positive results, and patients have been diagnosed as re-positive when they were actually negative. In a study conducted by Katz et al., 3/43 (7.1%) patients had a false-positive result from an RT-PCR test [32]. This was explained as possibility laboratory contamination during the procedure or due to cross-reactivity with other human coronaviruses [33-34].

Vargas-Ferrer et al. showed that viral replication continues to take place in Lower Respiratory Tract (LRT) as compared to Upper Respiratory Tract (URT) due to high expression of ACE-2 enzyme(an essential receptor for the entry of SARS-CoV-2) in LRT compared to that in the URT. This explains longer positivity of COVID RT-PCR in sputum samples, in comparison to nasopharyngeal samples. Therefore, re-positive results in LRT samples among discharged patients (with negative results from URT swabs) are related to the sampling site [35]. This also means that virus exists in small amounts in the lower respiratory tract at the time of discharge. Though the nasopharyngeal swab initially tested negative; after a while, when the virus multiplied, the patient turned positive again [36].

Exposure of discharged patients with contaminated environmental surface can be another rare cause of re-positive tests. In a report by Lei et al., five patients who had recovered from severe COVID-19 infection and who had been quarantined in an isolation ward still tested positive. Surface sampling was done from 182 environmental surfaces. Of these, two air samples in the bathroom, two surface samples from floor in the patient's room, two patients' mobile phones, and one sample from the patient's face mask were found to be positive. Interestingly, high viral loads were detected in LRT swabs, while URT samples remained negative in one patient. Literature reports that molecular tests have low sensitivity showing repeatedly false negative results which can be as high as 30%. The false-negative rate of RT-PCR varies from 3 to 41%, according to the type of clinical specimen tested [37-39]. There are many reasons for false-negative RT-PCR results which include the sensitivity/specificity of the nucleic acid test kit, quality of sample, type of samples, and the sampling procedure itself [40-41]. In a retrospective analysis involving 161 COVID-19 patients, the authors showed that false-negative RT-PCR results of SARS-CoV-2 were mainly caused by poor-quality sampling and insufficient quantity of cellular materials in swabs. Furthermore, thermal inactivation also decreases the sensitivity of RT-PCR tests for SARS-CoV-2 [42-43].

False negative results could be due to the contamination of the samples, but it's quite rare due to stringent infection control policy being followed [44]. Single negative swab could be misleading due to intermittent respiratory shedding of SARS-CoV-2 [45]. Performed a study in which patients were divided into three groups: two consecutive (257 cases), three consecutive (37 cases), and four consecutive (5 cases) negative detections. They showed that the proportion of re-positive patients was 20.6%, 5.4%, and 0%, respectively. They concluded that the proportion of re-positive was significantly lower for those with three consecutive negative results than for those with only two consecutive negative tests at the time of discharge ($p = 0.026$) [32].

Intermittent virus shedding was proven by another study conducted on discharged patients, 14 (37.8%) had at least one false-negative result while five patients after having tested positive, had two consecutive false-negative results before ultimately testing positive on 4th attempt (defined as positive-negative-negative-positive) through RT-PCR for SARS-CoV-2, suggesting intermittent virus shedding [38]. Also described 2/81 patients who had a double-negative test in nasopharyngeal and oropharyngeal swabs before having one more positive sample, and who eventually turned negative again (negative-negative-positive-negative). Studies have shown that the Nasal swab sampling, rather than throat swabs for SARSCov-2 testing, could reduce the false-negative rate of nucleic acid detection based tests [46-47].

Ling et al. suggest that, to reduce the number of false-negatives an anal swab or stool samples must be used. They conducted a survey of 66 convalescent patients with COVID-19 where viral RNA could be detected in the stool of 54 (81.8%) patients including some of those with negative RT-PCR from pharyngeal swabs. The mean duration of viral RNA presence in stool samples was longer than pharyngeal swabs (11.0 [range 9.–16.0] days versus 9.5 [range 6.0–11.0] days, respectively) [48].

Re-infection

Though various guidelines and criteria on re-infection have been given by different authorities; true re-infection can be hypothesized if isolation of the complete genome of the virus (instead of genomic fragments) in the second episode, phylogenetic differences in two virus strains in two episodes of infection, virus isolation to confirm infectivity of virus in the second episode, demonstration of cytopathic effect in cell culture, differences in immune responses, longer time interval between two episodes and presence of re-exposure history to COVID-19 patient in the second event is recorded [49,50].

Mechanisms for re-infection have been proposed by Khoshkam, based on the type of immune response i.e. ineffective, strain-specific, or short-lived [44]. Infected cases with very mild symptoms/moderate symptoms/asymptomatic presentation without any humoral response may develop severe disease in the future due to the absence or low levels of acquired immunity; while cases with moderate or severe symptoms if with both humoral and cellular response are more protected from further exposures as they may have long-term immunity [51]. It has been proposed that in the absence of cellular immunity, long term immune response is not possible. Antibody formation and longevity of immunity in a subject could be dependent on the strain of virus, its severity, age of the subject and presence of escape mutants [52]. This could mean that patients remain resistant to SARS-CoV-2 infection even after mutations, with antibody responses that are 50–80% efficacious.

Positive PCR results after recovery may be due to presence of leftover genetic material from previously active infection. Hence repeated RT-PCR positive does not necessarily signify re-infection [53].

Re-activation

Till now many studies have documented cases with re-activation of COVID-19 in patients who recovered from primary COVID-19 infection following standard discharge criteria. These cases presented second time with RT-PCR positive results within 15 days [54-56]. Another study documented symptomatic re-activation in 7% patients and asymptomatic re-activation with positive RT-PCR result in 27% cases, in recovered patients, within~29 days after discharge from hospital. Chen et al determined that a lymphocyte count <1500 cells/μL or having two symptoms or less at the first presentation were independent predictors of re-activation [57].

The re-activation of dormant virus is commonly seen in immunosuppressed patients with some viruses of herpes group, such as Epstein Barr, cytomegalovirus [58].

Analysing re-infection definition of CDC, it becomes easier to understand re-activation; the cases who present with second episode in less than 45 days with associated clinical/radiological/laboratory investigations which suggests active viral replication.

Apart from clinico-radiological analysis, active viral replication can be documented by sub genomic RT-PCR, viral culture isolation, cyotopathic effect, serial CT value testing or low CT value on RT-PCR.

Infectivity of Re-detectable SARS-CoV-2

Many studies have shown presence of virus in respiratory tract as well as in the feces and rectal swabs from re-positive patients, however, no living virus was found in these specimens. Studies emphasized that the lack of viral re-activation in these cases was also supported by the lack of increase in lung infections as revealed by the chest CT scan. It is also suggested that it is impossible for the virus to survive in COVID-19 patients who carry protective antibodies after recovery [14].

A study of recurrence was done in 285 Korean patients who had recovered from COVID-19, and no active virus was identified in the body of these patients (viral cultures were negative). [59]. This confirmed that the re-positive test for the SARS-CoV-2 virus was likely to be the detection of deactivated viral RNA rather than re-activation or re-infection. Infectivity in subjects with recurrence was absent which was proven by fact that all the 790 contacts were COVID RT-PCR negative [60].

Although few studies claim lack of infectivity in re-positive cases, most researchers believe that re-positive cases really do carry the live virus which can be the potential new source of infections for others. Therefore, it is necessary to monitor the patient even after discharge in order to prevent the spread of the pandemic. Monitoring CT values *via* serial RT-PCR testing, sub genomic RT-PCR can be good alternative to genome sequencing; and viral culture or demonstration of cytopathic effect for identifying transmissibility in terms of viral replication. Sub genomic RNAs are transcripts generated during the viral life cycle as the templates for protein synthesis but are not carried in the viral particle along with genomic RNA. In several studies, detection of sub genomic RNA has been adopted as a surrogate for active replication; however, sub genomic RNA has also been detected late in the clinical course and correlated poorly with viral culture, perhaps due to persistence in cellular vesicles [61-64]. Hence its correlation with CT value will be a better supporting evidence of viral replication.

Re-detectable SARS-CoV-2 and immune response

There is presence of Cellular and humoral immune response in COVID-19 but because of limited follow-up data, it's difficult to know with certainty, the expected duration of immune response achieved from previous infection which can protect against COVID-19 re-infections [65].

It is known that SARS-CoV-2 infection induces specific and durable T-cell immunity, with multiple viral spike protein targets (or epitopes) as well as other protein targets. The broad diversity of T-cell recognition serves to enhance protection against SARS-CoV-2 variants, with recognition of at least the alpha (B.1.1.7), beta (B.1.351), and gamma (P.1) variants of SARS-CoV-2 [17]. Researchers have also found that people who recovered from SARS-CoV infection in 2002–03 continue to have memory T cells that are reactive to SARS-CoV proteins, 17 years after that outbreak [15]. Additionally, a memory B-cell response to SARS-CoV-2 evolves few months after infection, which is consistent with longer-term protection (66-67). An innate immune response involving T cells and B cells too is activated, leading to production of neutralizing antiviral antibodies. The specific IgM antibody response starts to peak within the first 7 days [68]. Specific IgG and IgA antibodies develop a few days after IgM and are hypothesized to persist at low levels, conferring lifelong protective antibodies [69]. Several studies are there which document good immune response to COVID-19. Individuals who had experienced mild SARS-CoV-2 infection reported a robust antigen-specific, long-lived humoral immune memory [65].

In fact, an outbreak of the virus on a fishery vessel showed that fishermen with prior neutralizing antibodies against SARS-CoV-2 were not re-infected [70]. An early study by Public Health England, indicatedthat antibodies provide 83% protection against COVID-19 re-infections over a five month period. Out of 6614 participants, 44 had "possible" or "probable" re-infections in their study [71].

While this hypothesis may hold true for symptomatic patients, emerging data have revealed negative IgM and IgG during the early convalescent phase in asymptomatic patients, and also that 40% of asymptomatic patients became sero-negative for IgG 8 weeks after discharge compared with 12.9% who were sero-negative amongst the symptomatic group [72]. A sero-negative status could leave open the possibility of re-infection. Immuno-suppression and co-morbid diseases can be the other risk factors for a re-infection [73].

Re-detectable SARS-CoV-2 in Immuno-compromised patients

There have been reports of possible re-infection with SARS-CoV-2 in immuno-compromised Patients. Reported a case of a 69-year-old diabetic lady with recently diagnosed urinary tract neoplasm who had evidence of two positive reports of anti-SARS-CoV-2 IgM along with RT-PCR positivity, with four negative RT-PCR reports and one negative anti-SARS-CoV-2 IgM between the two; and Luciani. Report a case of recurrent COVID-19 pneumonia in a patient with newly diagnosed classic Hodgkin's lymphoma with mixed cellularity [74-75]. The Indian Council of Medical Research (ICMR), New Delhi, has been on-record claiming three cases of re-infection in India [76].

Ye et al. also suggested a possible viral re-activation in 5/55 (9.1%) discharged patients, previously diagnosed with COVID-19. Of these, four were symptomatic with fever and associated symptoms. Viral factors, host immune status and degree of immune-suppression are potential risk factors for the re-activation of the SARS-CoV-2 virus [77].

Three patients of hematologic malignancy who most probably had re-infection with SARS-CoV-2, after complete (documented) recovery from first infection have been reported in literature. In two of these three patients, the second infection was severe as per risk stratification [78].

Many reasons have been put forth to explain severity of re-infection in immune-compromised patients including likelihood

of "antibody-dependent enhancement" similar to severe dengue infection or due to the absence of protective antibodies in their immuno-suppressed state or low level of antibodies at the time of re-infection. Another possibility to be considered is re-activation of dormant virus which is commonly seen in immuno-suppressed individuals with Herpes group of viruses like Cyto Megalo Virus (CMV) and Epstein Barr Virus (EBV). This issue of viral re-activation or re-infection with a different strain can be resolved by sequencing of viral genome during the suspected re-activation [79].

Vaccine strategy to combat Re-detectable SARS-CoV-2

Emerging new variants can be a big hurdle in combating re-infection in COVID pandemic. Variants present with mutations in different spike domains, such as in alpha variant or B.1.1.7 lineage (also known as 501Y.V1 or VOC202012/01), the beta variant or B.1.351 lineage (501Y.V2), the gamma variant or P.1 lineage (501Y.V3) and the delta variant or B.1.617.2 lineage [80]. The 501Y.V2 variant, or beta variant, is characterized by eight mutations in the spike protein coding sequences that can improve its ability to transmission. showed that beta variant can be more aggressive than non-VOC SARS-CoV-2 [81]. Also P681R and L452R mutations are helping in the spread of delta variant, all these variants have cumulated at least nine non-synonymous mutations/deletions throughout the spike coding region [14].

A study from Qatar showed that of the 1304 identified re-infections, 413 (31.7%) were caused by the B.1.351 variant, 57 (4.4%) by the B.1.1.7 variant, 213 (16.3%) by "wild-type" virus, and 621 (47.6%) were of unknown status [31]. Recently, Omicron variant has been reported from South Africa. Action of currently available vaccines on this variant is unclear as yet [82].

For these reasons it is necessary to investigate, urgently, the possibility of these new variants escaping the vaccine action. The immune responses generated by mRNA and Adenoviral vector-based vaccines are restricted to the Spike glycoprotein, so new variants with big antigenic drift could reduce their efficiency and determine a growing number of re-infections

To reduce the cases of re-infection it's important to design a strategy where common circulating variants should be targeted. Studies need to be done to understand level and type of immune response at primary episode and secondary episode and vaccine should be modified so as to maintain long term protective level in human body to combat re-infection. Although arranging booster dose can be burdensome for health authorities, its role in prevention and in reducing the severity of re-infection can't be ignored.

Another aspect of vaccination is presented by researcher that if vaccines will only reduce symptoms during a second infection, rather than prevent it altogether. This possibility could turn vaccinated individuals into asymptomatic carriers of SARS-CoV-2, putting vulnerable populations at risk of re-infection [14].

Understanding Re-detectable SARS-CoV-2 in terms of other Respiratory viruses

For some virus like measles, the first infection can provide lifelong immunity while in case of seasonal corona viruses protective immunity is short-lived [83]. It has been seen that Coronavirus HCoV-NL63 and the human respiratory syncytial virus present with re-infection, despite the presence of antibodies.

Some studies showed that protection from re-infection is strong and persists for more than 10 months of follow-up 3, it is still too early to say how long protective immunity will truly last.

Further MERS-CoV and dengue viruses have shown that pre-existing, non-neutralizing or poorly neutralizing anti bodies that developed as a result of infection or vaccine' enhanced

Subsequent infection (antibody-dependent enhancement)) and a similar phenomenon may be occurring with SARS-CoV-2. Due to lack of understanding of immune response mechanism behind other respiratory viruses similar to SARS-CoV-2, we have yet to widely explore the immune pathogenesis and protective mechanism behind SARS-CoV-2.

Conclusion

Upon understanding the available literature it is observed that true prevalence of re-positive cases is yet to be estimated globally as complete genomic data is not available due to lack of bio-banking, lack of testing in patients with milder symptoms at the early phase of pandemic and in asymptomatic cases. Criteria to define and differentiate Re-infection, Re-activation and RT-PCR false positive and negative results are not clear and may need to be modified. We can exclude re-infection cases on the bases of criteria given by CDC, while cases of re-activation can be identified on the basis of clinical and radiological analysis.

Re-positive COVID-19 can present as mild or severe infection based on the immune response, however there is need for elaborate studies over a long period of time in different waves of infection to understand immune mechanism, in general and high risk population. Designing effective vaccine is another miles stone which should target almost all the variants in the manner that protective level will reach to combat re-infection episodes.

Since infectivity of Re-detectable cases is an urgent issue to fight this pandemic, long term clinical and laboratory follow up by various tests to determine viral replication or serial RT-PCR testing on samples collected from other body sites has been suggested which is a tedious task.

A brighter side can be seen with seasonal "common-cold" corona viruses, which elicit short-term immunity against mild re-infection but longer-term immunity against more severe illness with re-infection. If this were the case with SARS-CoV-2, the virus (or at least the variants studied to date) could adopt a more benign pattern of infection when it becomes endemic. This fact is evidenced in recently emerging viral variant Omicron which is anticipated to displace delta variant and is supposed to be comparatively milder.

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