



Re-Infection and Sustained Viral Detection

Disclaimer:

This *Quick Response Report* was published on May 1, 2020. Given the rapidly changing nature of the coronavirus pandemic, some of the references included in this report may quickly become out-of-date. We further caution readers that researchers at the Newfoundland & Labrador Centre for Applied Health Research are not experts on infectious diseases and are relaying work produced by others. This report has been produced quickly and it is not exhaustive, nor have the included studies been critically appraised.

Readers should note that some text below is **highlighted** for emphasis

Original Inquiry

1. Is re-infection likely or are the results out of China simply positive polymerase chain reaction (PCR) tests post-infection? What is the current evidence differentiating between: a) a new, second (or subsequent) infection for a recovered COVID-19 case; and b) a positive test result from a PCR test that is picking up the first (or original) infection?
2. What is the significance of sustained viral detection (positive PCR) after incubation period is complete? What does the current evidence indicate about elevated viral loads, measured by polymerase chain reaction tests, in terms of potential for [re-]developing COVID-19 and/or becoming infectious?

Key Definitions

Antibody: An antibody, also called an immunoglobulin, is an immunological protein complex produced in response to a foreign substance (antigen), e.g., virus or bacteria. Antibodies are specific to antigens and affix to them as part of the immunological response. ([LINK](#))

Immunity and Reinfection: Immunity to a pathogen through infection is a multi-step process that typically takes 1-2 weeks. A viral or bacterial infection triggers a non-specific innate response involving macrophages, neutrophils, and dendritic cells. It is followed by **cellular immunity**, an adaptive specific response involving B-cells, which produce antibodies, and T-cells which target infected and/or foreign cells. Cellular immunity may clear the virus from the body, and may prevent progression to severe illness or **re-infection** by the same virus. ([LINK](#))

Immune Response Test: A serological (blood) test that assesses immune response to a virus or bacteria by detecting the presence of antibodies specific to the infection. Traditional tests are laboratory-based and require a blood draw, while newer systems require finger prick blood samples. ([LINK](#))

Immunity Passports: Some piece of identification to “enable individuals to travel or to return to work assuming that they are protected against re-infection.” ([LINK](#))

PCR Test: Polymerase Chain Reaction (PCR) tests for the presence of the virus’s genetic material (RNA) from a sample (e.g., nasal or throat swab). PCR can indicate an active, current infection. They do quantify viral load. ([LINK](#))

Summary

We found a small number of guidelines and expert statements. While we did not find any systematic reviews at this time, we did find 5 other reviews. We found several primary research articles as well as several news articles. We also found two studies that are on-going or awaiting prioritisation that were included for future reference. Our findings are summarized below.

The literature indicates that there is insufficient evidence to conclude one way or the other if COVID-19 can re-infect, and inconsistent evidence to interpret the significance of sustained viral detection.

Guidance

CDC. Clinical Questions about COVID-19: Questions and Answers. Updated April 16, 2020. ([LINK](#))

- “The immune response, including duration of immunity, to SARS-CoV-2 infection is not yet understood. Patients with MERS-CoV are unlikely to be re-infected shortly after they recover, but it is not yet known whether similar immune protection will be observed for patients with COVID-19.”

ECRI (USA). Prudent use of SARS-CoV-2 antibody testing: Avoiding false assumptions. April 13, 2020. ([LINK](#))

- “Although the presence of antibodies against a specific virus typically suggests an individual has protection from that virus, it is still unknown whether the presence of antibodies specific to SARS-CoV-2 means that someone cannot be reinfected.”
- “Whether mild or asymptomatic cases confer the same level of immune response and immunity as more severe cases has yet to be determined. It is also unknown how long any potential immunity from these antibodies could last.”

CDC. Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19). Revised April 3, 2020. ([LINK](#))

- “Reinfection: There are no data concerning the possibility of re-infection with SARS-CoV-2 after recovery from COVID-19. Viral RNA shedding declines with resolution of symptoms, and may continue for days to weeks. However, the detection of RNA during convalescence does not necessarily indicate the presence of viable infectious virus. Clinical recovery has been correlated with the detection of IgM and IgG antibodies which signal the development of immunity.”

Systematic Reviews

None found at this time.

Other Reviews

Jacofsky et al. **Understanding Antibody Testing for COVID-19.** April 27, 2020. ([LINK](#))

- “A very recent report from China that has not yet been peer-reviewed found a wide range of antibodies among people with mild cases of the virus. Most strikingly, younger people had fewer antibodies in the wake of the disease — and 30 percent of those sampled had low levels. Some individuals had no trace of antibodies. That has raised the question of whether a person with a mild or asymptomatic infection, but confirmed by the sensitive PCR test, might still be susceptible to a second infection.”
- “Longitudinal serological studies are urgently needed to determine the extent and duration of immunity to SARS-CoV-2.”

Kellam & Barclay. **The Dynamics of Humoral Immune Responses Following SARS-CoV-2 Infection and the Potential for Reinfection.** April 21, 2020. ([LINK](#))

- Abstract: “we review what is known about the human humoral immune response to epidemic SARS CoV and MERS CoV and to the seasonal, endemic coronaviruses. Then we summarize recent, mostly non-peer reviewed studies into SARS-CoV-2 serology and reinfection in humans and non-human primates...”
- **Conclusion:** “There is a paucity of information about the longevity of the antibody response to SARS-CoV-2, but it is known that antibodies to other human coronaviruses wane over time, and there are some reports of reinfection with homologous coronaviruses after as little as 80 days. Thus, reinfection of previously mild SARS-CoV-2 cases is a realistic possibility that should be considered in models of a second wave and the post pandemic era.”

Alberta Health Services. **COVID-19 Scientific Advisory Group Rapid Response Report. Key Research Question: Can people with previous COVID-19 infection become re-infected by the virus?** April 8, 2020. ([LINK](#))

- Key Messages from the Evidence Summary
 - Experts suggest the reports of reinfection may relate to the reliability of the testing (false positives or negatives) instead of these being cases of reinfection.
 - RT-PCR positivity from respiratory samples can be prolonged even when no viable virus was detected and in the presence of an antibody response.
 - The evidence is limited and evolving so the possibility of re-infection is not completely excluded. However, the bulk of epidemiological evidence and laboratory and clinical suggests that this likely does not occur (over a short time frame) and if it were to – it is exceedingly uncommon.
 - Although most experts feel that recovered individuals will have some degree of immune protection from reinfection, there is currently not enough data to confirm the proportion of individuals expected to develop a detectable antibody

response to SARS-CoV-2 infection, the correlation of this response to protection, and the potential duration of protection.

The Health Information and Quality Authority (HIQA). **Evidence summary for COVID-19 viral load over course of infection.** April 1, 2020. ([LINK](#))

- Results: “There was some evidence of patients testing positive again for COVID-19, despite having previously had two subsequent negative PCR tests. This suggests that test sensitivity may be an issue when viral load is relatively low.”
- Seven studies were “pre-print” while the reviewers had concerns related to how cases were selected in 9 studies.
- Discussion: “The available evidence to date would appear to suggest that viral load throughout the duration of COVID-19 peaks around symptom onset and decreases within one to three weeks. The relationship between SARS-CoV-2 viral load and infectiousness is also not fully [understood]; however, there is emerging evidence that after 7-10 days of symptoms, there is a reduction in infectiousness.”

Norwegian Institute of Public Health. **Immunity after SARS-CoV-2 infection - a rapid review.** April 2020. ([LINK](#))

- “Even if it is likely that sustained levels of antibodies are related to some level of protection against reinfection, we do not at present know if they ensure full protection against reinfection by the same virus or may result in less severe infection at future exposure to the virus.”

Expert Opinion

WHO. **"Immunity passports" in the context of COVID-19.** April 24, 2020. ([LINK](#))

- “There is currently no evidence that people who have recovered from COVID-19 and have antibodies are protected from a second infection.”
- “Most of these studies show that people who have recovered from infection have antibodies to the virus. However, some of these people have very low levels of neutralizing antibodies in their blood, suggesting that cellular immunity may also be critical for recovery. As of 24 April 2020, no study has evaluated whether the presence of antibodies to SARS-CoV-2 confers immunity to subsequent infection by this virus in humans”

Primary Research

Zhang et al. **Positive rectal swabs in young patients recovered from coronavirus disease 2019 (COVID-19).** April 23, 2020. ([LINK](#))

- “Six patients had positive rectal swabs but negative throat swabs, and one patient had positive throat swabs. All the patients continued to be asymptomatic and had unchanged chest computed tomography from previous images. The time from hospital discharge to positive RT-PCR after recovery was 7-11 days. The time from positive to negative rectal swabs was 5-23 days.”

- “Conclusion: The study might suggest the positive RT-PCR after recovery did not mean disease relapse or virus reinfection.”

Victor, A. Estimation of the Probability of Reinfection with COVID-19 Coronavirus by the SEIRUS Model. Posted April 9, 2020 ([LINK](#))

- “The objective of this study was to evaluate the probability of reinfection in the recovered class and the model equations which exhibits the disease-free equilibrium state for COVID-19 coronavirus. [The] most significant result for this study is the rate of reinfection by the recovered population which will decline to zero over time as the virus is cleared clinically from the system of the recovered class.”

Xiao et al. False-negative of RT-PCR and prolonged nucleic acid conversion in COVID-19: Rather than recurrence. April 9, 2020. ([LINK](#))

- “We studied the characteristics of nucleic acid conversion for SARS-CoV-2 from 70 COVID-19 patients. We found that 15 (21.4%) patients experienced a "turn positive" of nucleic acid detection by RT-PCR test for SARS-CoV-2 after two consecutive negative results, which may be related to the false negative of RT-PCR test and prolonged nucleic acid conversion”.

Kai-Wang et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. March 23, 2020. ([LINK](#))

- Most patients had an antibody response at 10 days or later after onset of symptoms.
- SARS-CoV-2 RNA could be detected for 20 days or longer in a third of patients who survived in our cohort, and one patient had SARS-CoV-2 RNA detected for 25 days.
- One patient with complete symptom resolution tested positive for SARS-CoV-2 again after 2 days of negative findings. Our results suggest that SARS-CoV-2 might be excreted at low levels despite clinical recovery.
- Both serial viral load monitoring and antibody response should be considered when making decisions about infection control measures, because viral load seemed to be related inversely to serum antibody response in this study.

Ye et al. Clinical characteristics of severe acute respiratory syndrome coronavirus 2 reactivation. March 20, 2020. ([LINK](#))

- “5 (9%) patients who discharged from hospital presented with SARS-CoV-2 reactivation. Among the 5 reactivated patients, other symptoms were also observed, including fever, cough, sore throat, and fatigue. One of the 5 patients had progressive lymphopenia and progressive neutrophilia. All 5 reactivated patients presented normal aminotransferase levels. Throat swab samples from the 5 reactivated patients were tested for SARS-CoV-2, indicating all positive for the virus.”
- “Findings from this small group of cases suggested that there was currently evidence for reactivation of SARS-CoV-2 and there might be no specific clinical characteristics to distinguish them.”

Wang et al. **Positive RT-PCR Test Results in Discharged COVID-19 Patients: Reinfection or Residual?** March 18, 2020. ([LINK](#))

- “The current study summarized the clinical course, radiological features and laboratory test results of two COVID-19 patients who tested positive again during the quarantine after hospital discharge... These results implied that the positive result is unlikely caused by the reinfection from others or the remained virus. Rather, it may derive from the remained virus transferred from the lower respiratory tract to the throat or nose with coughs.”

Bao et al. **Reinfection could not occur in SARS-CoV-2 infected rhesus macaques.** March 14, 2020. ([LINK](#))

- This article is a preprint and has not been peer-reviewed. It reports new medical research that has yet to be evaluated and so should not be used to guide clinical practice.
- “The longitudinal tracking of re-exposure after the disappeared symptoms of the SARS-CoV-2-infected monkeys was performed in this study. Notably, neither viral loads in nasopharyngeal and anal swabs along timeline nor viral replication in all primary tissue compartments at 5 days post-reinfection (dpr) was found in re-exposed monkeys. ...our results indicated that the primary SARS-CoV-2 infection could protect from subsequent exposures...”
 - Also published In Brief in *Nature Reviews Immunology*, April 17, 2020. ([LINK](#))

Zhou, F. et al. **Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.** Published March 9, 2020. ([LINK](#))

- “Median duration of viral shedding was 20.0 days (IQR 17.0–24.0) in survivors, but SARS-CoV-2 was detectable until death in non-survivors. The longest observed duration of viral shedding in survivors was 37 days.”
- “Sustained viral detection in throat samples was observed in both survivors and non-survivors.”

News Articles

Yonhap News Agency. (LEAD) **Recovered virus patients retest positive due to 'dead' virus fragments: experts.** April. 29, 2020. ([LINK](#))

- “South Korean health experts said Wednesday that recovered coronavirus patients may have tested positive again due to traces of virus fragments that have been inactivated.”
- “The experts said this PCR test is so sensitive that it can still pick up parts of the small amount of RNA from a cell even after the person has recovered from COVID-19.”

BBC. **Coronavirus immunity: Can you catch it twice?** April 28, 2020. ([LINK](#))

- “Some have argued people are genuinely being infected twice. Another school of thought is the virus goes into stealth mode in the body before being reactivated. However, the scientific consensus is that testing is the issue with patients being incorrectly told they were free of the virus.”

New York Times. **Let's Get Real About Coronavirus Tests.** April 28, 2020. ([LINK](#))

- “Scientists worldwide are working to determine if in the case of SARS-CoV-2, too, infection confers immunity, and if so, how effectively and for how long. But the first serological studies made public to date have been flawed or too easy to misinterpret.”

UN News. **‘No evidence’ that recovered COVID-19 patients cannot be reinfected, says WHO.** April. 25th, 2020. ([LINK](#))

- “In a scientific brief issued on Friday, the UN health agency said there was no proof that one-time infection could lead to immunity, and “laboratory tests that detect antibodies to SARS-CoV-2 [the virus that causes COVID-19] in people...need further validation to determine their accuracy and reliability.””
 - Similar article published in Time. **WHO: 'No Evidence' That COVID-19 Antibodies Protect From Potential Re-infection.** April 25, 2020. ([LINK](#))
 - Similar article published in the New York Times. **'No Evidence' That Recovered COVID-19 Patients Cannot Be Reinfected: WHO.** April 25, 2020. ([LINK](#))

New York Times. **South Korea Finds Patients Testing Positive Post-Recovery From Coronavirus Barely Infectious.** April 22, 2020. ([LINK](#))

- “Patients who tested positive for novel coronavirus after recovering from their first bout of the illness appeared to be far less infectious the second time round, South Korea's health authorities said on Wednesday.”
- “More than 180 such cases have been reported so far in South Korea but none were found to have infected anyone else.”
- “Among the main possibilities are re-infection, a relapse, or inconsistent tests, experts say, and Jeong has said the virus may have been "reactivated" rather than the patients being re-infected.”

Nature. **Will antibody tests for the coronavirus really change everything?** April 18, 2020. ([LINK](#))

- “Another big question surrounding antibody tests is the extent to which being infected with a pathogen confers immunity to reinfection. To have protective immunity, the body needs to produce a certain type of antibody, called a neutralizing antibody, which prevents the virus from entering cells. But it’s not clear whether all people who have had COVID-19 develop these antibodies.”
- “So far, researchers say they have not seen any evidence that people can get reinfected with the virus.”

Time. **Can You Be Re-Infected After Recovering From Coronavirus? Here's What We Know About COVID-19 Immunity.** April 13, 2020. ([LINK](#))

- “There remains a lot of uncertainty, but experts say that it’s likely the reports of patients who seemed to have recovered but then tested positive again were not examples of re-infection, but were cases where lingering infection was not detected by tests for a period of time.”
- “Oh Myoung-don, a professor of internal medicine at Seoul National University and a member of the WHO’s Strategic and Technical Advisory Group for Infectious Hazards,

says the most plausible explanation is that the tests picked up lingering viral genetic material, rather than reemergent infection.”

Scientific American. **What Immunity to COVID-19 Really Means: The presence of antibodies to the SARS-CoV-2 virus could provide some protection, but scientists need more data.** April 10, 2020. ([LINK](#))

- “At this early stage of understanding the new coronavirus, it is unclear where COVID-19 falls on the immunity spectrum. Although most people with SARS-CoV-2 seem to produce antibodies, “we simply don’t know yet what it takes to be effectively protected from this infection,” says Dawn Bowdish, a professor of pathology and molecular medicine and Canada Research Chair in Aging and Immunity at McMaster University in Ontario.

On-going Research

Goossens et al. **Immune Response to Covid-19 in 300 Health Care Workers with Mild Symptoms.** Posted April 22, 2020. ([LINK](#))

- This study is currently enrolling by invitation. The estimated study start date is April 30, 2020.
- “Three hundred healthcare workers with mild symptoms for Covid-19 will be followed [for] three months. [Every] two weeks, serological tests will be performed. Re-infection will be monitored by saliva-swabs.”

Cochrane Rapid Review. **What are the reinfection rates for people who have already been infected with SARS-CoV-2 virus?** Added March 25, 2020. ([LINK](#))

- Submitted to Cochrane COVID Rapid Reviews website Question Bank.
- Status: Awaiting Prioritisation

Methodology

Newfoundland and Labrador Centre for Applied Health Research (NLCAHR) COVID-19 Quick Response reports are initiated by, and shared with, our partners in the provincial health system, including the four Regional Health Authorities, the Departments of Health and Community Services and Children, Seniors and Social Development, and public health officials.

NLCAHR staff work with topic submitters to clarify the research question. We then search for related systematic reviews, meta-analyses, other reviews, interim and other guidance statements, primary research, expert opinion and health and science reporting.

We use several search strategies, with a focus on the following databases:

- [CADTH](#)
- [Canadian Pharmacists Association](#)
- [Campbell Collaboration](#)
- [Cochrane Collaboration](#)
- [Centre for Disease Control](#) (CDC)
- [Centre for Evidence Based Medicine](#) (CEBM)
- [Evidence for Policy and Practice Information and Co-ordinating Centre](#)
- [European Centre for Disease Prevention and Control](#)
- [Health Canada](#)
- [Joanna Briggs Institute](#)
- [Johns Hopkins](#)
- [MedRxiv](#)
- [National Institutes of Health](#) (NIH)
- [National Institute of Allergy and Infectious Diseases](#) (NIAID)
- [National Library of Medicine](#)
- [Public Health Agency of Canada](#)
- [Trip Database](#)
- [World Health Organization](#)

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