



Rapid Review Update 2: What is known on the potential for COVID-19 re-infection, including new transmission after recovery?



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Executive Summary

Background

The potential for COVID-19 re-infection is an important public health issue, as potential for re-infection will significantly impact future infection prevention and control measures, particularly related to vaccine development and immunization efforts.

This rapid review was produced to support public health decision makers' response to the coronavirus disease (COVID-19) pandemic. This review seeks to identify, appraise, and summarize emerging research evidence to support evidence-informed decision making.

This rapid review is based on the most recent research evidence available at the time of release. A previous version was completed on May 29 with evidence available up to May 26, 2020. This version includes evidence available up to August 18, 2020. In this rapid review, we provide the most recent research evidence to answer the question: **what is known on the potential for COVID-19 re-infection, including new transmission after recovery?**

What has changed in this version?

- A meta-analysis (Azam et al., 2020) found that the percentage of recovered cases who subsequently tested positive for COVID-19 infection was 14.8%, based on included studies that were generally low or moderate quality. The Azam synthesis found no evidence that re-positive cases can transmit the infection to contacts. The overall certainty of evidence is very low (GRADE), meaning that the findings are very likely to change as more evidence accumulates.
- More syntheses and single studies with more rigorous, prospective designs are emerging in the recently found evidence. Only syntheses, meta-analyses and recent single studies (published since the Azam meta-analysis search was completed and of similar design criteria) are included in this rapid review.

Key Points

- Across studies, the rates of re-detection following a previous negative test range from 3% to 30% with one meta-analysis calculating the mean rate of re-detection as 14.8%; the overall certainty of this evidence is very low (GRADE), and findings are very likely to change as more evidence accumulates.
- Despite evidence of cases testing positive after having recovered, most syntheses and studies find no evidence of actual COVID-19 re-infection. The detection of re-positive cases is thought to be due to ongoing virus shedding or testing inaccuracies (such as false positives at the initial or follow-up test, or false negatives indicating that the virus had cleared). The Azam meta-analysis reported the pooled estimate of the interval from negative test to repeat positive test to be 9.76 days. The overall certainty of this evidence is very low (GRADE), and findings are very likely to change as more evidence accumulates.
- To date there is no evidence in the included syntheses and studies that re-positive cases can transmit the infection to contacts. Evidence that the virus is viable for a median of 9 days is in line with current isolation periods. The RT-PCR test detects the presence of viral nucleic acid, but the test does not differentiate between live (or viable) and non-infective virus. The overall certainty of this evidence is very low (GRADE), meaning that the findings are very likely to change as more evidence accumulates.

Overview of Evidence and Knowledge Gaps

- Compared with recovered cases who do not test re-positive, cases who test positive following a previous negative test were younger, experienced minimal or moderate symptoms at first admission and were asymptomatic at the time of the re-positive test. The overall certainty of this evidence is very low (GRADE), meaning that the findings are very likely to change as more evidence accumulates.
- This rapid review is limited to syntheses of single studies and single studies that used research designs more rigorous than case reports and case series. While much of the available evidence comes from case reports and case series, these types of studies have an inherently high risk of bias due to the likelihood of selection bias (i.e., those who are included in the study are fundamentally different from those who were not in the study) and the lack of a comparison group needed to properly calculate a rate of re-detection. Prospective cohort studies, which are generally at a lower risk of bias compared to case reports and case series, are emerging in the recently found evidence.
- The majority of current evidence comes from China where patients enter a 14-day quarantine following discharge from hospital. Because of this quarantine measure, some researchers believe it is highly unlikely that subsequent detection of COVID-19 is due to a re-infection, but rather, is more likely due to testing inaccuracies; however, there is insufficient evidence to conclude that re-infection cannot occur.
- More rigorous, prospective research designs and standard testing protocols are needed to answer key questions related to re-infection. This question should be reviewed regularly as new information becomes available from around the world where quarantine measures differ. Longer follow-up of patients following COVID-19 infection is needed to answer questions about long-term immunity and ability to transmit the virus to others.

Methods

Research Question

What is known on the potential for COVID-19 re-infection, including new transmission after recovery?

Search

On May 11, 2020, May 25 and 26, 2020, and again on July 31, August 4 and 18, 2020, the following databases were searched for evidence of re-infection with COVID-19.

- Pubmed's curated COVID-19 literature hub: [LitCovid](#)
- [PubMed](#)
- [Trip Medical Database](#)
- World Health Organization's [Global literature on coronavirus disease](#)
- Joanna Briggs Institute [COVID-19 Special Collection](#)
- [COVID-19 Evidence Alerts](#) from McMaster PLUS™
- [Public Health +](#)
- [COVID-19 Living Overview of the Evidence \(L·OVE\)](#)
- Cochrane Rapid Reviews [Question Bank](#)
- [Prospero Registry of Systematic Reviews](#)
- NCCMT [COVID-19 Rapid Evidence Reviews](#)
- [MedRxiv preprint server](#)
- NCCDH [Equity-informed Responses to COVID-19](#)
- NCCEH [Environmental Health Resources for the COVID-19 Pandemic](#)
- NCCHPP [Public Health Ethics and COVID-19](#)
- NCCID [Public Health Quick Links](#)
- NCCID [Disease Debrief](#)
- NCCIH [Updates on COVID-19](#)
- [Institute national d'excellence en santé et en services sociaux \(INESSS\)](#)
- [Public Health Ontario](#)
- [BC Centre for Disease Control](#)

A copy of the search strategy is available on request.

What has changed in the methods for this version?

- Only syntheses, meta-analyses and recent single studies (published since the search was completed for the Azam meta-analysis and of similar design criteria) are included in this version. Case reports and case series on patients testing positive after a negative test or apparent recovery have been excluded from this review in favour of more rigorous research designs including cohort and cross-sectional studies.

Study Selection Criteria

The search first included recent, high-quality syntheses. If no syntheses were found, single studies were included. English-language, peer-reviewed sources and sources published ahead-of-print before peer review were included. Grey literature and surveillance sources were excluded.

	Inclusion Criteria	Exclusion Criteria
Population	Individuals with cases of COVID-19 confirmed by RT-PCR test	Presumptive cases of COVID-19
Intervention		
Comparisons		
Outcomes	Subsequent COVID-19 infection following recovery	

When available, findings from syntheses are presented first, as these take into account the available body of evidence and therefore can be applied broadly to populations and settings. Single studies published since the search in the most recent meta-analysis (Azam et al., 2020) was conducted, and following the same design criteria (cross-sectional, cohort, case control), were included.

Data Extraction and Synthesis

Data on study design, setting, location, population characteristics, interventions or exposure and outcomes were extracted when reported. We synthesized the results narratively due to the variation in methodology and outcomes for the included studies.

Appraisal of Evidence Quality

We evaluated the quality of included evidence using critical appraisal tools as indicated by the study design below. Quality assessment was completed by one reviewer and verified by a second reviewer. Conflicts were resolved through discussion.

Study Design	Critical Appraisal Tool
Synthesis	Assessing the Methodological Quality of Systematic Reviews (AMSTAR) AMSTAR 1 Tool
Cohort	Critical Appraisal Skills Programme (CASP) Cohort Study Checklist

Completed quality assessments for each included study are available on request.

The Grading of Recommendations, Assessment, Development and Evaluations ([GRADE](#)) approach was used to assess the certainty in the findings based on eight key domains.

In the GRADE approach to quality of evidence, **observational studies**, as included in this review, provide **low quality** evidence, and this assessment can be further reduced based on other domains:

- High risk of bias
- Inconsistency in effects
- Indirectness of interventions/outcomes
- Imprecision in effect estimate
- Publication bias

and can be upgraded based on:

- Large effect
- Dose-response relationship
- Accounting for confounding.

The overall certainty in the evidence for each outcome was determined taking into account the characteristics of the available evidence (observational studies, some not peer-reviewed, unaccounted-for potential confounding factors, different tests and testing protocols, lack of valid comparison groups). A judgement of 'overall certainty is very low' means that the findings are very likely to change as more evidence accumulates.

Findings

Summary of Evidence Quality

This version, updated August 27, 2020, adds 5 new completed syntheses, 1 update to a previously included synthesis, and 6 new single studies, and removes 1 in-progress synthesis which has a different focus than this review and 4 single studies that were covered within the search reported in the Azam meta-analysis. In total, 15 publications are included in this review. Case reports and case series were excluded from this update due to the risk of bias inherent in these study designs.

Outcome	Evidence found		Overall certainty in evidence
Re-detection of COVID-19 following recovery	Completed syntheses	4	Very low
	Single studies	6	
Re-infection with COVID-19 following previous infection	Completed syntheses	3	Very low
Transmission of re-positive COVID-19	Completed syntheses	2	Very low
	In progress syntheses	1	
Clinical characteristics of re-positive cases	Single studies	3	Very low
Interval between recovery and re-positive test	Completed syntheses	1	Very low

Warning

Given the need to make emerging COVID-19 evidence quickly available, many emerging studies have not been peer reviewed. As such, we advise caution when using and interpreting the evidence included in this rapid review. We have provided a summary of overall certainty of the evidence to support the process of decision making. Where possible, make decisions using the highest quality evidence available.

Table 1: Syntheses

Reference	Date Released	Description of Included Studies	Summary of Findings	Quality Rating: Synthesis	Quality Rating: Included Studies
New evidence reported August 27, 2020					
<p>Health Information and Quality Authority. (2020, August 6). Evidence summary of the immune response following infection with SARS-CoV-2.</p>	<p>Aug 6, 2020 (Search completed Jul 6, 2020)</p>	<p>This review included 26 studies (case reports, case series, and cohort designs) that reported re-detection of SARS-CoV-2 following recovery.</p> <p>A standard definition for re-infection (as opposed to re-detection) was not identified in the studies.</p> <p>The majority of studies relevant to this question were from China.</p>	<p>Of the 12 studies that followed a cohort of recovered patients, the re-detection rate ranged from 3% to 30.7%.</p> <p>Nearly all patients who were re-detected positive did not show new clinical symptoms or disease progression. However, two case series and one case study reported new-onset or worsening symptoms among re-detected cases. An additional case study reported new IgM seroconversion in an asymptomatic re-detected case, suggestive of re-infection. These four studies suggest that re-infection may be possible, although the majority of evidence does not show any evidence of re-infection.</p> <p>The review suggests that most re-detection cases are likely due to technical issues, including intermittent false negatives from the inconsistent viral shedding in the later course of the disease, or the detection of dead viral remnants by RT-PCR when no viable virus is present.</p> <p>No study was found that was intended to explore whether individuals re-detected with SARS-CoV-2 or other human coronaviruses are infectious to others, but 5 studies explored whether close contacts of re-positive cases became infected. No cases of onward transmission were reported.</p>	<p>Moderate</p>	<p>Low</p>

<p>Park, M., Pawliuk, C., Nguyen, T., Griffitt, A., Dix-Cooper, L., Fourik, N., & Dawes, M. (2020). Determining the period of communicability of SARS-CoV-2: A rapid review of the literature. Preprint.</p>	<p>Jul 30, 2020 (Search completed Jul 1)</p>	<p>The objective of this rapid review was to identify the reported communicable period of the virus causing COVID-19 infection.</p>	<p>The median length of time until viral clearance across all viral isolation studies (looking at when live virus could be cultured from samples) was 9 days, with a maximum of 32 days. The median length of time until viral clearance for viral shedding (when virus can still be detected in RT-PCR tests, but is not necessarily viable) was 24 days, with a maximum of 95 days.</p> <p>The authors suggest that a 10-day period of isolation is probably sufficient, given the viral isolation median of 9 days, but that for patients entering high-risk settings after isolation, a longer time of isolation may be advised.</p>	<p>Moderate</p>	<p>Moderate (more than 50% had 1 or 2 study concerns, out of 5 possible areas)</p>
<p>Azam, M., Sulistana, R. Ratnawati, M., Fibriana, A.I., Bahrudin, U., & Aljunid, S.M. (2020). Recurrent SARS-CoV-2 RNA positivity after COVID-19: A systematic review and meta-analysis. Preprint.</p>	<p>Jul 21, 2020 (Search completed Jun 12, 2020)</p>	<p>This meta-analysis included 14 studies of 2,568 individuals from cross-sectional (n=6), case control (n=0) or cohort (n=4 prospective and n=4 retrospective) designs that reported the incidence of recurrent positivity (positive RT-PCR result in individuals who had recovered from COVID-19 infection). 13 of the studies reported on findings in China and one in Brunei.</p>	<p>The incidence of recurrent COVID-19 positivity was 14.81% (95% CI: 11.44–18.19%).</p> <p>The pooled estimate of the interval from disease onset to recurrence was 35.44 days (95% CI: 32.65–38.24 days), and from the last negative to recurrent positive result was 9.76 days (95% CI: 7.31–12.22 days).</p> <p>No studies were found that provided evidence of new infections in the family members or close contacts of the recovered patients who experienced recurrent positivity.</p>	<p>Moderate</p>	<p>Low in 7 studies (50%) Moderate in 6 studies (43%) High in 1 study (7%)</p>
<p>Han, Z., Battaglia, F., & Terlecky, S.R. (2020). Discharged COVID-19 patients testing positive again for SARS-CoV-2 RNA: A minireview of published studies from China. <i>Journal of Medical Virology</i>. Epub ahead of print.</p>	<p>Jul 1, 2020 (Search completed Apr 27, 2020)</p>	<p>Twelve studies were included that reported recurrent positivity in 90 individuals who had recovered from COVID-19 infection. The majority of studies were case reports. All of the studies reported on findings in China.</p>	<p>Although most included studies were small case reports, two of the included studies included larger numbers of patients, and these studies reported a 10.5%-14.5% re-positivity rate following discharge.</p>	<p>Low</p>	<p>Not reported</p>

Public Health Ontario. (2020, June 16). <u>COVID-19: Ongoing viral detection and repeat positives.</u>	Jun 16, 2020 (Search date not reported)	This review included existing Public Health Ontario evidence summaries, as well as published and surveillance evidence regarding the laboratory and epidemiological evidence for virus viability and communicability of individuals with repeat positive results.	This review suggests that repeat positive tests after recovery represent ongoing shedding of non-viable virus that do not pose a transmission risk.	Low	Not reported
Newfoundland & Labrador Centre for Applied Health Research. (2020, May 1). <u>Re-infection and sustained viral detection.</u>	May 1, 2020 (Search date not reported)	5 evidence summaries and 8 single studies.	The authors conclude that there is insufficient evidence to conclude one way or the other if COVID-19 re-infection can occur, and inconsistent evidence to interpret the significance of sustained viral detection.	Low	Not reported

Previously reported evidence					
Health Information and Quality Authority. (2020, May 13). Evidence summary of the infectiousness of individuals reinfected with SARS-CoV-2 or other human coronaviruses.	May 13, 2020 (Search completed Apr 23, 2020)	No studies were found that examined whether re-detected cases were infectious to other humans. <ul style="list-style-type: none"> • Four studies were included that followed detected cases of COVID-19 over time. 	No evidence of onward transmission was noted; however, little to no information was given as to how this was determined, and in most cases, patients were under quarantine or self-isolation so potential for spread was limited.	Moderate	Low
Alberta Health Services: COVID-19 Scientific Advisory Group. (2020, May 12). Can people with previous COVID-19 infection become re-infected by the SARS-CoV-2 virus?	May 12, 2020 (Search completed May 4, 2020)	Relevant to this question, 5 publications and 2 pre-prints specific to COVID-19 in humans were included. All were case series or single group observational studies.	To date there is no evidence to answer the question as to whether re-infection is possible or long-term immunity may exist, given the short time frame since the virus was first seen in humans. Within the studies available, it is not possible to determine whether a positive test for COVID-19 following a negative test is confirmation of re-infection or simply re-detection due to a prior false negative.	Low	Low

<p>Flodgren, G.M. (2020, April). Immunity after SARS-CoV-2 infection. 1st update - a rapid review. Oslo: Norwegian Institute of Public Health.</p>	<p>Apr 2020 (Search completed Apr 23, 2020)</p>	<p>This rapid review included 3 studies published from 2019 to 23 April 2020, relevant to this question, one of which was a pre-print. Two of the studies were conducted in China and the third is unknown. Study designs included modelling, and cohort.</p> <p>No studies were found for COVID-19 re-infection in humans, but one animal modelling study was found.</p> <p>Two studies examined re-infection from SARS in 2003 in healthcare workers and patients.</p>	<p>No studies of re-infection with COVID-19 conducted in humans were found.</p> <p>One animal modelling study of re-infection with COVID-19 suggested there could be immunity, but this study provides no insight into the duration of potential immunity.</p> <p>In a study of 34 healthcare workers infected with SARS in 2003 whose antibody levels were followed up for 13 years, high levels of IgG were not sustained after one year.</p> <p>Similarly, among 173 patients infected with SARS in 2003 whose antibody levels were followed up for three years, high levels of IgG decreased after two years. Even if sustained levels of antibodies are related to some protection against re-infection, it is not known if this would ensure full protection against re-infection or may result in less severe infection in the future. The extent to which these findings apply to COVID-19 are unknown.</p>	<p>Low</p>	<p>Not reported</p>
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Table 3: Single Studies

Reference	Date Released	Study Design	Population	Setting	Summary of Findings	Quality Rating:
New evidence reported August 27, 2020						
Yang, C., Jiang, M., Wang, X., Tang, X., Fang, S., Li, H., ... Hu, Q. (2020). Viral RNA level, serum antibody responses, and transmission risk in discharged COVID-19 patients with recurrent positive SARS-CoV-2 RNA test results: a population-based observational cohort study. <i>Preprint.</i>	Jul 26, 2020	Cohort	N=497	China	<p>This study describes viral RNA levels and serum antibody responses in patients with recurrent positive RT-qPCR test results during the period of February 1 to May 5, 2020.</p> <p>Of the 479 patients:</p> <ul style="list-style-type: none"> • 93 (19%) had re-positive results <ul style="list-style-type: none"> • The median time from discharge to the first re-positive test was 8 days (95% CI 7–14 days) • Of these, 36 had multiple re-positive results • They were younger in age, had mild or absent symptoms and no disease progression • There was no significant difference in antibody levels between re-positive and non-re-positive discharged patients. 	High
Yuan, B., Liu, H.Q., Yang, Z.R., Chen, Y.X., Liu, Z.Y., Zhang, K., ... Song, S. (2020). Recurrence of positive SARS-CoV-2 viral RNA in recovered COVID-19 patients during medical isolation observation. <i>Scientific Reports, 10</i> , 11887.	Jul 17, 2020	Cohort	N=182	China	<p>This study reports on 182 recovered patients followed under medical isolation, of whom 20 (10.99%) tested re-positive for SARS-CoV-2 RNA using nasopharyngeal and/or anal swabs.</p> <ul style="list-style-type: none"> • Patients under age 18 had higher re-positive rates (30.8%) than those over age 18 (9.5%) • No patients who had been severely ill (21.4%) tested re-positive • There were no differences in sex between re-positives and non-re-positives • All patients (n=182) carried antibodies against SARS-CoV-2 • There was no association found between viral load and antibody titer • There were no significant differences in antibodies between non-re-positive patients and re-positive patients • No re-positives showed symptoms 	High

<p>Chen, S., Xu, H., Feng, H., Sun, J., Huang, S., Deng, Y., ... Fang, M. (2020). Epidemiology and clinical findings of recurrence for SARS-CoV-2 RNA in discharged COVID-19 cases: An observational study. <i>Preprint.</i></p>	<p>Jul 14, 2020</p>	<p>Cohort</p>	<p>N=1282</p>	<p>China</p>	<p>This study reports on the recurrence of positive SARS-CoV-2 RNA using nasopharyngeal and anal swabs, in discharged patients from January 14 to March 10, 2020.</p> <ul style="list-style-type: none"> • Of 1282 discharged patients, 155 (12.1%) tested re-positive during a 14-day follow-up period • Median time of recurrence was 7 days • Compared to negative patients, re-positives: <ul style="list-style-type: none"> ○ Were younger (35 years vs 45 years mean, $p < 0.001$) ○ Had less comorbidities (12.3% vs 22.2%, $p = 0.004$) ○ Experienced moderate symptoms at first admission (95.5% vs 84.7%, $p < 0.001$) ○ No re-positives showed symptoms ○ 67 re-positives had identified close contacts (N=202) of whom 0 developed COVID-19 infection 	<p>High</p>
<p>Zou, Y., Wang, B.R., Sun, L., Xu, S., Kong, Y.G., Shen, L.J., ... Chen, S.M. (2020). The issue of recurrently positive patients who recovered from COVID-19 according to the current discharge criteria: Investigation of patients from multiple medical institutions in Wuhan, China. <i>The Journal of Infectious Diseases.</i> Epub ahead of print.</p>	<p>Jun 3, 2020</p>	<p>Cohort</p>	<p>N=257</p>	<p>China</p>	<p>This retrospective study examined the differences in the recurrence rates, medical conditions, symptoms and serum-specific antibodies among COVID-19 patients who were admitted to hospital between January 1 to March 10, 2020. Of the 257 patients studied:</p> <ul style="list-style-type: none"> • 53 (20.6%) had recurrence of positive results using a throat swab • Median age of re-positives was 60.37 years (range 22-98 years) • Serum specific IgG and IgM antibodies against SARS-CoV-2 were detected in 150 of 257 and there was no significant difference between patients with recurrence of a positive result and those without recurrence <p>Findings of this study suggest that recurrence of positive results is the incomplete elimination of the SARS-CoV-2 virus which results in subsequent virus replication.</p>	<p>High</p>

<p>Zhao, W., Wang, Y., Tang, Y., Zhao, W., Fan, Y., Liu, G., ... Zhang, F. (2020). Characteristics of children with reactivation of SARS-CoV-2 infection after hospital discharge. <i>Clinical Pediatrics</i>, 59(9–10), 929–932.</p>	<p>May 28, 2020</p>	<p>Cohort</p>	<p>N=14</p>	<p>China</p>	<p>This retrospective study reports on 14 children who had been hospitalized with COVID-19 from January 21 to April 18, 2020, examining their clinical features after hospital discharge. Of the 14 children in the study:</p> <ul style="list-style-type: none"> • 7 children (50%) experienced reactivation of infection according to a nasopharyngeal swab • Of these, 2 experienced a second reactivation after discharge • Median age was 5.7 (range 2.9-7.3 years) and were older than the children who did not experience reactivation • Median time to reactivation from discharge was 14 days (range 7-17 days) 	<p>High</p>
<p>Wang, X., Xu, H., Jiang, H., Wang, L., Lu, C., Wei, X., ... Xu, S. (2020). Clinical features and outcomes of discharged coronavirus disease 2019 patients: A prospective cohort study. <i>QJM: An International Journal of Medicine</i>. Epub ahead of print.</p>	<p>May 22, 2020</p>	<p>Cohort</p>	<p>N=131</p>	<p>China</p>	<p>Of the 131 discharged patients in the cohort, 94 patients were re-tested and 8 of these (6% of total cohort) were positive following hospital discharge.</p>	<p>High</p>

Please note that this information is not available in both official languages because the source of the information is not subject to the Official Languages Act.

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