Background

The coronavirus disease-2019 (COVID-19) is a severe acute respiratory disease that is caused by SARS-COV-19 infection. The first case was detected in Wuhan, China in December 2019 and it rapidly spread worldwide as of that it was declared by the World Health Organization (WHO) as a Pandemic on 11th March 2020. Since then it has caused 32,110,656 confirmed infections and 980,031 deaths worldwide (as on 25 September 2020). In India, there have been 5,818,570 number of cases and 92,290 deaths so far.\[1\]

Owing to novelty, COVID-19 has been a mystery in itself since the beginning. Some cases develop severe complications while some remain asymptomatic. With research being done in all parts of the world, many lacunae in the etiology and pathophysiology of the disease have been filled. As we move ahead with the pandemic new information is getting added to the existing knowledge pool. The residual damages and long-term health effects are yet to be encountered. The question that has been in the minds of many researchers and is still being explored remains that about re-infection. There are multiple cases worldwide where the discharged patients have been detected positive once again. In India, the guidelines for prophylaxis, testing strategy, quarantine, home isolation, and discharge policies have been revised time and again by the ministry and ICMR. It is difficult to label ones re-detected positive status, taking into consideration strain of coronavirus, dead viral particles, antibodies and reliability of tests. The role of vaccine and herd immunity also becomes controversial with number of such cases arising. We have tried to compile and find out the scientific causes, its effects on individual and what can be the implications on the Public Health and scope of development of strategies required for such occurrences. Efforts need to be taken in such a way that there is neither a panic situation nor should there be a false sense of security post-recovery.

Keywords: COVID-19, reactivation, reinfection, relapse
recovered patients. It will also increase the burden on the health system. And with that, it raises the questions regarding herd immunity, efficacy, and longevity of vaccine. More importantly, it increases ambiguity around policy decisions. The WHO and Indian Council of Medical Research (ICMR) believe that there is no evidence for reinfection or relapse of infection among the recovered cases of COVID-19.\textsuperscript{[1,4]} Despite that, there are recurrences around the world where patients have tested positive for COVID-19 after their discharge/recovery from the hospital.

Many countries have started detection of antibodies to the SARS-CoV-2 in community, and believe that it could serve as the basis for an “immunity passport” or “risk-free certificate” that would enable individuals to travel or to return to work assuming that they are protected against re-infection.\textsuperscript{[3]}

In India, the guidelines for prophylaxis, testing strategy, quarantine, home isolation, and discharge policies have been revised time and again by the ministry and ICMR. The current discharge policy states that “a patient can be discharged after 10 days of symptom onset and no fever for three days and that testing before discharge is not needed.”\textsuperscript{[9]} Though the patients are advised to isolate at home and self-monitor their health for the next seven days post-discharge, we will never know if and when the patient turns negative, as compared to the previous guidelines of discharging the patient after two consecutive swabs for Real-time Polymerase Chain Reaction (RT-PCR) tests negative. This might cause more confusion on whether one’s infection post-discharge is due to prolonged positive status, relapse, or actual re-infection. With these, we also need to consider, before labeling a re-positive, the possibility of RT-PCR showing false-negative results due to sampling procedures or techniques of the collection which might have occurred at the time of discharge.

**Immunology of SARS CoV-2**

A group of spherical or pleomorphic enveloped RNA viruses, carrying pent or club-shaped peplomers on their surface has been classified as coronaviruses (Corona, meaning crown) resembling the solar corona.\textsuperscript{[9]} They are divided into four sub-groupings, called alpha, beta, gamma, and delta. Seven of these viruses can infect humans-229E (alpha); NL63 (alpha); OC43 (beta); HKU1 (beta); MERS-CoV (a beta virus that causes Middle East respiratory syndrome); SARS-CoV, (a beta virus that causes severe acute respiratory syndrome); and SARS-CoV-2 (causes COVID-19).\textsuperscript{[7] 129E, NL63, OC43, HKU1 are seasonal respiratory viruses causing common cold and minor URI. MERS and SARS have potentially caused severe pneumonia.

When the virus enters into the human cells, at first the innate immunity comes into the picture where the macrophages, neutrophils, and dendritic cells engulf the pathogen and hence slow the progress of multiplication and prevent it from causing major symptoms. After this, the cellular immunity is activated and immunoglobulins, i.e., the antibodies against the specific virus are formed along with memory T cells to recognize and eliminate the same pathogen and infected cells in further episodes. This entire process is considered to prevent severe illness and also plays role in preventing re-infection with a similar pathogen.\textsuperscript{[9]} Hence, in general, viral infections are followed by solid immunity to reinfection, which may often be lifelong. Apparent exceptions like the common cold and influenza are not due to lack of immunity but to re-infection being caused by antigenically different viruses.\textsuperscript{[6]}

The immune system can neutralize viruses by lysing their envelope or aggregating virus particles; these processes prevent subsequent infection but do not eliminate nucleic acid, which degrades slowly over time. The immune system generates antibody responses to the surface protein of viral particles, the genetic material (RNA, DNA) left behind degrades over time. Thus, positive PCR results after recovery may not necessarily signify re-infection, but rather the presence of leftover genetic material from previously active infection.\textsuperscript{[9]}

**Reactivation V/S Reinfection**

Diagnostic tests (typically involving a nasopharyngeal/throat swab) can be inaccurate in two ways. A false-positive result erroneously labels a person infected, with consequences including unnecessary isolation, contact tracing, and quarantine. False-negative results are more consequential, because infected persons, who might be asymptomatic, may not be isolated and can infect others.\textsuperscript{[10]} RT-PCR is considered as a diagnostic test of COVID-19. The sensitivity of rapid antigen tests is generally lower than RT-PCR.\textsuperscript{[11]}

Serologic test (ELISA based Antibody detection) has a specificity of greater than 99% and a sensitivity of 96% based on initial performance evaluations. It can be used to identify past SARS-CoV-2 infection in people who were infected at least 1 to 3 weeks previously.\textsuperscript{[11]} COVID Kavach ELISA kit developed by ICMR to test the samples; these kits are 97.9% specific and 98.7% sensitive.\textsuperscript{[12]} A recent study shows that nearly 70% of people undergo IgG seroconversion in COVID-19 infection within 6 days.\textsuperscript{[13]} The efficacy of serological testing is debatable. Patients who test positive for IgG may have a level of resistance to SARS-CoV-2, possibly with reduced efficacy if escape mutations were to arise. But, a year from now, the presence of IgG may not be sufficient to assume immunity in a patient. Robust immune response with the formation of memory CD8+ T-cells and helper CD4+ T-cells will lead to better immunity if exposed to the virus.\textsuperscript{[14]}

Recurrence in COVID-19 can be either due to reactivation of a previous virus, i.e., relapse, or reinfection with a new strain. There is a possibility that dead viral particles (nucleic acid) could have been detected in the RTPCR test in re-tested positives.\textsuperscript{[15,16]} For re-infection, a history of another exposure and positive virus culture is needed. Serologic test results may be variable, depending on the timing. Neutralizing antibodies must be low.
for re-infection to occur, but they may rise during the re-infected period. Hence, reactivation is an endogenous process and re-infection is exogenous [Table 1].

Looking back at the H1N1 pandemic in 2009, Perez Carlos et al. described patients who were re-infected during the high rate of community infection due to their incomplete immunologic protection within the period of re-exposure. Hence, they concluded that, during the pandemic of influenza subtype H1N1, healthcare workers and patients should be aware that symptomatic re-infection might occur after the first episode of infection.[17] Even In 2015, when MERS-CoV infection was of Global public health concern, there were instances where after a period, waning off of antibodies that were previously developed during the infection were noticed.[18]

Even in the case of SARS-CoV-19, there have been cases where post-recovery patients have again tested positive by RTPCR. WHO and Korea Centre for Disease Control (KCDC) had started investigating the cases of re-positive SARS-CoV-2 patients in Korea. Here re-detection could be because of clinical relapse due to a low level of neutralizing antibodies. The virus can drop to a low level to be negative in the test but can later increase. For re-infection, a history of another exposure and positive virus culture is needed. Serologic test results may be variable, depending on the timing. Neutralizing antibodies must be low for re-infection to occur, but they may rise during the reinfected period.[19]

In the month of April 2020, Lan L et al. had reported four cases who had mild to moderate symptoms along with features suggestive of COVID-19 on the CT scan. Some of them were discharged from the hospital after 2 RT-PCR tests done consecutively and later within 2 weeks were again tested positive for SARS-CoV-19 by RT-PCR. None of them had symptoms and only one had CT changes on the second time, and there were no contacts of these as they had followed quarantine rules so their infectivity could not be assessed.[20] These cases are reported as re-detectable positive (RDP) having a concern that they must have been virus carriers resulting in re-activation.

J. Yuan et al., in their brief report on their discharged patients out of which 25 patients (14.5%) were tested positive for RTPCR again reported that, though these patients were discharged only after two negative RT-PCR swabs, probably, two negative RT-PCR tests 24 hours apart may not be sufficient for viral clearance evaluation. Repeated viral RT-PCR testing separated by prolonged duration, such as 48 hours, is essential to ensure that the virus has cleared and the discharged patients no longer can transmit the virus. Of the 25 patients, 24 were non-severe types at the first onset. At the time of hospital re-admission, only 8 patients (32%) had a mild cough.

To check for the response of neutralizing antibodies to re-infection, Bao Linlin et al. conducted a study on rhesus macaques. They were re-challenged with SARS-CoV-2 during an early recovery phase on day 28 from initial infection, which was characterized by interstitial pneumonia and systemic viral dissemination mainly in respiratory and gastrointestinal tracts. No detectable viral dissemination, clinical manifestations, and histopathological changes were seen in them.[21] The strain used while re-infected was identical to the previously infected strain of SARS-CoV-2. Probably previous antibodies were actively present in sufficient quantity during the early recovery phase.

Amin Addetia et al., while describing an outbreak of SARS-CoV-2 on a fishing vessel reported a high attack rate on board of 85.2% and the crew members who had neutralizing antibody titers pre-departure neither experienced any symptoms during the viral outbreak nor tested positive for virus by RT-PCR on return to the shore. They concluded that the presence of neutralizing antibodies from prior infection was significantly associated with protection against re-infection ($P = 0.002$).[22]

But there are previous studies of natural infection and volunteer studies that have shown that re-infection with coronaviruses is common, demonstrating that infection does not induce a stable protective immunity.[23] A case of reinfection was reported in Hong Kong during the last week of August. Author J. Parry reports that the patient was asymptomatic for the second time and the viral strain detected from the second infection was a total of 24 nucleotides different from the first infection. The second infection showed a higher viral load.[24] This case is a clear example of re-infection as the two infections were from different strains of SARS-CoV-2.

Recently, print media has mentioned several cases around India where patients recovered from COVID, have tested positive again after being cured.[25-29] There is no clear evidence if these can be called re-infection yet. These cases are being studied in detail at various institutes.

As reported by J. Shastri et al., the second infection among the four Health Care Workers in Mumbai was confirmed by combination of clinical symptoms, investigations and whole-genome sequencing analysis. The genomes in all four samples in 2 episodes had distinct mutations and it was reported

| Table 1: Mechanism of infections and terminologies used in COVID-19 |
|-----------------|-----------------|
| Terminology     | Meaning                                              |
| Primary infection | Initial infection with an organism in a host is termed primary infection. |
| Re-infection    | Subsequent infections by the same organism in the host are termed re-infections. It can be due to different strains of organisms or due to the waning of antibodies. |
| Re-activation   | It is the process by which a latent virus switches to a lytic phase of replication. It may be provoked by a combination of external and/or internal cellular stimuli. |
| Re-detectable positive | Detection of infection again after being treated and discharged with stable symptomatic status with or without testing negative. |


that the second episode was more severe compared to the first.[34] Another similar case reported by R. Tillete et al. in Nevada with a positive test two months after the first positive test separated by two negative reports. The SARS-COV-2 identified in both instances showed significant differences on genomic analysis.[31]

It is being predicted that an immunity to SARS-CoV-2 is not permanent. After mild COVID-19 infection, neutralizing antibody decrease within the first 2 months.[32] If so, it is likely to enter into regular circulation, and there is a possibility of annual, biennial, or sporadic patterns of SARS-CoV-2 in the next five years predicting secondary and tertiary waves of transmission. But at the same time, if the immunity is permanent, the SARS-CoV-2 infection will disappear for five or more years after this major outbreak.[33] Rolling ahead with the pandemic only will we know the outcome of these predictions. But being equipped, considering both the possibilities would be the wiser way.

Consequences of re-infection on public health
COVID-19 has already taken a huge toll on health care and the mental wellbeing of the population worldwide. Understanding the behavior of viruses in re-detected cases and its causes is urgently required so that future dynamics of the pandemic can be assessed and considered while formulating strategies. It is still difficult to comment on whether a particular factor might be related to the reappearance of the virus and what effect would it lead.

As important it is to decrease the transmission rate at this point and flatten the curve, it is also of importance to be prepared with strategies and guidelines predicting the resurgence of COVID-19 cases which might be due to re-detected cases. Efforts need to be taken in such a way that there is neither a panic situation nor should there be a false sense of security post-recovery. Primary care physicians can play a massive role in this. They have identified patients with respiratory symptoms for early diagnosis and helped patients cope with anxiety related to the disease. An understanding of recurrence pattern of Covid-19 will help them to better equip themselves and guide the patients cured successfully with COVID-19 for follow-up as immunity checks and make sure there is no harm to the patient themselves and the community. Being prepared before-hand and learning lessons from the current scenario will have a long-term positive impact.

Questions arise whether the cases found to be re-infected should be counted as new cases or as old cases. There is no clear and common policy on how these cases would be depicted in the surveillance and hence increasing the confusion in the data. If the COVID-19 vaccine is successful, then considering re-infection, vaccination of people cured of COVID-19 should be taken into consideration too. Infectivity of re-infected or re-detectable positive cases is not very clear, but patients with active viral replication are infectious, about which is not known in cases with re-detectable positive. Though it was found that most of the contacts of re-detectable positives were not found to be infected.[20,34]

Many policy decisions like the discharge of patients from the hospital after being asymptomatic irrespective of the RT-PCR status, home isolation, not keeping a follow-up of the viral load and antibody status of the patient at the end of isolation might have an impact on the detection of re-infection or re-activation in previously positive recovered patients.

Multiple vaccine candidates are currently in Phase III trials. The success of these vaccines could be helped by further insights into the protective nature of neutralizing antibodies in humans. Vaccines that are still under trial aim at generating an immune response in the human body through active immunity by injecting the inactivated virus or viral proteins.[35-37] But with the occurrence of re-infection or re-activation, the long-term effect of vaccines is again under question.

Concluding remarks
At present, there is no data on the exact number of cases present in the community that are re-infected. General precautionary measures for COVID like respiratory hygiene, social distancing, wearing a mask, hand washing should be followed even by people cured of COVID-19. It will help to contain the disease in long term and be a step forward in preventing the second wave in the surge of cases. Feeling of security due to antibodies built from COVID infection and believing that one is immune can have adverse effects.

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