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Criteria for the identification of suspect SARS-CoV-2 reinfection cases

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Owing to limited knowledge about the SARS-CoV-2 virus, in the initial few months of the pandemic, COVID-19 patients were not expected to be reinfected[1]. As the pandemic progressed and more information about the disease has now become available, consensus among health experts has started emerging that those who have recovered from COVID-19 can be reinfected. This has been acknowledged by various organizations[2]. According to a report published by Centers for Disease Control and Prevention (CDC), 'cases of reinfection with COVID-19 have been reported but remain rare'[3]. Multiple criteria are being used across different geographies to identify a reinfection[2]. However, there is no well-defined and consistent definition for deciding what constitutes true SARS-CoV-2 reinfection. This note aims at establishing a criterion for the identification of cases of reinfection. After studying different approaches that are being used globally, the goal is to determine a criterion that is accurate and practical in its application on a large scale in India.

Identification of reinfection

Identification of SARS-CoV-2 reinfections is critically necessary for public health control and related risk assessments. Reinfection refers to a case where a person who has been infected previously (confirmed tested positive) and thereafter recovered (tested negative at least once) is found to be infected again (tested positive again after at least one negative test). However, it is important to make sure that these cases are reinfections because SARS-CoV-2 residue can remain in the body for several weeks[4]. Therefore, ensuring whether these are actual cases of reinfection and not residual infection from the initial infection is necessary.

There are various methodologies under consideration for the identification of reinfection episodes based on the following approaches.

Using genetic sequencing data. CDC has set up a gold-standard investigation protocol for the confirmation of SARS-CoV-2 reinfection[2]. This includes a comparison between viral genome sequences from the first infection and reinfection. The two sequences should not differ significantly for reinfection[2], as the virus is expected to mutate at the rate of about two single nucleotide variants (SNVs) per month[2]. The protocol requires a positive confirmatory test of the first infection and virus detection across two distinct time periods (without any specification on the time frame of the tests). Along with the positive confirmatory test, genetic sequencing data are also needed to support the conclusion with a high probability that reinfection has occurred. However, it mentions that reinfection cannot be confirmed if clinical specimens from the initial SARS-CoV-2 illness are not available.

Analysing survey data available on potential reinfection cases. Many countries have identified potential cases of reinfection and there are a few organizations that are tracking the confirmed[5,6] and suspected[7] number of SARS-CoV-2 reinfections. The confirmed cases indicate that after being infected for the first time, reinfection can occur as early as 10 days. However, the average time period noted in one of the trackers[5] (organizations that are tracking reinfection instances) is 78 days[5], whereas another study found the median time for reinfection to be 64.5 days with the time range for reinfection being 45 to 129 days[6]. According to a report published by Pan American Health Organization/ World Health Organization (PAHO/WHO), the time range for a suspected case is ≥90 days from the first SARS-CoV-2 infection, or it can follow a period ≥45 days from the first infection with SARS-CoV-2 (ref. 2).

Based on these studies and the data on reinfection available, a possible way of identifying a set of potential reinfection cases statistically is to use the average days it takes for a person to test positive again after recovering from the infection. This method, although not definitive, will significantly decrease the number of cases that need to be clinically investigated further to arrive at the true instances of reinfection.

It must be noted that the available dataset on confirmed reinfection cases is small. Hence as new reinfection cases are reported, the parameters used for this method would also change.

Using the characteristics of infection caused by the virus. A few studies use the viral shedding time of patients infected with the SARS-CoV-2 virus to ascertain that these are cases of reinfection, with a high degree of confidence[8,9]. The criteria used in these studies were based on the findings that in most COVID-19 cases, viral shedding reaches a minimum 28 days after an initial acute SARS-CoV-2 infection[4,10–12]. Therefore, if a person tests positive, followed by a negative test, and then again tests positive with the interval between the two positive occurrences being at least 28 days, these might be the possible cases of reinfection and should be investigated further. The antibodies against the virus start to rise 5–10 days post-onset of the primary infection, peaking by days 12–15 (ref. 10) and will contain a proportion of neutralizing antibodies[4]. This will make any SARS-CoV-2 reinfection unlikely within this time period. Hence it is highly unlikely that SARS-CoV-2 reinfection would occur within the first 28 days post-illness onset (first positive test). As patients move beyond the 28 days post-illness onset, SARS-CoV-2 IgG antibodies gradually decrease[6], thus increasing the possibility that SARS-CoV-2 reinfection may occur.

These methodologies must be accurate in identifying cases of reinfection and must also be practical in their application in analysing them at a large scale.

Criteria to identify SARS-CoV-2 reinfection

It is important to quickly identify and study suspected cases of SARS-CoV-2 reinfections to understand their implication on public health policies. Therefore, using a statistical approach is appropriate, since in the Indian context doing a clinical analysis to retrospectively study reinfection cases is impractical. It must be noted that there are several caveats and limitations associated with using a statistical approach. Some of these caveats are mentioned below.

Statistical analysis of reinfections depends on the testing data. Commercially used tests are not 100% sensitive or specific, and thus can give false negatives and false positive results[6]. Since a statistical reinfection analysis would use these test results, it might provide an inaccurate outcome and might wrongly classify cases.

The SARS-CoV-2 residue can linger for weeks after a person has been cured of the illness. Therefore, it is possible that one might test positive for a long time after being infected. Although such cases would be small, these might distort the actual number of reinfection cases[13].

There can also be instances when a person has two positive tests more than 90 days apart, but there was no test done to conclusively prove that he/she recovered during these 90 days[14]. This methodology would not be able to identify such cases.

Factors considering the assessment of reinfection

Some factors need to be considered while assessing the reinfection of SARS-CoV-2.

(i) False-positive results – Contamination and sample handling error can affect the sensitivity of RT-PCR test results[15].
(ii) Time period – Longer time lapse between two infections will increase the likelihood of reinfection.
(iii) Virus identification – Viral RNA fragments chosen for testing should be checked for viable virus fragments and non-viable viral remnants using CT values of viral load.
(iv) Genome sequencing – Sequencing can indicate whether the virus responsible for reinfection is from a previous strain or is different[15–18].

Reinfection in the Indian context

As the second wave of the pandemic in India was more contagious with the emergence of several new SARS-CoV-2 variants, the reported incidences of reinfection cases highlight the urgent need for the establishment of a protocol to monitor such cases in the country[16–18]. For identifying and analysing reinfection cases, a methodology that is sufficiently accurate and applicable on a large dataset needs to be selected. The method of using genetic sequencing data, although highly accurate, is impractical in identifying reinfection cases on a large scale due to the lack of availability of clinical samples of all the tests done in the past. The testing guidelines of ICMR do not state the requirement of laboratories to store the tested specimens for the future. Therefore, it cannot be assumed that the specimens for all the tests have been stored for future analysis. The problem with using the average time as a criterion is that the time for reinfection significantly varies between the various trackers. Also, the cases that will be used to calculate the average time have to be clinically confirmed cases of reinfection, and therefore would be small in number and thus not statistically significant to be applied over a broad population of suspected reinfection cases. Using the viral shedding time is a good alternative to the other two methodologies. Since viral shedding reaches its minimum after four weeks of infection, chances of the virus being from the same infection are small making the criterion accurate. Also, this method is easily applicable for a broad population group and on a large dataset.

Conclusion

It can be concluded that to identify cases of reinfection using only the data of tests available, the viral shedding time criterion can be employed. It is an appropriate alternative to the gold standard set by CDC and is also best suited in the Indian context.

The methodology used is as follows:

(1) An initial SARS-CoV-2-positive confirmed test (with or without symptoms).
(2) Followed by clinical recovery with at least one negative SARS-CoV-2 test.
(3) Followed by a confirmed SARS-CoV-2-positive result (with or without symptoms) at least 28 days after the previous positive result.

This criterion is not deterministic and non-confirmatory. It provides a characterization based on which further clinical investigations should be done. It must be noted that although confirmed cases of reinfection have been observed in less than 90 days since the first infection, these are uncommon[14]. Therefore, cases that are categorized as reinfections using the above criterion in a span of less than 90 days (i.e. 28–90 days) would require a sound and comprehensive investigation[14].

It is important to understand that the emergence of SARS-CoV-2 reinfection cases does not affect public health or clinical management interventions for cases of

primary infection, or the management of subsequent secondary SARS-CoV-2 infections. These methodologies for deciding a reinfection criterion are not perfect and will inevitably be refined as new findings accumulate. However, given the dynamic nature of the progress of the pandemic, the best possible alternatives available should be used for now.

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