

COVID-19 Scientific Advisory Group

Rapid Evidence Report

Topic: Can people with previous COVID-19 infection become re-infected by the SARS-CoV-2 virus? [updated May 12, 2020]

Context

- Questions have arisen around whether a person who has recovered from COVID-19 related illness can be re-infected by the SARS-CoV-2 virus within a short time period, with implications for both individual risk and societal pandemic control.
- The media has reported on cases where reinfection was apparently suspected and this has caused public concern.
- The possibility of reinfection would affect the risk of ongoing exposures to HCW and the public after recovering from COVID-19
- Demonstrated reinfection would also change the current theories around the likely development of at least partial immunity from both natural infection and potential future vaccination.

Key Messages from the Evidence Summary

- No well documented cases of suspect reinfection have been described, specifically there have been no reports of culture based documentation of a new infection after clearance of the preceding infection, or evidence of reinfection with a molecularly distinct form of the virus. Currently, it is felt that reports of reinfection after confirmed COVID-19 may relate to prolonged shedding of likely nonviable viral RNA after active infection, which may last for 28 days or longer by some reports. Upon repeat testing, fluctuation in test positivity may occur when viral loads are at levels around the lower limit of detection of the assay used. Thus clinical cases appear to test negative and then positive later by RT-PCR if followed after acute infection, but this is likely due to declining amounts of non-viable virus which is inconsistently detected. A preprint paper suggested that this may be a fairly common occurrence: 14% of individuals in a cohort of patients followed after hospital discharge had a 're-detectable positive' (RP) on serial PCR testing. In a serologic study preprint, PCR was found to be positive as late as 50 days after symptom onset and 34 days after symptom resolution in a cohort of 182 patients with followup PCR testing. The antibody levels in these patients were not different than other patients.
- Clinical studies describing detailed testing protocols with respiratory sample viral RT-PCR, virus cultivation and evolution of an antibody response suggest that in a moderately symptomatic cohort, viable virus was detected in many subjects in the first week of illness, with evolution of a neutralizing antibody response over days 7-14. RT-PCR positivity from respiratory samples can be prolonged even when no viable virus was detected and in the presence of an antibody response.
- Similarly, findings from one non-peer reviewed animal study (in Rhesus macaques) suggested the development of immunity to rechallenge under experimental conditions after the first infection.
- Limited studies from the SARS and MERS coronavirus experiences suggest possible immunity to reinfection. The duration of the immunity seen is also unclear with waning antibody levels over time but likely prolonged T cell responses, raising the possibility of more prolonged immunity.
- Therefore, current evidence suggest that viable virus declines relatively quickly in initial infection, but RT-PCR positivity can be prolonged, and rising antibody titers over the second and third week of illness are likely protective or partially protective. The duration of likely immunity is unclear as yet, but reinfection is felt unlikely in the short term. However, the evidence is limited and evolving. Therefore, the possibility of re-infection is not completely excluded although currently the bulk of epidemiological laboratory and

clinical evidence suggests that this likely does not occur (over a short time frame) and if it were to – it is likely exceedingly uncommon.

- Although most experts feel that recovered individuals will have some degree of immune protection from reinfection, data on the proportion of individuals expected to develop a detectable antibody response to SARS-CoV-2, optimal specific testing modalities, and the titer that appears to be required to confer immunity is still evolving. In addition, the possibility of viral mutation affecting the likelihood of reduced protection (from natural or eventual immunization related antibodies) is not excluded but has not been seen with other coronaviruses.
- Relevant information can also be found in Scientific Advisory Group Rapid Reviews on [Priorities for Serologic Testing in COVID-19](#), and [Testing Characteristics of RT-PCR](#).

Committee Discussion

The committee appreciated the update, with most discussion taking place around the concept of immunity in different populations. It was suggested that links to existing testing documents be provided, and some concerns were raised around whether specific immunocompromised populations (e.g. BMT patients) may be at a more significant risk of actual reinfection, although it is also noted that they would be at risk of prolonged RT-PCR positivity as well, whether or not there is potentially transmissible virus present as well, and data are lacking in this group.

Recommendations

There are no specific actionable recommendations. There is an evolving understanding of the immune response in COVID-19 disease, and the possibility of reinfection with SARS-CoV-2 appears very unlikely but has not been completely excluded. However, there have been no well substantiated cases of reinfection to date and most of the suspect cases are likely related to inconsistent detection of prolonged viral RNA shedding. This information may be useful in public and HCW messaging and this review will need to be updated.

Research Gaps

Characterization of optimal serologic testing methodologies, correlations of antibody titers with the likelihood of immunity, and further analysis of shedding of transmissible virus in an expanded group of patients including those with immunocompromise were highlighted as areas to follow to better address this question.

Strength of Evidence

The rapidly changing information and literature related to COVID-19, the current literature on COVID-19 and particularly reinfection by SARS-CoV-2 is limited primarily to descriptive papers, observational studies, published letters, and news articles. Not enough time has passed since the introduction of SARS-CoV-2 to the human population to carry out studies that can show whether immunity occurs after infection, or how long this immunity may last.

Limitations of this review

- Rapid turnaround time resulted in a limited time to conduct a thorough search of the research and grey literature
- Small sample sizes
- A lack of peer-reviewed literature due to the novel nature of the SARS-CoV-2 and the length of time needed to show whether immunity can occur, or how long it will last.

Summary of Evidence

Literature for this review was collected from a pragmatic search of literature on coronaviruses. Key limitations of this review are related to a few observational studies in peer-reviewed publications focused on SARS-CoV-2, and limited numbers of studies on SARS-CoV and MERS-CoV in peer-reviewed publications. Some of the information is from media reports with comments from experts, as well as evidence from preprint, published correspondence, or observational, with lower rigor than formal studies (epidemiological or clinical trials). This review updates the

previous review from March 30, 2020 to May 4, 2020. Literature includes both that from the original search and newly added references.

The evidence included in this rapid review included a literature search performed by Knowledge Resource Services (KRS) within AHS and literature collected from internet searches. A total of 13 relevant references (peer-reviewed and not peer-reviewed) were added after screening for inclusion/exclusion criteria to 19 references from the March 30 version.

Evidence from secondary and grey literature

Grey literature is limited to news articles or evidence summaries from the World Health Organization. No guidelines or policies are currently available.

Evidence from the primary literature

To date, no studies have been able to show that immunity to SARS-CoV-2 is certain after recovery from COVID-19. If immunity is possible, there is no evidence to show how long this immunity will last.

Evolving Evidence

The evidence available to answer this research question is evolving because the human population is naïve to SARS-CoV-2 infection, and studies of population based antibody responses, and correlation of this with protection against reinfection are not yet possible. There is limited information on whether individuals develop protective immunity following COVID-19 recovery.

Three studies at the pre-print (non-peer reviewed) stage may be relevant after quality assessment. The first study found that monoclonal antibodies from recovering patients' B-cells had neutralizing activity in a pseudovirus model (Ju et al., 2020). An observational study by Dong et al. (2020) showed that patients discharged from hospital appeared to have neutralizing antibodies out to a short 2 weeks follow-up, suggesting at least short-term immune protection, with neutralizing antibody titers higher at discharge than at later follow-up. The third study was a rechallenge experiment on rhesus macaques, and found that those re-challenged with SARS-CoV-2 after recovering from their first infection did not develop COVID-19 a second time (Bao et al., 2020). Finally, a recent detailed laboratory publication of 9 COVID-19 cases in Germany revealed early and prolonged viral RNA shedding that outlasted symptoms, with live virus only detectable in the first week of illness. Notably, at day 7 half of the patients had seroconverted with detectable neutralizing antibodies and at 14 days all had developed an antibody response. This would support an association of an antibody response with infectious viral clearance (Wölfel et al, 2020).

Several studies have documented of newly positive RT-PCR testing in previously negative patients. In a series of 20 patients, Zheng et al. (2020) showed repeat positive PCR tests in 3 patients on day 7 after discharge after 2 negative salivary and 1 negative fecal PCR tests prior to hospital discharge. The 3 patients had all improved clinically at the time of repeat testing, were in strict isolation post discharge, and further testing at day 14 after discharge was negative in all. In a retrospective study of 55 patients, Ye et al. (2020) showed 5 patients (1 asymptomatic, and 4 with symptoms) with a positive test 4-17 days after a negative test, though details on the timing of the tests in relation to initial symptom onset were lacking.

Some authors suggest that positive PCR testing after a negative test represents recurrent infection, thought to occur due to age, underlying diseases, clinical status, immune function, (Cao et al., 2020; Luo et al., 2020; Ye et al., 2020). Cases with recurrence of PCR positivity cases have varied in initial symptom severity (Jiang et al., 2020). The Korean Centres for Disease Control and Prevention (KCDC) was reported to reassure against such results representing reinfection, stating that “the SARS-CoV-2 does not get into the nucleus of host cells, so it will not cause a chronic infection that reoccurs at a later date” (Bo-gyung, 2020). In these cases no viral cultivation or sequencing was done and the patients did not develop recurrent symptoms.

Evidence from other coronaviruses:

Studies on SARS-CoV showed that SARS antibodies prevent reinfection in animal models (Chen & Subbarao, 2007). In human studies, antibody titers decreased significantly after 16 months (Liu, 2006). Because SARS-CoV antibodies may eventually vanish, re-emergence and thus reinfection may be possible (Wu, 2007; Tang, 2011). However, SARS-CoV-specific T cells have been found in individuals recovering from SARS-CoV, and the cellular immune response has been found to last up to 11 years after infection (Ng et al., 2016) suggesting the possibility of an anamnestic response upon rechallenge which would imply longer immune protection after natural infection.

MERS-CoV has been shown to produce variable serologic responses. Robust antibody responses were detected in all survivors who had severe disease (detectable for ≤ 1 year), but an antibody response was often undetectable when disease was mild (Choe et al., 2017). The CDC report that “Patients with MERS-CoV are unlikely to be reinfected shortly after they recover, but it is not yet known whether similar immune protection will be observed for patients with COVID-19” (CDC, 2020).

On the other hand, Kiyuka (2018) showed that the human coronavirus HCoV-NL63, a fairly recently described pathogen affecting children and the immunocompromised, was able to reinfect individuals without any detectable genotype switching, showing that “initial exposure was insufficient to elicit a protective immune response.” As well, it has been shown with other endemic human coronaviruses (causing the common cold) that symptomatic reinfection by the same coronavirus soon after recovery is possible (Holmes, 2003).

Degree and Duration of Possible Immunity post infection is uncertain:

Media reports of expert opinion suggest that based on available data, it is thought that people who recover from COVID-19 will develop protective immunity which is likely to last at least for the duration of the initial pandemic wave (Su, 2020; Campbell, 2020; Woodward, 2020). However, as COVID-19 cases only started occurring in late 2019, confirmation and correlates of functional natural immunity and its duration are unclear (McKenna, 2020). To date, many studies of the immune response are limited to hospitalized symptomatic patients (Gil Melgaço et al., 2020). Reassuringly, however, a preprint study by Wajnberg et al. (2020) enrolled 1,343 total participants who had experienced mild to moderate symptoms as outpatients (only 3% were seen in the emergency department or hospital). They found that over 99% of the patients who self reported or had lab documented SARS-CoV-2 developed IgG antibodies using their assay. Other studies have shown that some people with confirmed infection do not have detectable levels of protective antibody, and neutralizing antibodies can be low or absent in hospitalized patients suggesting other cellular immune responses that may make these patients more prone to recurrence (Wu et al., 2020).

Possible causes of apparent reinfection:

Technical issues in testing may underlie apparent “reinfection” cases, including sample type, sample processing, and analytical test performance. In addition, intermittent negative results in samples with low viral loads around the lower limit of detection of the assay are a proposed mechanism for this phenomenon. There is evidence that patients may have prolonged RT-PCR based positivity from respiratory samples. It is important to note that the reverse transcription PCR test used to detect SARS-CoV-2 can be very sensitive, and scant RNA fragments can be detected even though the individual is not infectious, shows no symptoms, and has recovered from COVID-19 (Xing et al., 2020; Lan et al., 2020; Xiao et al., 2020; An et al., 2020). Studies have demonstrated that cultivatable virus may no longer be recovered from infected hosts 7 days after symptom onset, but viral RNA may be detected by PCR for more than 28 days (Wölfel et al., 2020; Wajnberg et al., 2020). In the scenario of prolonged PCR positivity, **it is important to note that the result of the SARS-CoV-2 RNA test depends on the quality of sample collection (operator dependent) and the viral load of the specimen** (Chen et al., 2020). Supporting this, An et al. (2020) in a preprint paper showed that 14% of individuals in a cohort of patients discharged from hospital had a ‘re-detectable positive’ (RP) on serial PCR testing, and that the antibody levels in these patients were not different between re-detectable positives and other patients. This study suggested different sensitivity between tests used as well (An et al., 2020, Tsang et al., 2003). An evaluation of three available tests revealed different lower limits of detection (Zhen et al., 2020). Jurisdictions have used multiple assays due to reagent

availability and so it is possible a patient may test negative with one assay but positive with another due to different sensitivity.

A recent media report from Korea suggested that 263 people who tested positive weeks after recovery was the result of follow up PCR tests picking up ribonucleic acid (RNA) fragments from likely nonviable virus, **around the threshold of detection of the test** (so a negative test may be followed by a positive PCR) (Bo-gyung, 2020). These RNA fragments may be detectable for many weeks and the PCR cannot distinguish between live and dead virus. The KCDC reports that virus culture tests have not been able to find live virus in recovered patients (Bo-gyung, 2020).

Finally, a false positive RT-PCR result from a non COVID infection could be followed by actual COVID-19 infection and documentation of a true positive result (Chen et al., 2020). The likelihood of this is felt to be much lower than the false negative scenario described above during a time of increasing population prevalence.

It is noted that to prove reinfection after recovering from COVID-19, the genomes of the virus from initial and subsequent infection would need to be sequenced, looking for evidence of different genetic backgrounds indicating a discrete reinfection (Su, 2020).

Implications of documented reinfection on the likelihood of immunity:

Although this has not been documented and is seen as unlikely, well documented reinfection in a person with detectable antibody would cast doubt on the role of serology and possibly on the likelihood of protective natural immunity. Confirmation of antibody mediated immunity is seen as a potential method of guiding return to work (WHO, 2020). It is still unknown whether having detectable antibodies to SARS-CoV-2 equates to immunity from protective, virus-neutralizing antibodies (Altman, 2020; Wajnberg et al., 2020), with some studies in COVID-19 have shown that 10-20% of people who had symptomatic infections do not have detectable antibody (Dong et al., 2020). Furthermore, most studies on SARS survivors or COVID-19 patients have been done on those who were hospitalized with severe symptomatic disease. Less is known about patients with milder symptoms, not requiring hospitalization, with only one preprint study available describing mild to moderate, non-hospitalized cases. Finally, the length of time that immunity lasts is also unknown (Dong et al., 2020), but it is suspected that the antibodies will confer some level of immunity based on what is known about antibody responses to other viral pathogens (Wajnberg et al., 2020). Finally, reports on serologic testing in special populations, particularly immunocompromised populations are not yet available and will be important going forward. The WHO (2020) states “there is currently no evidence that people who have recovered from COVID-19 and have antibodies are protected from a second infection.” Serologic testing can be highly variable and performance will also be affected by false negatives, false positives, and population prevalence of disease cross-reactivity with other circulating coronaviruses would be expected to result in possible false positives which could mislead as to the presence of a protective immune response. (WHO, 2020).

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Authorship and Committee Members

This review was written by Seija Kromm and Lyne Bourassa, and scientifically reviewed by Lynora Saxinger (co-chair), Alexander Doroshenko, Michael Parkins (external reviewer), Susanne Benseler (external reviewer), Kristen Brown (external reviewer), Jonathan Wong (external reviewer), Frances Carr (external reviewer), and Byron Berenger (external reviewer). The full Scientific Advisory Group was involved in discussion and revision of the document: Braden Manns (co-chair), John Conly, Shelley Duggan, Nelson Lee, Elizabeth MacKay, Andrew McRae, Jeremy Slobodan, James Talbot, Brandie Walker, and Nathan Zelyas.

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COVID-19 Scientific Advisory Group

Rapid Evidence Report

Appendix

List of Abbreviations

AHS: Alberta Health Services

CDC: Centers for Disease Control and Prevention

COVID-19: Coronavirus Disease-2019

HCW: Healthcare worker

MERS: Middle Eastern Respiratory Syndrome

RT-PCR: reverse transcription polymerase chain reaction

SAG: Scientific Advisory Group

SARS: Severe Acute Respiratory Syndrome

Methods

Literature Search

A literature search was conducted by Lauren Seal from Knowledge Resources Services (KRS) within the Knowledge Management Department of Alberta Health Services. KRS searched databases for articles published after the last update, from March 30, 2020 to date of search (May 1, 2020), and included: Medline/Pubmed, CINAHL, and grey literature sources. Search strategy is available below under “Search Strategy” section.

Identified articles were initially screened by title against the inclusion/exclusion criteria listed in Table 1 below. The PRISMA diagram in Figure 1 provides the flowchart for the newly added literature review evidence.

Figure 1. Flowchart of newly added literature

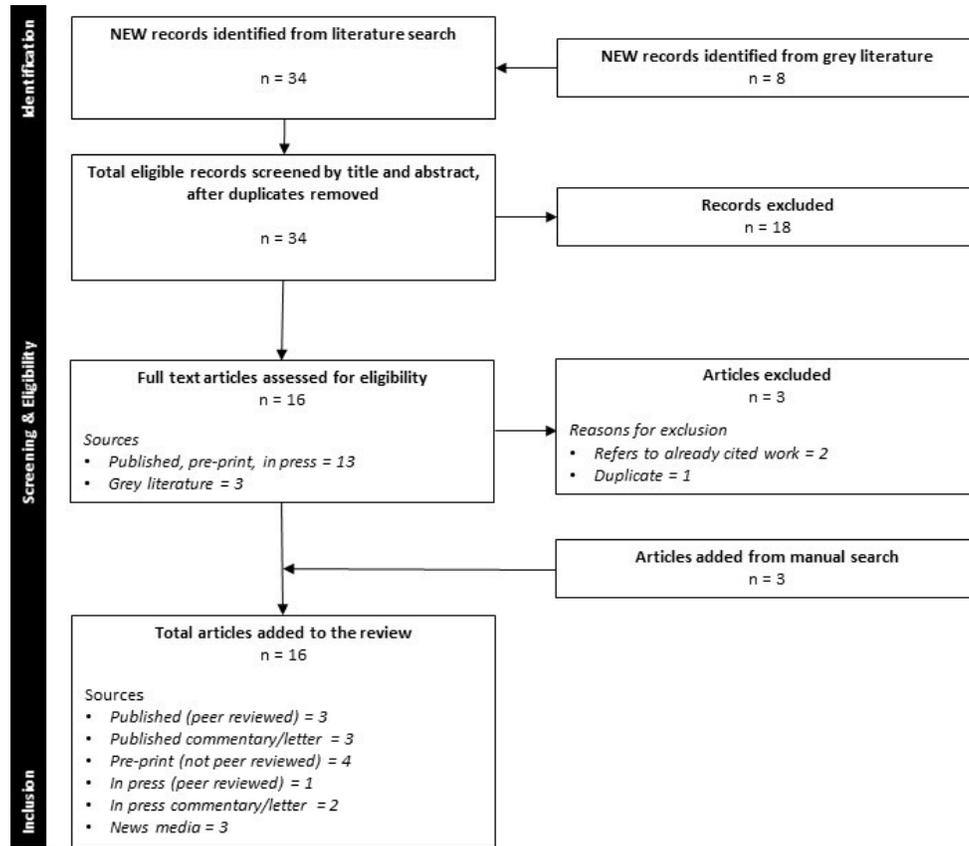


Table 1. Inclusion and exclusion criteria for results of the literature search

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> - Reinfection with SARS-CoV-2, SARS-CoV, or MERS-CoV - Humans or animal models - No limits on dates: SARS-CoV first in early 2000, MERS-CoV in 2012, thus a reasonable timeline for searching - UPDATE limited to 2020 - All methods: not likely to find many studies given how new SARS-CoV-2 is - English only (or with English translation) - Full text, peer-reviewed, non-peer reviewed (pre-print), grey literature - No limits on geographic location 	<ul style="list-style-type: none"> - Article is not from a credible source - Article does not have a clear research question or issue - Presented data/evidence is not sufficient to address the research questions - Not available in English - Repeats/cites what other articles already refer to (most commonly the case with newspaper articles and other media publications) - Not about re-infection by or immune response against a coronavirus - Focus is on common cold coronavirus with no apparent linkage to the novel coronavirus(es)

Critical Evaluation of the Evidence

Exclusion criteria for study quality were adapted from the Mixed Methods Appraisal Tool (MMAT) (Hong et al., 2018). Potential articles were evaluated on three criteria: 1) Peer reviewed or from a reputable source; 2) Clear research question or issue; 3) Whether the presented data/evidence is appropriate to address the research question. Preprints and non peer-reviewed literature (such as commentaries and letters from credible journals) are not excluded out of hand due to the novelty of COVID-19 and the speed with which new evidence is available.

Table 2 below is a narrative summary of the body of evidence included in this review. The categories, format, and suggested information for inclusion were adapted from the Oxford Centre for Evidence-Based Medicine, the Cochrane Library, and the AGREE Trust (Urwin, Gavinder & Graziadio, 2020; Viswanathan et al., 2012; Wynants et al., 2020; Brouwers et al., 2010).

Table 2. Narrative overview of the NEW literature included in this review.

	Description
Volume	<ul style="list-style-type: none"> • 13 articles <ul style="list-style-type: none"> ○ 1 retrospective observational study (peer-reviewed) from China ○ 3 observational studies (not peer reviewed, pre-print) from China ○ 1 observational study (not peer reviewed, pre-print) from USA ○ 2 case reports/presentations (peer-reviewed journal: 1 published, 1 in-press) from China ○ 2 letters to the editor (2 in-press) ○ 1 evaluation of tests to detect SARS-CoV-2 (in-press) ○ 2 commentaries (not peer-reviewed but in peer reviewed journals) ○ 1 commentary about SARS-CoV-1 (SARS) (peer-reviewed) • 3 grey literature <ul style="list-style-type: none"> ○ 1 magazine article – USA ○ 1 newspaper article – Korea ○ 1 web site (international health organization)
Quality	<p>Given the dearth of evidence available for reinfection, the included articles are comprised of observational studies, case reports, commentaries, and letters to the editor (scientific journal). Sample sizes are small, largest in a study was 262 (An et al., 2020) and the largest in a news report was 263 (Bo-gyung, 2020). The available study designs are potentially biased given they are observational – most likely impacted by selection bias and possibly confounding (due to pre-existing conditions in some study subjects). One study (Zheng et al., 2020) highlighted the limitations from small sample sizes and public health controls (compliance), emphasizing the need for further research with larger studies.</p>
Applicability	<p>The current evidence is mainly from Asia where they have had more experience with the SARS-CoV-2 virus and COVID-19. While public health controls may be different than in Alberta, this does not impact the applicability of the currently available evidence to Alberta.</p>
Consistency	N/A

*Search Strategy***Database: Medline/PubMed****Date search conducted: May 1, 2020****Search terms used/Strategy:**

- 1 exp Coronavirus/ or exp Coronavirus Infections/ or coronaviru*.mp. or "corona virus*".mp. or ncov*.mp. or n-cov*.mp. or "novel cov".mp. or COVID-19.mp. or COVID19.mp. or COVID-2019.mp. or COVID2019.mp. or SARS-COV-2.mp. or SARSCOV-2.mp. or SARSCOV2.mp. or SARSCOV19.mp. or Sars-Cov-19.mp. or SarsCov-19.mp. or SARSCOV2019.mp. or Sars-Cov-2019.mp. or SarsCov-2019.mp. or "severe acute respiratory syndrome cov 2".mp. or "2019 ncov".mp. or "2019ncov".mp. (21435)
- 2 exp Recurrence/ (182066)
- 3 reinfect*.mp. (9083)
- 4 recurren*.mp. (666349)
- 5 relaps*.mp. (178705)
- 6 recrudescence*.mp. (2864)
- 7 reoccur*.mp. (2591)
- 8 exp Immunity/ (337069)
- 9 immunity.mp. (283813)
- 10 immune.mp. (696151)
- 11 exp Antibodies, Viral/ (104432)
- 12 exp Antibodies, Neutralizing/ (10511)
- 13 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (1804707)
- 14 1 and 13 (4060)
- 15 limit 14 to yr="2020" (168)

Database: CINAHL**Date search conducted: May 1, 2020****Search terms used/Strategy:**

- S1 (MH "Coronavirus+")
- S2 (MH "Coronavirus Infections+")
- S3 coronaviru*
- S4 "corona virus"
- S5 ncov*
- S6 n-cov*
- S7 COVID-19 OR COVID19 OR COVID-2019 OR COVID2019
- S8 SARS-COV-2 OR SARSCOV-2 OR SARSCOV2 OR SARSCOV19 OR SARS-COV-19 OR SARSCOV-19 OR SARSCOV2019 OR SARS-COV-2019 OR SARSCOV-2019
- S9 "severe acute respiratory syndrome cov 2" OR "severe acute respiratory syndrome coronavirus*"
- S10 "2019 ncov" OR 2019ncov OR Hcov*
- S11 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 4,951
- S12 (MH "Recurrence") 50,020
- S13 reinfect* OR reccur* OR relaps* OR reoccur* OR recrudescence 35,793
- S14 (MH "Immunity+") 40,402
- S15 (MH "Antibodies+") 76,587
- S16 immunit* OR antibod* 103,188
- S17 S12 OR S13 OR S14 OR S15 OR S16 214,498
- S18 S11 AND S17 276
- S19 S11 AND S17 Limiters - Published Date: 20200101-20201231 48

Database: Grey literature

TRIP Pro/Google Scholar/Google/

Date search conducted: May 1, 2020

Search terms used/Strategy:

("covid-19" OR coronavirus OR COVID19 OR "corona virus" "covid-2019" OR covid2019 OR "SARS-COV-2" OR "sarscov-2" OR sarscov2 "severe acute respiratory syndrome") AND (reinfection OR reinfect OR recur OR recurrence OR reactivate OR reactivation OR reoccurrence OR "re-occurrence" OR relapse OR recrudescence OR immunity OR antibody) from:2020

Database: Grey literature

LitCovid/CEBM/Twitter/WHO/CDC/Stanford Medicine/REACTing/Nebraska Medicine COVID-19 resources/NEJM/ The Oakes Academy Coronavirus Clinical Collaboration/CochraneLibrary/covidevidence.org

Date search conducted: May 1, 2020

Search terms used/Strategy:

(reinfection OR reinfect OR recur OR recurrence OR reactivate OR reactivation OR reoccurrence OR "re-occurrence" OR relapse OR recrudescence OR immunity OR antibody)

Reference List

- Altmann DM, Douek DC, and Boyton RJ. (2020). What policy makers need to know about COVID-19 protective immunity. *The Lancet*. [https://doi.org/10.1016/S0140-6736\(20\)30985-5](https://doi.org/10.1016/S0140-6736(20)30985-5)
- An J, Liao X, Xiao T, et al. (2020). Clinical characteristics of the recovered COVID-19 patients with re-detectable positive RNA test. Pre-print. <https://doi.org/10.1101/2020.03.26.20044222>
- Bao, L., Deng, W., Gao, H., et al. (2020). Reinfection could not occur in SARS-CoV-2-infected rhesus macaques. Pre-print. <https://doi.org/10.1101/2020.03.13.990226>
- Bo-gyung K (2020). Tests in recovered patients found false positives, not reinfections, experts say. *The Korea Herald*. http://www.koreaherald.com/view.php?ud=20200429000724&fbclid=IwAR2txK96Lvzsw9cdAmDYJcyNf-wZsE2_InLhOXUB5LIsV6_qmt6tfX6SfOY
- Brouwers, M. C., Kho, M. E., Browman, G. P., Burgers, J. S., Cluzeau, F., Feder, G., Fervers, B., Graham, I. D., Grimshaw, J., Hanna, S. E., Littlejohns, P., Makarski, J., Zitzelsberger, L., & AGREE Next Steps Consortium (2010). AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*, 182(18), E839–E842. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3001530/>
- Campbell, D. (2020). Can you get the coronavirus twice? The Guardian. <https://www.theguardian.com/world/2020/mar/16/the-big-question-over-coronavirus-can-a-person-get-it-twice> (dated March 16, 2020) Accessed March 30, 2020.
- Cao S, Wu A, Li J, et al. (2020). Recurrent recurrence of positive SARS-CoV-2 RNA in a COVID-19 patient. <https://dx.doi.org/10.21203/rs.3.rs-23197/v1>
- Centers for Disease Control and Prevention (2020). Q: Can people who recover from COVID-19 be re-infected with SARS-CoV-2? In: *Healthcare Professionals: Frequently Asked Questions and Answers*. <https://www.cdc.gov/coronavirus/2019-ncov/hcp/faq.html> Accessed March 30, 2020.
- Chen, J., Subbarao, K (2007). The Immunobiology of SARS. *Annual Review of Immunology*, 25: 443-472. <https://doi.org/10.1146/annurev.immunol.25.022106.141706>
- Chen, D., Xu, W., Lei, Z., Huang, Z., Liu, J., Gao, Z., & Peng, L. (2020). Recurrence of positive SARS-CoV-2 RNA in COVID-19: A case report. *International Journal of Infectious Diseases: IJID: Official publication of the International Society for Infectious Diseases*, 93, 297–299. Advance online publication. <https://doi.org/10.1016/j.ijid.2020.03.003>
- Choe, P., Perera, R., Park, W., et al. (2017). MERS-CoV Antibody Responses 1 Year after Symptom Onset, South Korea, 2015. *Emerging Infectious Diseases*, 23(7): 1079-1084. <https://dx.doi.org/10.3201/eid2307.170310>
- Dong C, Ni L, Fang Y, et al. (2020). Characterization of anti-viral immunity in recovered individuals infected by SARS-CoV-2. Preprint. <https://doi.org/10.1101/2020.03.17.20036640>
- Gil Melgaço J, Azamor T, Dinis Ano Bom AP (2020). Protective immunity after COVID-19 has been questioned: What can we do without SARS-CoV-2-IgG detection? *Cellular Immunology*, 353. <https://doi.org/10.1016/j.cellimm.2020.104114>
- Holmes KV (2003). SARS coronavirus: a new challenge for prevention and therapy. *Journal of Clinical Investigation*, 111:1605–1609. <https://doi.org/10.1172/JCI200318819>
- Hong, Quan Nha et al. (2018). The Mixed Methods Appraisal Tool (MMAT) Version 2018 for Information Professionals and Researchers'. 1 Jan. 2018 : 285 – 291. Retrieved from:

http://mixedmethodsappraisaltoolpublic.pbworks.com/w/file/attach/127916259/MMAT_2018_criteria-manual_2018-08-01_ENG.pdf

Jiang M, Li Y, Han M, et al. (2020). Recurrent PCR positivity after hospital discharge of people with coronavirus disease 2019 (COVID-19). *Journal of Infection*. Article in Press. <https://doi.org/10.1016/j.jinf.2020.03.024>

Ju, B., Zhang, Q., Ge, Z., et al. (2020). Potent human neutralizing antibodies elicited by SARS-CoV-2 infection. Preprint. <https://www.biorxiv.org/content/10.1101/2020.03.21.990770v2>

Kiyuka, P.K., Agoti C.N., Munywoki, P.K., et al. (2018). Human coronavirus NL63 molecular epidemiology and evolutionary patterns in rural coastal Kenya. *Journal of Infectious Diseases*, 217(11): 1728-1739. <https://dx.doi.org/10.1093/infdis/jiy098>

Lan, L., Xu, D., Ye, G., et al. (2020). Positive RT-PCR Test Results in Patients Recovered From COVID-19. *Journal of the American Association*. Published online February 27. <https://doi.org/10.1001/jama.2020.2783>

Liu, W., Fontanet, A., Zhang, P., Zhan, L., Xin, Z., Baril, L., Tang, F., Lv, H., & Cao, W. (2006). Two-year prospective study of the humoral immune response of patients with severe acute respiratory syndrome. *Journal of Infectious Diseases*, 193(6), 792–795. <https://doi.org/10.1086/500469>

Luo A (2020). Positive SARS-Cov-2 test in a woman with COVID-19 at 22 days after hospital discharge: A case report. *Journal of Traditional Chinese Medical Sciences*. In Press. <https://doi.org/10.1016/j.jtcms.2020.04.001>

McKenna S (2020). What Immunity to COVID-19 Really Means. *Scientific American*. <https://www.scientificamerican.com/article/what-immunity-to-covid-19-really-means/>. Accessed May 6, 2020.

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement*. *PLoS Med* 6(7): e1000097. [doi:10.1371/journal.pmed1000097](https://doi.org/10.1371/journal.pmed1000097)

Ng, OW, Chia, A., Tan, AT, et al. (2016). Memory T cell responses targeting the SARS coronavirus persist up to 11 years post-infection. *Vaccine*. 34(17): 2008-2014. <https://doi.org/10.1016/j.vaccine.2016.02.063>

Su, A. (2020). They survived the coronavirus. Then they tested positive again. Why? Los Angeles Times. <https://www.latimes.com/world-nation/story/2020-03-13/china-japan-korea-coronavirus-reinfection-test-positive>

Tang F., Quan Y., Xin, Z., et al. (2011). Lack of peripheral memory B cell responses in recovered patients with severe acute respiratory syndrome: A six-year follow-up study. *Journal of Immunology*, 186(12), 7264-7268. <https://dx.doi.org/10.4049/jimmunol.0903490>

Tsang O. T., Chau T., Choi K., et al. (2003). Severe acute respiratory syndrome: Relapse? Hospital infection?. *Emerging Infectious Diseases*, 9(9), 1180-1181. <https://doi.org/10.3201/eid0909.030395>

Urwin, S; Gavinder K, Graziadio S. (2020). What prognostic clinical risk prediction scores for COVID-19 are currently available for use in the community setting? Centre for Evidence-Based Medicine. Retrieved from: <https://www.cebm.net/covid-19/what-prognostic-clinical-risk-prediction-scores-for-covid-19-are-currently-available-for-use-in-the-community-setting/>

Viswanathan, M., Ansari, M. T., Berkman, N. D., Chang, S., Hartling, L., McPheeters, M., ... & Treadwell, J. R. (2012). Assessing the risk of bias of individual studies in systematic reviews of health care interventions. In *Methods guide for effectiveness and comparative effectiveness reviews [Internet]*. Agency for Healthcare Research and Quality (US). Retrieved from: <https://www.ncbi.nlm.nih.gov/books/NBK91433/>

Wajnberg A, Mansour M, Leven E, et al. (2020) Humoral immune response 1 and prolonged PCR positivity in a cohort of 1343 SARS-CoV 2 patients in the New York City region. Preprint. <https://doi.org/10.1101/2020.04.30.20085613>

Wölfel R., Corman V.M., Guggemos W. et al. (2020). Virological assessment of hospitalized patients with COVID-2019. *Nature*. <https://doi.org/10.1038/s41586-020-2196-x>

Woodward, A. (2020). Fauci said he's 'willing to bet anything' that people who recover from the new coronavirus are 'really protected from reinfection'. *Business Insider*. <https://www.businessinsider.com/coronavirus-fauci-those-who-recover-will-be-immune-2020-3> Accessed March 30, 2020

World Health Organization (2020). "Immunity passports" in the context of COVID-19, Scientific Brief. <https://www.who.int/news-room/commentaries/detail/immunity-passports-in-the-context-of-covid-19>. Accessed May 6, 2020.

Wu F, Wang A, Liu M, et al., (2020). Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. Preprint. <https://doi.org/10.1101/2020.03.30.20047365>

Wu L., Wang N., Chang Y., et al. (2007). Duration of antibody responses after severe acute respiratory syndrome. *Emerging Infectious Diseases*, 13(10):1562-1564. <https://dx.doi.org/10.3201/eid1310.070576>

Wynants, L., Van Calster, B., Bonten, M. M., Collins, G. S., Debray, T. P., De Vos, M., ... & Schuit, E. (2020). Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. *BMJ*, 369. Retrieved from <https://www.bmj.com/content/369/bmj.m1328.long>

Xiao AT, Tong YX, and Zhang S (2020). False-negative of RT-PCR and prolonged nucleic acid conversion in COVID-19: Rather than recurrence. *Journal of Medical Virology*. In Press. <https://doi.org/10.1002/jmv.25855>

Xing Y, Mo P, Xiao Y, Zhao O, Zhang Y, Wang F. (2020). Post-discharge surveillance and positive virus detection in two medical staff recovered from coronavirus disease 2019 (COVID-19), China, January to February 2020. *Euro Surveill*. 25(10):pii=2000191. <https://doi.org/10.2807/1560-7917.ES.2020.25.10.2000191>

Ye G, Pan Z, Pan Y, et al. (2020). Clinical characteristics of severe acute respiratory syndrome coronavirus 2 reactivation. *Journal of Infection*, 80: e14-e17. <https://doi.org/10.1016/j.jinf.2020.03.001>

Zhen W, Smith E, Manji R, Schron D, Berry GJ (2020). Clinical Evaluation of Three Sample-To-Answer Platforms for the Detection of SARS-CoV-2. *Journal of Clinical Microbiology*, Apr. <https://doi.org/10.1128/JCM.00783-20>

Zheng KI, Wang X-B, Jin X-H, et al. (2020). A Case Series of Recurrent Viral RNA Positivity in Recovered COVID-19 Chinese Patients. *Journal of General Internal Medicine*. <https://doi.org/10.1007/s11606-020-05822-1>