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COVID-19: Ongoing Viral Detection and Repeat Positives

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Introduction

- There is emerging evidence from laboratory and epidemiological studies regarding the duration of SARS-CoV-2 detection, viability of the virus, and infectiousness to contacts. Recent studies have provided reassurance for non-test based approaches to clearing cases from isolation.
- There is emerging evidence regarding repeat positive real-time reverse transcriptase polymerase chain reaction (RT-PCR) tests from respiratory specimens collected after cases have been cleared of their COVID-19 infection. Laboratory and epidemiological evidence to date suggest repeat positives after clearance represent ongoing shedding of non-viable virus that do not pose a transmission risk.

Background

- Prior to May 28, 2020, the Ontario testing and clearance guidance recommended a non-test based approach to clearance of COVID-19 cases for mild to moderate illness, and a test-based approach for COVID-19 cases that have been hospitalized for their infection, and either remain in hospital or are discharged to a congregate living setting.
- There is currently no guidance for the management of individuals who have a repeat positive result after clearance.

Methods

- We reviewed existing Public Health Ontario evidence summaries, as well as new relevant articles and evidence summaries to assess laboratory and epidemiological evidence related to the period of communicability after symptom onset.
- We reviewed published and surveillance evidence regarding the laboratory and epidemiological evidence for virus viability and communicability of individuals with repeat positive results.

Results

Laboratory Evidence of Viral Viability at the End of COVID-19 Infection

- Two studies were reviewed in PHO's [What We Know So Far About... Viral Detection](#)¹ summary that assessed viral culture results as an indication of virus viability.

- [Wölfel R et al.](#)² conducted cultures from oro- or nasopharyngeal swabs, sputum and stool from nine COVID-19 RT-PCR positive patients. In the first week after symptom onset 16.7% of swabs and 83.3% of sputum tested positive by culture. No PCR-positive stool samples (taken between day six and 12) ever tested positive by culture. No positives were found after day eight from symptom onset despite testing of one swab daily from days nine to 12 and one or two sputum samples on all but one day from days nine to 13.
- [Aarons et al.](#)³ described a COVID-19 outbreak in a skilled nursing facility in Washington State with 89 frail, elderly residents. Testing by nasopharyngeal or oropharyngeal swab was offered to residents twice, with a week between each round of testing. Of the 76 residents who were tested, 48 (63%) were positive. Viral cultures were positive from six days before to nine days after the onset of typical symptoms (one specimen was culture positive on day 13 after atypical symptom onset).
- [Bullard J et al.](#)⁴ assessed 90 respiratory specimens from which 26 samples were successfully cultivated. They found positive cultures were observed up to and including day seven post symptom onset, and most likely between days one and five.⁴ The authors found virus culture was negative when RT-PCR cycle-threshold (Ct) values were greater than 24. Ct values are inversely related to the viral load, so higher Ct values represent more weakly positive results.
- The [United States' Centers for Disease Control and Prevention](#)⁵ assessed 12 patients and found Ct values and duration of RT-PCR detection from respiratory specimens did not differ by hospitalization status or oxygen requirement. Viral cultures were obtained from nine patients from specimens collected between day 1–9 from symptom onset; however, virus isolation was not attempted on positive specimens collected after day nine from symptom onset. [Follow-up analysis](#) with inclusion of 14 patients found probability of successful isolation falls to 50% at day four after symptom onset, and to 20% at day eight, with probability approaching zero after day nine.⁶ Attempts to culture virus from upper respiratory specimens have been largely unsuccessful when viral burden is in low but detectable ranges (i.e., Ct values higher than 33–35).⁶

Epidemiological Evidence of Communicability at the End of COVID-19 Infection

- [He X et al.](#)⁷ analyzed data from 77 COVID-19 infectee-infectior transmissions based on publicly available sources within and outside China. In six transmissions, the secondary cases' exposure to the primary case occurred only after the onset in the primary case. Of the four transmissions that provided informative data, the exposure ranges of the secondary cases were 3–5 days, 4–5 days, 5–6 days and 5–10 days after onset in the primary case.
- [Cheng H-Y et al.](#)⁸ studied 100 COVID-19 patients and their 2761 close contacts. All 22 secondary cases had their initial exposure to the primary cases within five days or less of the onset in the primary case.

Laboratory Evidence of Repeat Positives after Clearance

- Four studies⁹⁻¹² were assessed in PHO's [What We Know So Far About... Viral Detection](#)¹ on the detection of viral RNA after recovery. The four case studies identified individuals with serial sampling who had confirmed clearance with two consecutive negative RT-PCR results 24 hours

apart, and then subsequent positive tests ranging from three to 13 days after confirmed clearance. All cases were asymptomatic on repeat positive testing.

- [Ye et al.](#)¹³ found five out of 55 patients followed after discharge from hospital subsequently had a positive PCR test between 4–17 days after their negative test result. Four of the five had mild symptoms.
- [Yuan et al.](#)¹⁴ found 25 out of 172 patients discharged from hospital after clinical improvement and two consecutive negative RT-PCR specimens tested positive again. Average time from negative to positive test was 7.32 days (range 2–13 days) during 14 days of follow-up post-discharge with respiratory specimen collection every three days. Mild symptoms were present in eight (32%) of the cases.
- [Korea Centers for Disease Control and Prevention \(KCDC\)](#)¹⁵ assessed 285 cases of repeat positive results. Of 226 cases with symptoms at time of initial infection, repeat positives after discharge (data not provided on whether discharge criteria included two consecutive negative RT-PCR specimens) ranged from 7–82 days from initial symptom onset, and 1–37 days from discharge from isolation to repeat positive. 44.7% had symptoms at the time of repeat positive; virus culture was attempted for 108 cases and all had negative results. Among 93 of the cases, eight (10.5%) had a Ct value 25–30, while the rest were greater than 30 (data not provided on reason for 15 cases with viral culture but no Ct value). Of 23 repeat positive cases with first and second serum samples, 96% were positive for neutralizing antibodies.

Epidemiological Evidence of Communicability of Repeat Positives after Clearance

- From 285 repeat positive cases, [the KCDC](#)¹⁵ assessed 790 contacts. Monitoring was for a minimum of 14 days. There were three newly confirmed cases among the contacts; however, all had other significant exposures in addition to the repeat positive case. One of the three newly confirmed cases had an indeterminate PCR result so could not be cultured, and virus culture was negative for the other two newly confirmed cases. The KCDC concluded that there were no transmissions from COVID-19 cases with repeat positive RT-PCR results.

Discussion

- Ontario's approach to non-test based clearance requires a minimum of 14 days from symptom onset, and that the case is afebrile and symptoms are improving (or 14 days from specimen collection date, if the individual has never had symptoms). This duration is longer than other jurisdictions (seven days in the [United Kingdom](#)¹⁶ and 10 days in the [United States](#)¹⁷ and [Public Health Agency of Canada](#)¹⁸). It is also longer than what has been reported as the last day from symptom onset when virus has successfully been cultured from respiratory specimens (most less than 10 days, one specimen at day 13), including cases with severe illness and frail, elderly residents of long-term care. It is also longer than what has been reported in the literature regarding epidemiological evidence of timing of when cases have transmitted to contacts. While some sub-populations have been under-represented in studies to date, the use of 14 days from symptom onset allows additional confidence that cases are unlikely to be communicable after clearance.

- As the pandemic continues, there have been several reports of repeat PCR-positive cases after clearance (so far less than three months after initial illness episode) in Ontario, arising from asymptomatic surveillance testing, as well as individuals presenting with new symptoms (with and without new high risk exposures prior to new symptom onset) after clearance. To date, the majority of these cases have had high Ct values (greater than 30) indicating lower viral load levels, which is most consistent with ongoing persistent shedding. However, at least one case has been reported in Ontario with new symptoms, new high risk exposure and a Ct value less than 25 two months after initial PCR-positive result.
- Based on the surveillance evidence from Korea, repeat positive results in the near-term after clearance do not appear to represent a public health transmission risk. Given uncertainty about duration of immunity, and likely potential for future waves of the pandemic, surveillance is still required to be vigilant for the possibility of true re-infection cases. Additionally, evidence to date is lacking on cases with new high risk exposures prior to repeat positive results.

Limitations

- Studies of virus viability are limited and may not fully represent all patient groups (e.g., immunocompromised individuals, children, individuals with severe infection) where variations in viral shedding would be anticipated.
- There has been limited follow-up time in the pandemic to assess the possible duration of viral shedding. The median range of viral shedding has been reported to be 11–20 days, with a single case report of persistent RT-PCR results for over 72 days after symptom onset.¹⁹
- The sensitivity of viral culture in some studies may be limited by use of frozen samples, and variability in culture methods used in different laboratories. The decreased sensitivity is demonstrated by the inability to culture virus from specimens with Ct values less than 25, and from samples collected near symptom onset when cases would be expected to be infectiousness⁴ and shedding virus.
- Ct values generated from different assay systems within the same laboratory, or from different laboratories, are not directly comparable and do not necessarily reflect the same viral load due to inter-assay and inter-laboratory variability.
- The majority of papers on repeat positives are among cases who were monitored in quarantine for an additional 14 days after clearance, which means it is unlikely they had new high risk exposures prior to their repeat positive, and were unlikely to pose a transmission risk to others if they were in quarantine. The Korea surveillance report on repeat positives did not provide information on whether the primary cases had a new high risk exposure prior to their repeat positive test.¹⁵
- Reports of repeat positives after clearance have been described for individuals up to 37 days from discharge from isolation. It is not known for how long repeat positives may occur after initial infection.

Conclusion

- This analysis supports the recently updated Ontario guidance on when cases of COVID-19 can be cleared from isolation:
 - All patients with COVID-19 can be cleared from isolation after 14 days from symptom onset if afebrile and other symptoms improving for at least 72 hours²⁰
 - Limit the use of test-based clearance for admitted patients with severe infection at the direction of hospital infection prevention and control
- This analysis suggests the public health management of cleared COVID-19 cases with repeat positive results should advise:
 - Avoidance of repeat testing in the near-term after clearance (within 90 days) as prolonged shedding of non-viable virus is not uncommon
 - Public health follow-up in terms of case and contact management is not required for repeat positive results in cases without re-infection risk.
 - Surveillance and public health guidance is needed to investigate and manage cases that may represent true re-infection risk, specifically:
 - New high risk exposure
 - New severe COVID-19-like illness presentation
 - New positive result greater than 90 days after initial result (based on reported duration of persistent positivity)¹⁹

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