

REINFECTION UPDATE OCTOBER 2020

RAG 21/10/2020

1. Context

Re-positivity, i.e. individuals tested positive for SARS-CoV-2 (PCR or antigen test) more than once, is frequent. This can be due to prolonged viral shedding, which is common during SARS-CoV-2 infections, or to a reinfection.

The current practice in Belgium for reporting is to count new cases based on a positive molecular test, but individuals with more than one positive test are counted only once, following a process of de-duplication. Until now, there has been no maximum time frame taken into consideration when performing this de-duplication process.

On the other hand, physicians are advised not to retest their patients within 8 weeks after a first positive test, unless the case presents severe symptoms, and to not re-quarantine individuals after high risk contact within 8 weeks after a first positive PCR test. Likewise, the contact tracing system considers a second positive test within 8 weeks as an old infection (prolonged shedding) and no further actions are taken.

The questions addressed in this assessment include the following:

- How can true reinfections and prolonged viral shedding be discriminated?
- What criteria should be used to define a reinfection case?
- What are the implications of possible reinfections for case management (and databases management)?

2. Recommendation

- **The occurrence or reinfection has been described in literature but the relative importance and frequency of it remain unknown.** Viral transmission from reinfected individuals is also unclear, while viral shedding-associated re-positive cases are thought to be non-contagious. Reinfection is currently differentiated from prolonged viral shedding on the basis of genomic sequencing.
- Based on the currently limited evidence and the practical implications, the RAG advises that:

- An interval of at least 8 weeks is maintained to consider a second positive PCR test as indicating a potential reinfection.
- The same rule should be applied when counting daily new cases (i.e. deduplication process limited to an 8-week time frame).
- If a positive PCR-result occurs **more than 8 weeks** after the initial result, laboratories should be encouraged to verify the previously established guidelines to discriminate between an old infection and a potential re-infection. As this evaluation contains multiple elements, it cannot be done at the level of the central Sciensano database (which is used both for reporting and for contact tracing) and old infections should be censored at a lower level. For completeness, we repeat this already existing guidance. A positive PCR result can be considered as an old infection (prolonged shedding) if:
 - the person does not present COVID-symptoms for at least one week (in case of severe symptoms, symptom onset should be at least 4 weeks ago)
 - there was no high-risk contact with a confirmed COVID-19 case in the past 3 weeks
 - the PCR has a low viral load (CT-value > ~32¹, <100,000 copies, negative E-gene)
 - a prior positive PCR (min. 1 week ago) or serology result is available
- In case of **new COVID-like symptoms in a patient that tested positive for SARS-CoV-2 previously, alternative diagnoses should be considered** and ruled out before considering a re-infection. Therefore, testing a panel of other respiratory pathogens is recommended (multiplex PCR).
- In case of suspicion of reinfection (time frame longer than 8 weeks, criteria above not met), a series of parameters should be evaluated:
 - viral load
 - possibility of viral culture from sample
 - serology including neutralizing antibodies
 - whole genome sequencing to assess phylogenetic differences between viruses from both infection episodes (provided the initial sample is still available). As whole genome sequencing also provides information on host cells, it will guarantee that the samples analysed come indeed from the same patient and will therefore exclude errors due to sample mix-up.
- The National Reference Centre should be alerted to possible reinfection cases. The NRC will assist in assessment and share the findings with Sciensano.

¹ should be locally evaluated by each lab individually

3. Background information

3.1. REPOSITIVITY DUE TO PROLONGED VIRAL SHEDDING

Several reports showed that prolonged viral shedding occurs after SARS-CoV-2 infections, positive PCR results have been observed for up to 40 and 60 days post-initial symptom onset (1). One study even described a positive PCR result 104 days after the first positive test in an obstetric patient (2). A Chinese study found that among 619 discharged COVID-19 cases, 87 (14%) re-tested as SARS-CoV-2 positive in circumstances of social isolation (3). Time between hospital discharge and the re-positive test ranged between 2 to 19 days. Re-positivity was more frequently observed in younger patients and/or patients with mild/moderate symptoms (3–5), but there is no established link between a weaker immunity in these cases and the re-positive test.

3.2. CONFIRMED CASES OF REINFECTION

Recently, several cases of reinfection have been documented worldwide (6–11).

- To et al. described reinfection in a 33 year old patient from Hong Kong, 142 days after the first infection episode. In this case the patient was symptomatic in the first episode and asymptomatic in the second (6).
- Tillet et al. described reinfection in a 25 year old male in Nevada, US, 48 days after the first infection episode. This patient was symptomatic during both episodes, but the second episode was more severe (hospitalization needed) (7).
- Larson et al. described reinfection in a 42 year old male in the US, 90 days after the first infection episode. The patient was symptomatic during both episodes, in this case the second episode was also more severe than the first (10).
- Van Elslande et al. reported reinfection in a 52 year old female from Belgium, 93 days after the first infection episode. This patient had mild symptoms during both episodes (8).
- Prado-Vivar et al. reported reinfection in a 46 year old male from Ecuador 63 days after the first infection episode. This patient was symptomatic during both episodes with mild symptoms during the first and moderate symptoms during the second. This patient had a contact with a positive case before the second infection (9).
- Gupta et al. reported reinfection cases in two young health care workers (25 and 28 years old). Both cases were tested during screening campaigns and were asymptomatic when both the first and the second test were carried out 110 days apart (11).

For all these cases, reinfection was established on the basis of comparative whole genome sequencing, and the identification of single nucleotides variations (SNV). Currently there is no clear definition of the phylogenetic differences that are required to consider viruses from two separate episodes as 'different'. Analyses were based on the fact that the virus is expected to mutate by two SNVs per month (7,11). When the viruses from two episodes are associated to different clades or lineages, the evidence of reinfection is stronger (6,8,9).

Intra-host virus evolution studies also indicate that care must be taken when comparing two samples from a same patient. A study by Jary et al. analysed genomic diversity of SARS-CoV-2 in one patient with longitudinal follow-up; they described minority viral populations during the course of infection (12). Although these variants were different between days of sampling and between anatomical sites suggesting that a same variant might not persist over time, population heterogeneity should be kept in mind when analyzing samples from a same patient at two different time points.

In most of the cases described above, the immune response during the first episode was not analyzed in depth. Therefore, an association between a possibly weaker initial immune response and the reinfection episode could not be studied. To et al, however, performed an analysis of the humoral response of the reinfected patient (13). They showed that the patient did mount a neutralizing antibody response during the first episode. This response was however not detected at the onset of the second episode, which indicates waning of the humoral response. Nevertheless, high avidity IgG and high titers of neutralizing antibodies were found some days after reinfection, suggesting a robust response during the second episode that might be due to priming of immunity from the first episode.

3.3. VIRUS REACTIVATION

Re-positivity can also be linked to virus reactivation, as shown in a case report by Lancman et al (14). This study described a patient with B cell acute lymphoblastic leukemia who presented two episodes of COVID-19, the second episode occurring after an immunosuppressive therapy targeting the patient's leukemia. As the second episode occurred when the number of cases was low, shortly after the anti-leukemia therapy, and in the absence of contact with a COVID-19 confirmed case, reinfection appeared unlikely. On the other hand, loss of COVID-19 antibodies due to the immunosuppressive therapy seemed compatible with virus reactivation. In addition, depletion of B cells is a known risk factor for other viral reactivations (14).

3.4. CONTAGIOUSNESS OF RE-POSITIVE CASES/REINFECTION

Prolonged viral shedding-associated re-positive cases are thought to be non-contagious. In the study of Lu et al, no infectious strain could be recovered by culture and no full-length viral genomes could be sequenced from re-positive cases analysed. The risk of virus transmission from the re-positive cases was therefore estimated to be very low (3).

Likewise, the Korean CDC published a report on the epidemiological and contact-investigation of 285 re-positive cases. Re-positive cases were detected either through screening (59.6%) or because of symptoms (44.7%). Time from initial symptom onset and re-positivity sampling ranged from 8 to 82 days (average 44.9 days). Additional virological testing was performed for 108 of these re-positive cases: low viral loads were found in a majority of cases (89.5% had Ct values >30) and viral cell culture was negative for all. For these re-positive cases, 790 contacts were identified, among which only 3 newly-confirmed cases were identified. These 3 cases had additional high-risk exposures to COVID-19 to the exposure to the re-positive case. Overall, no evidence indicating infectivity of re-positive cases was found (15).

On the other hand, onwards transmission following reinfection is currently unknown. No transmission was reported from the reinfection cases described above, but contact tracing and follow-up was not described in these studies.

3.5. ASSESSMENTS AND RECOMMENDATIONS FROM OTHER INSTANCES

- The ECDC published a threat assessment brief on Reinfection with SARS-CoV-2 on the 21 of September 2020.

<https://www.ecdc.europa.eu/en/publications-data/threat-assessment-brief-reinfection-sars-cov-2>

The ECDC highlighted factors to consider when assessing the evidence for a second SARS-CoV-2 infection. These included:

- false positivity, especially in low prevalence settings;
- the time period between the first and the second episode: a longer time-lapse would increase the likelihood of a second infection;
- the identification of infectious virus: virus cultures could be used to discriminate viable virus from non-viable viral RNA shedding; PCR Ct values could also be an indication of virus viability;
- sequence/phylogenetic analysis: differences between virus from two episodes need to be assessed carefully, since the virus can mutate within the host or double infections could happen.

The ECDC performed a survey of member states to identify current approaches for the management of reexposures to SARS-CoV-2. Two countries test potential cases of re-exposure if a time period of **at least two to three months** has elapsed since the first episode. One country (BE) recommends testing in previously positive individuals in case of severe illness requiring hospitalization. The countries holding policies to test only after a specific time period passes do not require quarantine of the re-exposed individuals during that time.

- CDC: (update September 10 2020)

<https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html>

CDC recommends that persons previously diagnosed with symptomatic COVID-19, who remain asymptomatic after recovery, should not be retested **within 3 months** after the date of symptom onset for the initial COVID-19 infection. For persons who develop new symptoms consistent with COVID-19 during the 3 months after the date of initial symptom onset, if an alternative etiology cannot be identified by a provider, then the person may warrant retesting.

4. Data from Sciensano databases

Data from the healthdata.be platform on 8th October indicates that patients with more than one positive tests performed on different weeks represent 7.5% of the total amount of patients tested positive.

Among those, 95,8 % have a time frame window of 8 weeks or less between the first and the last positive tests.

311 (4,2 %) show a novel positive test more than 8 weeks after the first positive test.

166 (2,2 %) show a novel positive test more than 12 weeks after the first positive test.

5. References

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