

Release from Isolation for Cases of COVID-19 in Australia Summary of Evidence

This paper is an attachment to the [joint CDNA and PHLN statement on Revisions to the Australian criteria for release from isolation and return to high-risk settings for persons recovering from COVID-19](#). This document summarises the evidence taken into account for the 4 June 2020 revisions to the release from isolation criteria in the [CDNA COVID-19 National Guidelines for Public Health Units](#); further details are outlined in the statement and the Guidelines.

Viral load characteristics

- Viral RNA levels from upper respiratory specimens appear higher in the initial stages of illness compared with later in the illness.^{1,2,3,4}
- Several studies indicate that viral RNA levels tend to peak in the first week of illness, with one study showing a peak at day 4,³ and another showing a peak at days 5–6.⁵ This indicates transmission is most likely to occur early in the illness with infectivity gradually reducing over time.¹
- A small study involving five patients used nasopharyngeal swabs to examine viral loads over the course of their illness⁶. In all but one patient (who died), viral load became negative between days 9 and 14, decreasing over time. The other patient remained PCR positive until death. The duration for the PCR test to become negative, after resolution of symptoms, was reported for two patients at 1 and 8 days respectively.⁶
- In one study, of the 21 patients out of a sample of 23 who survived, one-third had persistent viral shedding for >20 days post symptom onset.²
- Viral shedding has also been shown to continue after symptom resolution.^{3,7}

These findings have led many countries to implement a range of release from isolation criteria with varying requirements for time since symptom onset, time since symptom resolution and negative PCR tests.

Factors affecting duration of viral shedding

Studies have shown varying durations of viral RNA shedding among COVID-19 cases, including duration of viral shedding following resolution of symptoms.

- Viral shedding *may* depend on severity of illness.
- Research shows prolonged durations of viral shedding are more likely in hospitalised patients.
 - o One study indicated a median duration of 20 days (range 8–37 days) of viral RNA shedding in hospitalised patients. The median duration of viral shedding in severe cases was 19 days (17–22) and 24 days (22–33) in those with critical disease status.⁸
 - o Another study showed a median duration of viral shedding of 17 days (range 13–22 days); patients with longer SARS-CoV-2 RNA shedding also tended to have greater duration of fever (median 11 days, IQR 8–14 days).⁹

- Comparatively, patients with mild illness were found in some studies to have a shorter duration of viral RNA shedding.
 - o Several studies indicate asymptomatic and mild cases tend to shed for approximately 9 to 10 days (range 6 to 15 days), with 90% of patients with mild illness testing negative on nasopharyngeal swabs by 10 days post onset of symptoms,^{7,10,11} and all severe cases testing positive at or beyond day 10 post onset of symptoms.¹⁰
- Conversely to this evidence, other studies found a *longer* duration of viral RNA detectable for mildly symptomatic patients.
 - o One study showed a median of 12 days after symptom onset,¹² whilst another showed a median of 15.6 days after symptom onset (95th percentile 32.8 days).¹³ It is important to note that one study only involved hospitalised patients and the other a small sample size which may impact the reliability of this data.
- Advanced age may be correlated with prolonged viral shedding.
 - o One study found a median duration of viral shedding of 23 days. Older age was associated with an increased likelihood of prolonged (>23 days) viral shedding (OR 1.03, 95% CI 1.00–1.05, p=0.03), independent of comorbidities.¹⁴
 - o A study involving 56 people, with 299 samples of RT-PCR tests for SARS-CoV-2 detection showed that median duration of viral RNA shedding from naso- or oropharyngeal specimens was 24 days, and the longest was 42 days. Those with prolonged viral shedding (>24 days) tended to be older, and more likely to have co-morbidities (such as diabetes and hypertension).¹⁵
 - o Studies have supported delayed clearance of SARS-CoV-2 RNA in older people.^{15,16} This may be because older patients typically generate less robust innate and adaptive immunity, limiting the viral clearance, and hence accounting for prolonged viral shedding.
- A small number of studies have shown that being male is an independent risk factor for prolonged viral shedding.^{9,9}

Viral shedding and infectivity

The detectability of viral RNA does not always correlate with viral transmissibility. Nucleic acid detection cannot differentiate between infective and non-infective (dead or antibody-neutralised) viruses, which is a major limitation of this method of testing.

- One study found viral RNA was detectable for more than one month after illness onset, however live virus could not be detected after 3 weeks.¹⁷
- In a study of nine patients with mild COVID-19 infection, infectious virus was able to be isolated from naso/oropharyngeal and sputum samples during the first 8 days of illness, but not after this, despite continued high viral RNA levels. Infectious virus was also not able to be isolated when the viral RNA level was <10⁶ copies/mL.
- A study of 4 medical professionals who had 2 consecutive negative RT-PCR tests found all four had positive tests when repeated 5 to 13 days later. They continued to be asymptomatic, with no radiological changes. No family members (i.e. close contacts) were reported to have contracted COVID-19, however this should be interpreted with caution, as they were medical professionals, and took special care to mitigate risks during home quarantine.¹⁸

- A Taiwanese study examined over 2,500 close contacts of 100 patients with COVID-19. Of the 22 secondary cases, all had their first exposure to the index case within 6 days of symptom onset. No infections were documented in the 850 contacts whose exposure was after 6 days.⁴
- A study that followed 262 COVID-19 patients post discharge, found that 38 (14.5%) were re-detected to be SARS-CoV-2 RNA positive during their follow up period.¹⁹ 97.4% of these (n=37) were under 60 years, and patients under 14 years old were more common than the 14-60 years age group.
 - o Re-positive patients more likely had earlier RNA negative conversion than those who remained PCR negative
 - o As all those in the study were required to remain in isolation, 21 close contacts of the re-positive patients were reported. None of these were found to be positive for SARS-CoV-2 and none had symptoms consistent with COVID-19.

Of those who continued to have detectable RNA, concentrations of detectable RNA 3 days post recovery are usually in the range at which replication-competent virus has not been reliably isolated by CDC (excludes data from children).²¹

- A study incubated 90 SARS-CoV-2 RT-PCR positive samples on Vero cells. Viral growth was demonstrated in 28.9% of samples. There was no growth in any samples collected >8 days after symptom onset in the case, or in samples with a cycle threshold of >24. This indicates that patients may have low infectivity if their PCR tests have a cycle threshold of >24 or if >8 days have transpired since symptom onset.²⁰
- The US CDC changed the rules for release from isolation from 7 days to 10 days after symptom onset and at least 72 hours after recovery (i.e., the resolution of fever with no anti-pyretics, and progressive improvement or resolution of other symptoms), as RNA concentrations at this time have been found to be below the levels of replication-competent viral isolation.²¹
 - o Live SARS-CoV-2 has not been isolated from upper respiratory specimens more than 9 days after onset of illness.²¹

Recent Korean CDC investigation and analysis of re-positive cases

A recent report from the Korea Centers for Disease Control and Prevention examined 285 patients who tested positive for SARS-CoV-2 after previously being cleared from isolation (447 were identified, but contact and epidemiological investigation were not completed for all at the time of reporting).²²

- Of 108 re-positive cases selected for live virus culture isolation, infectious virus was not isolated in any viral cell culture testing.
- Of 790 contacts, 27 cases were found, but 24 had been previously confirmed as cases. Of the three newly confirmed cases, other than their exposure to the re-positive cases during their respective re-positive period, all had history of contact with Shincheonji religious group or a confirmed case in their family, suggesting transmission did not occur from re-positive cases.
- A higher percentage of re-positive cases were found in nursing home patients.
- The study concluded that management of confirmed cases after discharge from isolation and management of re-positive cases will no longer be conducted.

Other studies have also commented on re-positive PCR after two consecutive negative PCR tests previously:

- One study¹⁵ found that of the 56 patients recruited, four had two negative RT-PCR tests, followed by a positive result.
- Another study² found that one patient with complete symptom resolution tested positive for SARS-CoV-2 again after 2 days of negative findings (from 23 patients).

High-risk settings

There is limited evidence regarding the risk of onward transmission within a high-risk setting from cases who have clinically recovered but remain PCR positive. High-risk settings are considered to be settings where there is potential for rapid transmission and ongoing chains of infection to occur.

- One study of persistent PCR positive COVID-19 cases following hospital discharge suggested two weeks were needed for ongoing observation and supervision prior to release from isolation.²³
- Supporting this, another study suggested that, to account for persistent PCR positives, all hospital discharged patients should be home quarantined for at least 14 days.²⁴
- Evidence supports the importance of infection control and return to work policies to be balanced with potential healthcare worker shortages:²⁵
 - o If using RT-PCR and requiring two consecutive negative results 24 hours apart, the window of infectivity may be over-estimated and healthcare workers may be unnecessarily excluded from work. It would, however ensure that viral shedding has ceased.
 - o Serology may be informative, but is not part of most return to work strategies. The biggest limitation is its application to those who do not seroconvert or who are weak seroconverters, which has been estimated to be as high as 16.7% for IgG at 42-day follow-up in one study.²⁵
- The US CDC has more stringent requirements for people whom there is low tolerance for post recovery shedding and infectious risk given the potential for adverse outcomes. This includes:²¹
 - o Persons who could pose a risk of transmitting infection to:
 - Vulnerable individuals at high risk for morbidity or mortality from SARS-CoV-2 infection, or
 - Persons who support critical infrastructure.
 - o Persons normally residing in congregate living facilities (e.g. correctional/detention facilities, retirement communities, ships) where there might be increased risk of rapid spread and morbidity or mortality if spread were to occur.
 - o Persons who because they are immunocompromised may have prolonged viral shedding.⁷

Singapore Academy of Medicine—Position statement on period of infectivity

The Chapter of Infectious Disease Physicians and the National Centre for Infectious Diseases at the Academy of Medicine, Singapore, released a joint paper on the period of infectivity for COVID-19 patients and how this can inform release from isolation protocols. The paper summarised available evidence on the Epidemiologic, microbiologic, and clinical data for the period of infectivity, as well as data on the shedding of viral RNA, 're-positive' cases, and the uncertainty of infectiousness in asymptomatic and pre-symptomatic persons. The paper concludes that the infectious period may persist for about 7–10 days after the onset of symptoms, and that viable virus has not been identified after week two of illness, regardless of any PCR positive results.²⁶

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