Investigative Criteria for Suspected Cases of SARS-CoV-2 Reinfection (ICR)

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CDC is aware of recent reports of suspected cases of SARS-CoV-2 reinfection among persons who were previously diagnosed with COVID-19 [1–3]. There is currently no widely accepted definition of what constitutes SARS-CoV-2 reinfection and the reports use different testing methods, making reinfection diagnoses difficult. To develop a common understanding of what constitutes SARS-CoV-2 reinfection, CDC proposes using both

1) **investigative criteria for identifying cases** with a higher index of suspicion for reinfection and
2) **genomic testing of paired specimens**.

CDC examined appropriate time periods following initial SARS-CoV-2 infection or illness to investigate reinfection. Since August 2020, CDC has recommended *against* the need for retesting persons with asymptomatic infection within 90 days of first SARS-CoV-2 infection or illness because evidence *to date* suggests that reinfection does not occur within this time window (CDC Guidance on Duration of Isolation and Precautions for Adults with COVID-19).

At this time, we propose two time windows for investigation as listed below:

a. For persons with or without COVID-19–like symptoms **≥90 days** after initial infection/illness; and
b. For persons with COVID-19–like symptoms **45–89 days** after initial infection/illness.

For persons with detection of SARS-CoV-2 RNA from a respiratory specimen ≥90 days after their first laboratory-confirmed SARS-CoV-2 infection/illness, we apply a standard set of criteria detailed below. Investigating highly suspicious COVID-19–like cases in the 45–89-day window is also important. However, we propose stricter criteria to select cases in this earlier timeframe using a higher index of suspicion for reinfection. If evidence of reinfection during this time window is identified, it will further inform future prevention efforts and guideline development.

CDC notes that SARS-CoV-2 reinfection is a rapidly evolving area of research. This initial set of proposed criteria might not capture *all* instances of reinfection; we offer these initial investigative criteria in an effort to better understand the potential for reinfection. This

initial set of proposed criteria will be refined if new evidence suggests other avenues of investigation, with the goal of creating a standardized case definition of SARS-CoV-2 reinfection.

1. **Investigate cases that meet criterion A or B**
    a. **For persons with detection of SARS-CoV-2 RNA ≥90 days since first SARS-CoV-2 infection**
    Persons with detection of SARS-CoV-2 RNA* ≥90 days after the first detection of SARS-CoV-2 RNA, whether or not symptoms were present
    AND
    Paired respiratory specimens (one from each infection episode) are available
    *If detected by RT-PCR, only include if Ct value <33 or if Ct value unavailable

    b. **For persons with COVID-19–like symptoms and detection of SARS-CoV-2 RNA 45–89 days since first SARS-CoV-2 infection**
    Persons with detection of SARS-CoV-2 RNA* ≥45 days after the first detection of SARS-CoV-2 RNA
    AND
    With a symptomatic second episode and no obvious alternate etiology for COVID-19–like symptoms **OR** close contact with a person known to have laboratory-confirmed COVID-19
    AND
    Paired respiratory specimens (one from each infection episode) are available*If detected by RT-PCR, only include if Ct value <33 or if Ct value unavailable.
    In settings of limited genomic testing capacity, CDC suggests prioritizing investigation of persons in the ≥90 day time window because the longer time interval between first and second infection might have higher suspicion for reinfection.

2. **Deciding which laboratory tests to conduct**
    Genomic sequencing of paired specimens—that meet the quality criteria below—is needed to investigate reinfection. Single nucleotide polymorphism analysis alone may or may not be sufficient to distinguish reinfection from long-term shedding, as intra-host variation in the mutation rate of SARS-CoV-2 is poorly understood. However, identification of paired specimens from distinct lineages (as defined in Nextstrain or GISAID) serves as higher quality evidence for SARS-CoV-2 reinfection. The quality criteria for testing and levels of evidence are described in more detail below. Genomic testing should meet all of the following **quality criteria** for investigation of reinfection with SARS-CoV-2:

- Genome coverage >100/per base position is recommended for consensus generation
- Q score of consensus >30 with 99% of the genome covered
- 1000x average genome coverage recommended for analysis of minor variation
- Removal of amplicon primer contamination from assembly

In addition:

- Use of high-fidelity sequencing platforms (Q score per read >30) preferred for consensus generation
- If low fidelity sequencing platforms (Q score per read <30) are used, verification of SNPs via alternate sequencing method is encouraged

Evidence level for reinfections using genomic data is as follows:

Best evidence

Differing clades as defined in Nextstrain and GISAID of SARS-CoV-2 between the first and second infection, ideally coupled with other evidence of actual infection (e.g., high viral titers in each sample, positive for sgmRNA, or culture)

Moderate evidence

>2 nucleotide differences per month* in consensus between sequences that meet quality metrics above, ideally coupled with other evidence of actual infection (e.g., high viral titers in each sample, positive for sgmRNA, or culture)

Poor evidence but possible

≤2 nucleotide differences per month* in consensus between sequences that meet quality metrics above or >2 nucleotide differences per month* in consensus between sequences that do not meet quality metrics above, ideally coupled with other evidence of actual infection (e.g., high viral titers in each sample, positive for sgmRNA, or culture)

** The mutation rate of SARS-CoV-2 is estimated at 2 nucleotide differences per month; thus if suspected reinfection occurs 90 days after initial infection, moderate evidence would require >6 nucleotide differences.*

At this time, only paired specimens are being tested to determine reinfection, as protocols for determining reinfection from a single specimen *do not yet exist*.

Other information can provide supporting but not definitive evidence for reinfection, such as culture or sub-genomic mRNA analysis (to detect the presence of replication-competent virus) or serology, which could be useful to document a serologic response to SARS-CoV-2. Aside from laboratory evidence, other supporting evidence for reinfection could include clinical course (COVID-19–like symptoms) and epidemiologic links to a confirmed case.

References

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3. Tomassini S, Kotecha D, Bird PW, Folwell A, Biju S, Tang JW. Setting the criteria for SARS-CoV-2 reinfection – six possible cases. Journal of Infection [Internet]. **2020**. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0163445320305466

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