SARS CoV-2 Re-infection: MAC advisory / guidance

Final version – 6 September 2020

Preamble

SARS-CoV-2 and COVID-19 have been known for less than 9 months. Thus much still has to be learnt, including pathogenesis, disease presentations, recovery, humoral and cellular immune responses, immunity, and the possibility and implications of re-infection.

To date, a small number of cases have been reported in which re-infection is highly likely (meaning that someone who had COVID-19 previously would have been infected again). Several potential re-infection cases and case series had been published previously, but in these other possible scenarios, such as persistence of viral RNA shedding or incorrect laboratory test results, have not been ruled out or are regarded as likely explanations.

Our current understanding of infection with SARS-CoV-2 suggests shedding of infectious virus from 2 – 3 days prior to onset of symptoms for a period of c. 7 days thereafter. It has been observed frequently that infected individuals may test positive for viral RNA (using the gold standard diagnostic assay, based on viral nucleic acid detection, usually by PCR) for much longer, sometimes several weeks. The relatively few cases in whom it has been attempted, infectious virus could not be isolated; it is therefore generally accepted that these individuals are no longer infectious. Low levels of viral RNA shedding are though to explain cases in whom results oscillated between positive and negative over time, being around the limit of detection of the assay which sometimes detects them and sometimes not. Such cases may be mis-interpreted as "re-infection."

It is also well known that the diagnostic PCR test is not 100% accurate and may produce both false positive and false negative results; the former e.g. through contamination of negative samples with positive ones and the latter e.g. due to a suboptimal sample or the timing of sample collection. Results that are "strange" or do not fit the clinical or epidemiological picture should therefore be confirmed by repeat testing, as a first step in investigations of such cases.

Assays to test for specific antiviral antibodies are available but their performance, which depends on the viral antigen used, assay format, timing of sample in the disease process, population prevalence etc., has yet to be characterised across different epidemic settings.

In the meantime, the following are reported from some patients diagnosed with COVID-19:

i. Individuals who test persistently positive by PCR for several weeks after disease onset raising concerns about whether they are infectious;

ii. Individuals who continue to display signs and symptoms of disease for several weeks or months (sometimes referred to as "long Covid" or "long-haulers");

iii. Individuals who test positive on PCR then subsequently negative and at a later stage positive again.

iv. In late August 2020, a small number of cases have been reported of patients who had documented COVID-19 infection and were subsequently found to be infected again; genetic analyses suggest these were genuine re-infections with a genetically different virus (rather than persistent infection).

While the frequency of these scenarios is currently unknown, and while true re-infections are thought to be rare, they give rise to concerns about ongoing viral replication and transmission risk to others, especially in health care and other occupational settings. It is assumed but has not been shown beyond doubt yet whether past infection confers immunity against renewed infection, and if so, for how long. Such constellations of results also lead to speculations about the best clinical management of patients with "long Covid". Finally, it needs to be determined how to differentiate between a subsequent new infection (i.e. genuine re-infection) as opposed to reactivation of a possibly persistent infection, neither of which has so far conclusively been shown to occur.

This advisory provides guidance to clinicians and health care workers on how to interpret or investigate these scenarios better and highlights opportunities for further research to understand underlying mechanisms of immune responses and transmission dynamics.

Problem statement

Can someone who has recovered from COVID-19 be re-infected with the SARS-CoV-2 virus? There are several reports in the peer-reviewed literature, press and social media of cases of possible re-infection. If this is possible, within the short time period that SARS-CoV-2 has been spreading, it would have important clinical and public health implications as it would indicate that no reliable protective immunity persists after initial SARS-CoV-2 infection.

Literature reviewed

The Alberta Health Services COVID-19 Scientific Advisory Group has updated its guidance on the matter on 12 May 2020. This has remained valid by and large until 22 August 2020. Other agencies, including the NICD and the U.S. CDC, have also issued guidance. The MAC Advisory is largely in line with all three but has been updated to account for the cases of plausible re-infection published in late August 2020.

There is a conclusive body of evidence about the period of infectiousness and the required duration of isolation, with very little uncertainty and previously issued MAC advisories have addressed this notably for the workplace and other settings. The issue of immunity following COVID-19 is being debated heatedly, with new studies (many using specific methods looking at certain aspects only, and often not yet peer-reviewed) appearing almost daily. There is a need to distinguish between a detectable immune response (often used as an epidemiological marker) and a functional immune response, which may be deleterious (e.g. through "enhancing" antibodies) or give protective immunity – whether it be cellular or humoral. Further investigative research is required to identify which immune parameters correlate with protection or plausible susceptibility to re-infection. Currently, this is unknown; South African immunologists are providing very useful regular updates on https://www.saimmunology.org.za and https://www.immunopaedia.org.za.

The following are questions and answers to salient points about re-infection:

- ***Does re-infection with SARS-CoV-2 occur in human beings?***

Until recently, no cases or case series had been documented well enough for any to be recognised as proven re-infection; in all of them, alternative explanations for the findings were plausible. During the last week of 22 August 2020, however, a number of cases have become known (only one of them published *(Hung et.al*), another is available as a manuscript (*Tillett et.al*) yet to be peer-reviewed, and several more (*Promed*) have been reported in press conferences only with varying degrees of detail. At least some of these recent reports seem to provide good evidence for re-infections with a genetically different virus. Not all seem to have confirmed the implicated samples as being from the same patient or to have undertaken immunological investigations.

There now appears to be some evidence for SARS-CoV-2 re-infection; how common this is and its implications at an individual and population level remain to be elucidated. The patient in Hong Kong who was previously infected with SARS-CoV-2 was only identified because of a returning traveller testing policy in place but had no signs and symptoms to indicate that he was infected. Comparing viral sequences from his previous infection with the current infection confirmed that the current virus was different from that isolated during his earlier bout of infection.

- ***Is there evidence of SARS-CoV-2 re-infection from animal experimentation?***

Rhesus macaques and domestic cats that previously had been infected with SARS-CoV-2 experimentally were re-challenged between 28 and 35 days post infection. They did not develop active infection again, suggesting at least short-term protective immunity against renewed infection is possible (*Chandrashekar et.al, Deng et.al. York et.al*).

A recent, not yet peer-reviewed paper (*Addetia et.al*) describes an observational study ("natural experiment") in which individuals with pre-existing neutralising antibodies from previous COVID-9 seemed to be protected against renewed infection during an outbreak with a high attack rate.

- ***Does re-infection occur with any of the other six coronaviruses known to infect human beings?***

There is no definitive evidence of re-infection from the original SARS-CoV-1 outbreak in 2003 or with MERS since 2012 (SARS-CoV-1 is about 70% related genetically to SARS-CoV-2). However, the SARS outbreak was well controlled through a massive global effort before there was extended human-to-human transmission, minimising the chances of subsequent exposure of someone previously infected. For the endemic human coronaviruses (HCoV 229E, OC43, HKU1, NL63), repeated infections have been described by a number of studies conducted over four decades. These re-infections may occur at relatively short intervals (in a recently published study, re-infection was found after a median time interval of 37 weeks) (*Galanti et.al*).

- ***Is there evidence for re-infection from other acute viral infections of humans?***

There is very little evidence of re-infection with other viruses causing acute illness and death in a proportion of infected people. Ebola is a case in point – where there is very little, to no, evidence of re-infection in those people who recover (*MacIntyre et.al).*

- ***Does antigenic variability make SARS-CoV-2 prone to evade immune responses?***

Not according to current knowledge. While several different clades of SARS-CoV-2 can be distinguished (https://nextstrain.org/narratives/ncov/sit-rep/2020-08-14), the virus evolves comparatively slowly and the biological significance of mutations found so far is uncertain. A phenomenon akin to "antigenic drift" as seen in influenza viruses has not been found in SARS-CoV-2. However SARS-CoV-2 only emerged very recently so there are no longer-term observations so far.

- ***Does persistent SARS-CoV-2 infection occur?***

This has not been described. The occurrence of "long Covid" syndrome with lingering symptoms that may persist for many weeks and months after acute COVID-19 is by now widely accepted. However this is not considered to be due to ongoing active SARS-CoV-2 infection (which would mean active viral replication) but more likely to be caused by an over-exuberant inflammatory host response. These patients suffering from "long Covid" do not seem to be infectious (*Mahase et.al, Alwan et.al*).

- ***How long can patients be SARS-CoV-2 positive?***

One has to distinguish carefully between detectable viral genome (RNA, usually diagnosed by PCR) and infectious virus (which can only be identified using isolation on cell culture which is not widely available). While a substantial proportion of COVID-19 patients seem to shed viral RNA for longer than 10 days after onset of illness, sometimes for several weeks or even months, no infectious virus has been found beyond day 10 after either illness onset in mild cases, or after no longer requiring oxygen support in more severe cases (*Wölfel et.al, Corsini et.al*). Do false-positive and false-negative SARS-CoV-2 tests occur?

False-positive PCR results would usually be due to contamination. This could happen at different stages in the testing process, more often when many infected patients are being tested as this increase the risk of contaminating negative samples with positive ones.

False-negative results can be due to poor sample quality or problems in the laboratory. Virus levels in patients' respiratory tracts are highest around the onset of symptoms; if a sample is taken a week or more afterwards there may be so little viral genome that the test result can be negative, even if the patient had infection (*Görzer et.al, Wernike et.al*).

- ***Can antibody testing help determine past infection and/or immunity?***

Being antibody positive will indicate viral exposure. However, if tested too early after infection, before an antibody response occurs (in most patients by days 7-14 and in the vast majority from 3 weeks after onset of symptoms), patients with COVID-19 may test antibody negative. Likewise, if tested too late (e.g., beyond 4-6 weeks), the antibody levels might have declined to below the detectable range of the test and the test will be negative. A false-positive result may be due to insufficient specificity of the test used or the presence of cross-reacting antibodies.

Furthermore, the detection of antibodies does not necessarily equate with immune protection.

  - It is thought that neutralising antibodies will better reflect immunity, but the minimum antibody titre needed to confer immunity is not known. The biological significance, if any, of other types of antibodies, as measured by different (including the commercially available) assays, is unknown.
  - Infections by some animal coronaviruses may lead to even more severe disease in the presence of so-called "enhancing antibodies", a phenomenon not yet described in human coronavirus infections.
  - Antibody tests do not measure cellular immune responses which may be relevant in conferring immunity.
  - A positive antibody test result should not be regarded as proof of immunity and must not be used to reduce or abandon protective measures (*Gray et.al, Mayne et. al*).

- ***What could be the reason for someone testing positive, then negative and then again positive for SARS-CoV-2?***

  (a) The initial diagnosis of COVID-19 could have been based on a false-positive test result.

  (b) The later time-point positive test result could be false-positive.

  (c) The negative test result in between the positive ones could be a false-negative.

  (d) All results could be correct but negative test results alternating with positive ones could be due to low levels of viral RNA which fluctuate around the lower limit of detection of the assay used. Low viral RNA levels may or may not be detected by the test, depending on the quality of the clinical specimen and the efficiency of its preparation and testing in the laboratory. If different tests are used, this could add to this kind of variability (refs).

  (e) Recently, more solid evidence has emerged of a few persons who had been diagnosed with COVID-19 previously being re-infected by the SARS-CoV-2 virus. One of these cases has been published (*Hung et.al*), another is available as a manuscript yet to be peer-reviewed (*Tillett et.al*), and the remaining ones are press reports (*ProMED*) providing varying degrees of detail. In contrast to previous reports of "re-infections", that could be explained by alternative scenarios, at least some of these recent reports seem to provide good evidence for re-infections with a genetically different virus. Not all seem to have confirmed the implicated samples as being from the same patient or to have undertaken immunological investigations.

  (f) At this stage, the phenomenon of possible SARS-CoV-2 re-infection does not have implications for both individual behaviour nor societal pandemic control. It is unclear how often this may occur and how it may be linked to certain patient or viral characteristics. Any such case should be investigated thoroughly for the benefit of the patient and for infection control purposes, but also to obtain much-needed scientific information (for advice see below).

Recommendations

- To fully address the problem statement, there is an urgent need to conduct scientific studies to investigate possible cases of re-infection. These would entail virus isolation and/or viral RNA detection and genetic sequencing, confirming the implicated samples as being from the same patient, as well as assessing humoral and cellular immune responses over time. Such studies will necessitate the medium-term storage of samples from SARS-CoV-2 positive patients so that all results can be confirmed by repeat testing and the virus causing the previous infection can be genetically analysed along with the current one. Assessing antibody and immune cell reactivities sequentially qualitatively and quantitively will be of great value. To allow such studies, it is highly recommended that laboratories attempt to store all positive samples for prolonged periods of time. As soon as, for whatever reason, the possibility of re-infection is raised, a concerted effort should be made to trace and preserve all previous and current samples from the patient, while approaching a research laboratory (Profs Penny Moore or Anne Gottberg, NICD, www.nicd.ac.za; Prof Tulio de Oliveira, KwaZulu-Natal Research Innovation and Sequencing Platform, https://www.krisp.org.za) to obtain further guidance.
- Once a diagnosis of SARS-CoV-2 infection has been made by a diagnostic laboratory using a viral detection assay following established guidelines and criteria, there is generally no need for repeat

testing to establish if the person tests negative after their 10 day isolation period. At this stage many patients will still have detectable viral RNA. Regardless, individuals are deemed non-infectious at that stage and do not pose a threat to co-workers or co-inhabitants and may thus be de-isolated and return to work.

- Repeat viral testing is not needed to assess fitness to return to work (which is based on clinical criteria, not virological tests), nor to determine whether isolation precautions can be lifted (which is based on time since onset of symptoms or no longer requiring oxygen support, depending on disease severity, and independent of possibly prolonged shedding of viral RNA which does not indicate infectiousness).
- A patient previously diagnosed with COVID-19 who now presents with signs and symptoms suggestive of or consistent with COVID-19, should in the first instance be investigated for alternative diagnoses, as other (infectious and non-infectious) diseases may present in a similar way. Repeat testing for SARS-CoV-2 infection by molecular tests may be considered, too, but a positive result must be interpreted cautiously. Within 3 months (90 days) of the diagnosed infection, and possibly beyond, it is likely to reflect ongoing shedding of viral RNA (genome).
- If the result is positive, especially in a patient first diagnosed more than 3 months (90 days) ago, it should be complemented by additional testing including virus isolation (viral culture), full genome sequencing, confirmation of specimen identity, and antibody tests. It is highly recommended at this stage to immediately make attempts to identify and try and have preserved any previous samples from this patient and to consult an expert laboratory.
- Both viral and antibody tests can be performed in individuals previously diagnosed with COVID-19, preferably as part of scientific studies, but should for the time being not be used for clinical decisions nor to decide on appropriate infection precautions.
- Given the lack of knowledge as regards immunity and its duration, everyone – including those who have had or is believed to have had COVID-19 and their contacts – should continue to practice all usual COVID-19 precautions, neither assuming immunity nor non-infectiousness.
- For an individual who has been diagnosed with COVID-19 previously and now has significant exposure within 3 months of the previous diagnosis, the advice is to not quarantine but strictly observe non-pharmaceutical interventions. If compatible illness develops, sick leave must be taken and the illness investigated (see above). If significant exposure occurs more than 3 months after the previous diagnosis, renewed quarantine is recommended.
- As criteria for SARS-CoV-2 testing may change, e.g. to incorporate screening prior to medical procedures or at hospital admission, it is likely that an increasing number of “strange” scenarios will be found, including what might be interpreted as possible re-infection.

This document is based on evidence available as of 2 September 2020. Given the rapidly evolving knowledge of SARS-CoV-2 infection and immune responses to it, this guidance likely will need to be revised regularly.

References

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