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Elucidating reasons of COVID-19 re-infection and its management strategies

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ABSTRACT

Background and aims: Reinfection is gradually being recognised after symptomatic or asymptomatic COVID-19 infection. We try to elucidate various explanations behind COVID-19 reinfection and suggest possible strategies to counteract this threat.
Methods: We carried out a comprehensive review of the literature using suitable keywords such as 'COVID-19', 'Pandemics', 'Reinfection', 'Vaccines' and 'India' on the search engines of PubMed, SCOPUS, Google Scholar and Research Gate in March 2021 and first half of April 2021 during the current COVID-19 pandemic. Epidemiology, risk factors and trends of reinfection were assessed.
Results: A multitude of factors have been associated with rising incidence of COVID-19 reinfection in India and across the world. Emergence of 'Variants of Concern (VOC)', pandemic fatigue and disregard of infection prevention strategies appear to be the most obvious reasons.
Conclusions: COVID-19 reinfection is an emerging concern amongst the worldwide population with newer mutant strains demonstrating increasing transmissibility and responsible for continuing waves of the pandemic. COVID Appropriate Behaviour (CAB), improvised vaccines and enhanced vaccination drives are necessary to mitigate global threat.

1. Introduction

Relapse, recurrence, resurgence, and re-infection of Coronavirus Disease 2019 (COVID-19) are not uncommon now. These are being increasingly reported in the media and literature in the present pandemic regarding COVID-19 despite vaccination drive [1–5]. Since the beginning of the COVID-19 pandemic, it was expected that re-infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections would occur based on past experiences of pandemics. India has recently seen a resurgence of COVID-19. Re-infection rate is likely to be a significant threat to the current measures to control the COVID-19 pandemic. Prevention, identification, and management of these patients will be essential to avoid mortality as re-infection can be severe and may have a variable presentation. The patients with COVID-19 re-infection may spread infection as well. Since the first documented case of reinfection from the Hong Kong, reinfection has put unpleasant question marks on long-term immunity, sampling technique standardization, viral mutation, and herd immunity efficacy [6]. Challenges and possible management strategies to manage COVID-19 remain a significant concern.

2. COVID-19 Re-infection

2.1. Definition

Definitions of reinfection, relapsed infection and recurrence of COVID-19 infection is being refined with evolving knowledge [7]. The European Centre for Disease Prevention and Control (CDC) in September 2020 has issued a report on criteria of definitions to these terms with guidelines for public health response considering recent developments [8]. The Centers for Disease Control and

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Prevention has defined the re-infection with SARS-CoV-2 using the criterion (Table 1): a) detection of SARS-CoV-2 RNA (with Cycle threshold or Ct values < 33 if detected by Reverse Transcription Polymerase Chain Reaction (RT-PCR) after 90 days of the first detection of viral RNA, whether or not symptoms were present, and b) paired respiratory specimens from each episode that belong to different clades of virus or have genomes with >2 nucleotide differences per month. Cases in which detection of SARS-CoV-2 RNA is present more than 45 days to 89 days apart are considered re-infections, provided the second symptomatic episode had no apparent alternative explanation for the COVID-19-like symptoms, or there was close contact with a person known to have laboratory diagnosed COVID-19, and paired specimens are available with the Ct values, and sequence diversity noted above". The Indian Council of Medical Research (ICMR) has published a report that suggests the working epidemiological case definition for re-infection after COVID-19 as two positive tests at an interval of at least 102 days with one interim negative test [9].

2.2. Incidence

The calculation of the risk of re-infection is complex due to underreporting. Most individuals who became infected during the first wave of the pandemic were asymptomatic, and hence data of confirmation with RT-PCR is not available. The suspects were managed in-home quarantine and did not access RT-PCR or antibody tests for COVID-19. Hence, their records are not available in various COVID-19 datasets [10]. The infection with COVID-19 in asymptomatic patients may be elucidated with a higher rate of neutralizing antibodies in the community than the actual rate of confirmed cases of COVID-19.

The reported re-infection rates may vary in different countries. A study from Qatar with data from RT-PCR testing within symptomatic population suggests an estimated re-infection risk of 0.2% [11]. The current records from the Indian Council of Medical Research (ICMR) suggest a re-infection rate of about 4.5% of SARS-CoV-2 infected individuals in India [9]. As the second wave is ongoing in India, more cases will be identified in the coming days. A systematic review estimated that the incidence rate of the recurrent SARS CoV 2 positivity to be 14.8% with re-infection could occur at an average period of 35.4 days from primary infection [3]. In another meta-analysis, the estimated cumulative rate of SARS-CoV-2 recurrent RNA positivity was 12% [12].

2.3. Aetiological factors/predictors/risk factors for COVID-19 Re-infection

Several possible factors could be responsible for re-infection in COVID-19 patients.

2.3.1. Low antibody titres

Infection with SARS-CoV-2 leads to a immunological response with sero-conversion in human subjects. Many re-infections are associated with a reduced antibody response during the initial illness (both with regards to the level of titres and their duration). In serological studies, it has been found; patients who have had severe COVID-19 diseases mount increased antibody response (SARS-CoV-2 antibodies) compared to asymptomatic patients or have less severe disease. After asymptomatic and lesser severe infection, a lower antibody level for a smaller duration is likely to be seen in these individuals. It is reported that the memory CD4 + T-cell responses tended to be greater in patients who had severe illness than in those with mild or asymptomatic disease [13]. A published study on 173 patients with COVID-19 found that patients who were critically ill with COVID-19 had significantly higher antibody titres than those in non-critically ill patients [14]. The severity of COVID-19 infection in the Indian population was relatively less severe than the Western population in the first wave [15]. Many of the SARS-CoV-2 infected population remained asymptomatic and hence the antibody titres may not have mounted or may have been of short duration. Therefore, the risk of re-infection may be seen in higher numbers in India than in other countries who reported severe cases in the first wave of COVID-19. It has also been observed that the body response and kinetics for sero-conversion for mounting anti-SARS-CoV-2 antibodies had different kinetics in patients who were asymptomatic or having mild diseases as compared to those who were critically ill because of severe COVID-19. Such weak immunological response in patients with lesser severe disease remains a critical concern for inadequate protective immunity against re-infection.

2.3.2. Shorter duration of immune prevention by the antibodies

It is well known that those viral infections that have viremia and lead to systemic manifestations mount long-lasting immunological responses with longer persistence of antibodies persist, sometimes for a decade. On the other hand, viruses causing localized infection such as those of mucosal surfaces and those who do not have systemic viremia (e.g. influenza virus, respiratory syncytial virus, and seasonal coronaviruses) mount a weaker response and persist

Table 1
Case definition of confirmed diagnosis of COVID-19 re-infection European Centre for Disease Prevention and Control (ECDC).

ECDC laboratory definition for proven SARS-CoV-2 reinfection will require	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 (minimum time to be estimated). a) Confirmation of a true first episode- description of the viral load of the first episode is necessary (Ct values > 35 might imply possible contamination rather than true infection). Re-testing of the original specimen is indicated whenever possible. (b) Proof of a reinfection with two positive SARS-CoV-2 RT-PCR tests with Ct < 35 (or proof of replicating virus by cell culture or detection of sub-genomic RNA) at different time-points. Plus: (c) Confirmation of infection with two different phylogenetic strains by high-throughput sequencing, corresponding to local epidemiology (proof of two distinct virus variants with any sequence variation between the two episodes). Plus: At least one, and ideally two, negative RT-PCR tests, on two different specimens collected between the first and second episodes, should be documented.

Abbreviations: Ct values= Cycle Threshold values; RT-PCR= Reverse Transcription Polymerase Chain Reaction

Reference: Centre for Disease Prevention and Control (CDC). Reinfection with COVID-19. https://www.cdc.gov/coronavirus/2019-ncov/your-health/reinfection.html (Accessed 21 April 2021).
European Centre for Disease Prevention and Control (ECDC). Reinfection with SARS-CoV-2: considerations for public health response 2020. https://www.ecdc.europa.eu/sites/default/files/documents/Re-infection-and-viral-shedding-threat-assessment-brief.pdf (Accessed 20 April 2021).

for a shorter duration. SARS-CoV-2 RNA has been observed in the blood of infected persons, but culture-positive infectious virus has not been reported from haematological samples [4].

2.3.3. Mutant viral strains

Several newly mutant strains of Coronavirus have emerged resulting in Variants of Concern (VOC) with evolutionary advantage over their ancestral types [16,17]. These mutations have been noticed due to changes in genes and predominantly due to alteration of the SARS-CoV-2 spike protein [18]. More concerning is the ability of these VOC in easier transmissibility of COVID-19 infection with greater infection rates [17,19]. The variant known as B.1.351, which was identified in South Africa and the UK variant (now known as B.1.1.7) may have the ability to re-infect people who have recovered from earlier versions of the coronavirus [20] The emergence of these variants of SARS-CoV-2 with a variable escape from natural and vaccine-induced immunity may also be the potential cause of re-infection. Eventually this will affect treatment, prevention and Control of the continuing COVID-19 pandemic [21].

Similar to South Africa and Brazil the new mutant variant could be the cause of concern in India for the recent surge of new cases and reinfections. This variant is double mutant or B.1.617; which is more contagious and has several known mutations (at least 15) [22].The person who has already had COVID-19 can be re-infected more easily with this strain. This B.1.617 dubbed as double mutation because of their spike proteins namely L452R and E484Q which were mutations of concern because of their immune escape property causing high infectivity and transmission rate [23]. Because of the two different spike protein markers; make them more efficient in attaching with the human host cells. The B.1.617 mutant separated further to give three sub-lineages of double mutations B.1.617.1, B.1.617.2, and B.1.617.3 [24].In samples collected from Maharastra state suggests, over 60% of cases were of the double-mutant variant [25].The recent reports suggest that the current vaccination can provide immunity against these variants.

2.3.4. Non-adherence to the COVID-19 Appropriate Behaviour (CAB) of the population

The CAB viz. social distancing, hand sanitation, and strict use of face masks is of paramount importance in the prevention of infection. The relaxation of lockdown rules, recurrent festivals, and other occasions of mass gatherings are the obvious causes of the recent rise in India's number of cases. It is observed that about 50% population is not using a mask, and about 50% do not know how to use it correctly [26].

2.3.5. Vaccine hesitancy

Vaccination drive for COVID-19 has multiple advantages as it helps to prevent COVID-19 infection, decreases the severity and transmission of the disease. However, there is growing reports of Vaccine hesitancy (VH) which implies a delay in acceptance or refusal to take the vaccine, despite its availability [27]. Though the reasons for VH is multifactorial, including lack of trust and confidence in the COVID-19 vaccine and permeates across racial and ethnic divisions [28].

Wallis [29] has suggested seven innovative ways to tackle vaccine hesitancy in his article These include:

1) Identifying and reaching out to ambivalent people,
2) Try to address the lack of trust or mistrust in people who are vary of vaccines,
3) Defuse mistrust of the Black, Asian, and Minority Ethnic (BAME) communities by inviting other trusted people of their community to canvass for the vaccine and reassure them
4) Overcoming the practical barriers of low-income people by providing vaccine free of cost and extending the vaccination hours during the vaccination drive,
5) Publicizing the popularity and efficacy of the vaccines,
6) Suggesting vaccination to people who are visiting outpatient, primary health care clinics and hospitals for some other reasons,
7) Information campaign using frequent reminders to the people.

2.3.6. Peltzman effect

The “Peltzman effect” is named after Sam Peltzman, a Professor of economics at the University of Chicago Booth School of Business and described the concept of “Risk Compensation” [30]. In the theory of “Risk compensation” it is postulated that people typically adjust their behaviour in response to perceived levels of risk. People become more careful where they sense greater risk and lesser careful if they feel more secure. Peltzman theorized that though the introduction of safety devices, like seatbelts or airbags reduced fatalities, however, it did not correspondingly reduce the number of accidents and thus effect of safety devices was not exponential. We extrapolate this phenomenon to COVID-19 vaccination. Vaccination drive, efficacy of COVID-19 vaccines seems to have given a sense of safety against the disease and for people to abandon protective and preventive strategies of ‘social distancing’, use of ‘face coverings’ etc. Peltzman effect leading to risky behaviour could thus be one of the reasons of COVID-19 resurgence even after an effective vaccination drive and threaten public health efforts [31].

2.3.7. “Pandemic fatigue”

Serial “Lockdowns”, socio-economic consequences and other mitigating circumstances has manifested as “pandemic fatigue” with decreasing adherence to risk reduction strategies of social distancing, ‘face coverings’ and hand washing in the population. ‘Pandemic fatigue’ amongst the population and reduced observance of infection control strategies is an inherent threat to global public health efforts to control the COVID-19 pandemic.

2.4. Protection by the vaccines and previous infection

Although not rampant currently, re-infection will remain a substantial issue in the Indian population. Most people have had an asymptomatic infection for the first time and an effective herd immunity has not been achieved. Currently available COVID-19 vaccination (e.g. Oxford-AstraZeneca or the Pfizer-BioNTech) including COVAXIN (inactivated) and COVISHIELD (Adenovirus carrier vaccine) in India have been found to be effective in providing a high level of protection against COVID-19 symptoms, serious illness and reduce the need of hospitalization [32,33]. Though the vaccination program is ongoing, a vast majority of the population remains unvaccinated. Robbins et al. showed that 16% of the recently admitted COVID-19 patients had previously received a COVID-19 vaccine [34]. It is debatable that prior SARS-CoV-2 infection or those who received vaccination had achieved adequate protection against symptomatic re-infection. To date, only one published study has confirmed that SARS-CoV-2 infection confers immunity to re-infection, as no symptomatic re-infections were found in a cohort of healthcare workers up to six months [35]. The apparent factors associated with an increased risk of severe symptomatic SARS-CoV-2 re-infection are increasing age, comorbidities (like obesity, asthma, type 2 diabetes mellitus), and previously laboratory-confirmed SARS-CoV-2 severe infection.

The degree and duration of infection with primary SARS-CoV-2 confers protection towards subsequent re-infection is not well understood. The previous infection confers 80.5% protection

against COVID -19 re-infection, decreasing to 47·1% in those aged 65 and older [36]. Hanrath et al. suggested that the immunity to re-infection is maintained for at least six months after primary infection [35]. In a meta-analysis, authors noted that patients with younger age and a more prolonged initial illness are more likely to have recurrent SARS-CoV-2 positivity; on the other hand, patients with diabetes mellitus, severe disease, and a low lymphocyte count are protective for re-infection [3]. The median time to re-infection varied among studies.

2.5. Differences in the first and the second COVID-19 infections

Recently authors have studied COVID-19 patients who showed symptoms after the total recovery from their first infection. Patients in their second episode has a more severe disease and without antibodies specific antibodies against COVID-19. This is attributed to the high mutation rate [37]. The mutated strains of COVID-19 are more infectious than the original one. These mutated viruses spread faster, are more lethal and renders vaccines less effective. In India, various mutated strains such as UK strain, South African strain, and Brazilian strains have been found which were not present in the earlier wave. The current vaccination working against these mutated strains is doubtful. A systematic review and meta-analysis of 56 studies evaluated 123 patients with repeated positivity and reported a more severe disease course could be expected if the positivity interval is shorter. The authors concluded that the second episode of SARS-CoV-2 positivity is more potent if it happens within 60 days after the first positive PCR [38].

2.6. Diagnosis of COVID-19 re-infection and genomics

Though, similar symptoms as seen in initial COVID-19 infection may be seen in reinfection, they may have different manifestations in the second episode [5]. ICMR and the European Centre for Disease Prevention and Control have published guidelines about definitions of reinfection [8,9]. It should be noted that to label anyone as true re-infection; the patient should have characteristic symptoms of COVID-19 with a positive RT-PCR test. The Centre for Disease Control (CDC) criteria is helpful to distinguish between disease recurrence and re-infection [39]. There is also a need to distinguish between re-infection, persistent infection with intermittent viral shedding, and a chronic infection reservoir's re-emergence. Superadded infection or pulmonary embolism is common; these should be ruled out, especially if recurrence occurs less than three weeks [1]. A viral culture shall prove the re-infection more conclusively as dead viral antigen may also be positive on RT-PCR testing from a research point of view. The viral RNA sequencing of nasopharyngeal samples from both episodes will show different strains. The duration of symptoms should be 90 days or more from the initial infection. In fewer than 90 days, the possibility of relapse or reactivation and or re-positivity is likely [6]. Also, to differentiate between the new infection from an old disease on radiography; a “new-baseline” imaging should be obtained from COVID-19 patients at the time of hospital discharge or clinical recovery to avoid a diagnostic challenge between recently infected patients and re-infections [40]. A detailed analysis of clinical history, serological information and the virus's genomic variations by Whole-genome sequencing is required while assessing cases of SARS-CoV-2 re-infection [41].

A Real-time whole-genome sequencing will prove helpful to rapidly identify new variants and re-infections, facilitating appropriate patient management [42]. Phylogenetic analysis to trace the viral lineages of COVID-19 is another tool to identify re-infection. After analyzing several studies, recently, authors strongly advised using repeated molecular testing on respiratory tract specimens at one and two months after the recovery from COVID-19 for early identification, isolation, and clinical management of subjects with SARS-CoV-2 recurrent RNA positivity [12].

3. Management strategies and guidelines for re-infections

The diagnosis and management of re-infection should be in line with the treatment of the first infection. The cases should be categorized as mild, moderate, and severe categories and treated accordingly. These patients might require more care and observation than the primary infection due to the severity of disease and compromised lung condition.

4. Prevention of re-infection

The preventive strategies which need to be reemphasized as primary modalities in this pandemic suggested as follows:

1. There is a need for ongoing vigilance without an assumption of protection after a first episode [43].
2. There is a need for optimum utilization of the country's vaccination capacity.
3. The population needs to step out from home, only if it is most needed.
4. Strict adherence to COVID-19 Appropriate Behaviour (CAB) and other preventive measures the key to the long-term management of this pandemic.
5. Introduction of new, updated vaccines based on the mutated virus and Variants of Concern [10].
6. Emphasis on enhanced, ongoing vaccination drive, as it shall reduce the severity of re-infection if it occurs.
7. Address ‘Vaccine Hesitancy’ with Public information policies with. Reassurance, engagement, and encouragement of the reassurance of communities [28].
8. Innovative steps to tackle ‘Vaccine Hesitancy’ and overcome practical barriers of misinformation in communities [29].
9. Counter acting ‘Peltzman effect and ‘Risk compensation’-similarity to the Peltzman effect must be considered when framing national COVID-19 management strategies with initiatives to reduce risk associated behaviours and strong public health message about adherence to social distancing, ‘face coverings and hand washing in the population.
10. Longitudinal studies and availability of rapid, real-time whole-genome sequencing tests to identify new mutations and Variants of concern to reinforce existing Vaccines.

The quality, quantity, and durability of protective immunity from vaccination are higher than the immunity elicited by natural infection with SARS-CoV-2 [10]. Therefore an increased vaccination drive is the key to halting the severity of re-infection. There seems to be clarity that the COVID-19 vaccination is not a guaranteed immunity against re-infection, and the person may remain vulnerable as the development of antibodies after vaccination is not instantaneous. Therefore, all the previously mentioned preventive measures must be followed to avoid re-infection. Finally, vaccination of all patients who suffered an initial infection should be the goal.

5. Conclusion

The re-infection toSARS-CoV-2 has emerged as a reality and has remained a significant concern in the ongoing pandemic. It is posing a serious and significant challenge for the public health measures, and is draining the health care resources, including the human resources. The preventive strategies need to be emphasized,

and vaccination drive needs to be enhanced and newer vaccines developed sooner.

Author's statements

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