

COVID-19 Scientific Advisory Group

Rapid Evidence Report

Topic: Can people with previous COVID-19 infection be reinfected by the virus? [updated November 6, 2020, replacing May 12, 2020 version]

Context

- The potential for reinfection by the SARS-CoV-2 virus has significant implications for both individual risk reduction behaviours after COVID-19 infection, and for societal pandemic control. A lack of durable natural immunity would manifest as increasing reinfections over time from the original epidemic waves. This would affect both individual infection risk, and the likelihood that “herd immunity” might protect against epidemic resurgence in areas with previously high infection rates.
- At the time of previous reviews (March 18, 2020 and May 12, 2020), there was no strong evidence of reinfection by SARS-CoV-2 after recovery from documented COVID-19 related illness. This update focuses on currently identified worldwide cases of reinfection.
- Suspected cases of reinfection require confirmation via RT-PCR positivity with genomic sequencing of both the first and reinfection sample to show evidence of genetically different viruses (which both may belong to a dominant strain or clade but would show sequence differences) indicating a discrete reinfection. Prolonged or intermittent test positivity is not sufficient to confirm either reinfection or active infection because some patients exhibit intermittent RT-PCR test positivity just around the limit of test detection for weeks after recovery.

Key Messages from the Evidence Summary

- Reinfection with SARS-CoV-2 after recovery from COVID-19 disease has been demonstrated to be possible, although is not frequently reported as yet. It is unclear whether reinfection will prove to be rare, or will become increasingly common over time. Therefore the average duration of natural immunity to this new pandemic virus is not yet able to be known.
- Suggested guidelines for the investigation, assessment and confirmation of reinfection cases are available from the US CDC.
- Documenting reinfection requires demonstration of a sufficiently different virus on paired specimens by genetic sequencing, or potentially by demonstration of viable virus of the same clade and sequence if a known exposure has occurred and a long duration of time since the first infection. Possible SARS-CoV-2 reinfection must be differentiated from persistent viral RT-PCR positivity by specific laboratory-based parameters to demonstrate the virus sequence is sufficiently different, as well as patient symptomology, and/or epidemiologic links.
- By sequencing criteria there have been 17 reasonably well demonstrated cases of SARS-CoV-2 reinfection worldwide confirmed by RT-PCR and viral sequencing to date although such reports appear to be increasing. Not all of these cases can be fully assessed by the proposed CDC criteria due to nonstandardized genetic mutation reporting. This relatively small number is in the context of more than 55 million cases of COVID-19 documented worldwide, seven months after the pandemic was declared. However, repeat swabs with sequencing or culture are resource intensive and not standard practice, so undetected or undocumented cases of reinfection may be occurring.
- The previous lack of defined criteria around both the reporting of genetic sequencing results and the lack of clarity around the threshold of difference between the first and subsequent isolates to be considered a reinfection is seen as a weakness in these reports. A protocol for assessment of reinfection cases from the US CDC suggests prioritization criteria of cases to assess, laboratory considerations and interpretative criteria of genetic testing which should improve data assessment going forward.
- In these 17 reported cases of reinfection:

- the severity of symptoms varied from asymptomatic through more severe than the initial infection, with no clear correlation between severity of the first infection and the reinfection., 3 individuals were asymptomatic when documented as reinfected.
- the time from first infection to reinfection varies suggesting individual variation in the durability of individual immune responses to SARS-CoV-2 infection.
- Documentation of these reinfection cases within seven months of declaration of the pandemic raises the possibility that immunity resulting from natural infection may not be durable. Human challenge studies using endemic human coronaviruses (such as HCoV 229E) have shown that immunity after induced infection waned over 6-9 months, whereas immunity to other epidemic coronaviruses, SARS-CoV and MERS appears to be potentially longer lasting.
- The concept of 'herd immunity' from natural infection with SARS-CoV-2, which is currently of public interest, relies upon the existence of long term immunity after infection, and would not be possible without a durable immune response. Additional considerations around the hypothesis that natural herd immunity to SARS-CoV-2 is possible (beyond whether is a durable natural immune response) includes patterns of mixing of immune persons and susceptible persons, which is not as significant a consideration in vaccine induced herd immunity as vaccination campaigns may be deployed across the population in a risk stratified fashion.
- Conversely, the likelihood of durable, vaccine-based immunity is not highly affected by reinfection considerations given that vaccine-induced immunity may induce a tailored and more robust immune response than natural infection, and could be boosted with repeated immunizations.
- Relevant information can also be found in Scientific Advisory Rapid Reviews on [Priorities for Serologic Testing in COVID-19](#), and [Testing Characteristics of RT-PCR](#).

Committee Discussion

The committee agreed with the content of the review but suggested some of the immunologic discussion and additional information about patterns of coronavirus immunity from the previous review be reincorporated and updated which was done. The recommendation for balanced messaging around the theory of herd immunity was supported, and it was suggested that specific messaging around implications of reinfections on personal risk behaviours also be reinforced. One member additionally pointed out that fluctuating symptoms post recovery have not been associated with cultivatable virus so post infection symptoms would potentially be related to immunologic phenomenon. Clinical considerations were amplified in the recommendations. This is covered more extensively in an upcoming SAG chronic symptom review so is out of scope of this discussion. It is also noted that the reviewed cases of purported reinfection have been documented by genetic analysis so should not reflect chronic symptoms and prolonged RT-PCR positivity.

Recommendations

Recommendation 1:

Laboratory assessment for COVID-19 reinfection may be considered if:

- 1) There is a very high index of clinical suspicion of reinfection i.e., resolution of a previous COVID-19 confirmed illness followed by a new illness occurring 45-90 days after an initial positive test compatible with COVID-19 (including compatible exposure history in settings of low community transmission). In this situation, repeat COVID-19 RT-PCR and a respiratory viral panel as well as other clinically indicated diagnostic tests should be completed. Follow up RT-PCR testing without new symptoms is not indicated.
- 2) A repeat positive test occurs >12 weeks after the first positive test. Expert evaluation and consultation is required including the assessment of the serial Ct values (considering testing platform and comparability). If the second sample Ct value is potentially compatible with acute or active infection as assessed by the responsible virologist, and with the agreement of Public Health, genomic sequencing to compare strains across episodes may be attempted. Other potential test modalities include viral culture and sgRNA can also be attempted (to attempt to document the presence or absence of replication-competent virus) and serologic testing to determine the immunologic response to initial infection if stored sample is available, and upon suspected reinfection.

Rationale: When there is a very high index of clinical suspicion of reinfection i.e., resolution of a previous COVID-19 confirmed illness followed by a new illness occurring 6 weeks or more after the first positive test, repeat testing

should occur. This situation should be distinguished from persistent and variable post COVID-19 symptoms which have been described in a Scientific Advisory Group review on chronic symptoms of COVID-19, or situations where RT-PCR has remained positive over a long duration, which is common particularly in people who are immunosuppressed (as described SAG reviews on [asymptomatic transmission](#) and [chronic symptoms of COVID-19](#)).

If positive on repeat testing, with a Ct value suggestive of possible active infection, genomic sequencing, and serologic testing may assist in determining whether the case reflects prolonged RT-PCR positivity, with an alternate cause of symptoms, or a true reinfection. The US CDC common investigation protocol is the basis for this recommendation.

Recommendation 2:

Public Health messaging should reinforce (1) the durability of the natural antibody response to SARS-CoV-2 is currently unknown, and (2) that reinfection has been shown to be possible (although it is not yet known how common this is). Specific implications for public health interventions and risk-mitigating behaviours following from that include:

- 2a) Until the durability of the natural immune response is better understood, control strategies for COVID-19 that are based on natural herd immunity should not be considered, as it is not clear that this is immunologically feasible. However, if natural immunity proves durable for most people and vaccines are not available within the next year, a formal risk-benefit analysis would be warranted in the future.
- 2b) Individuals who have recovered from COVID-19 infection should not assume they are immune, and should follow current public health guidance to mitigate risk.

Recommendation 3:

Alberta's medical laboratories should assess the feasibility of Laboratory Information Management Systems flagging repeat positive specimens (e.g., to identify repeat COVID-19 results with lower range Ct values occurring more than 6 weeks from a prior test, to allow for an assessment as in Recommendation 1. Repeat positive specimens could then be reviewed by the responsible virologist to assess the need to sequence the new positive and/or culture isolates, and to allow Public Health officials to be contacted to complete an epidemiologic review.

Rationale: An automatic flagging system would ensure that repeat positive cases are captured and assessed for need to investigate for "true" reinfection in a timely fashion.

Research Gaps

Adoption and validation of the proposed CDC reinfection criteria (CDC, 2020) has not yet occurred. The suggested criteria for assigning a significant level of difference between viral sequences is not validated and is based on an incomplete knowledge of the mutation rate of SARS-CoV-2 during infection. The degree to which single nucleotide variants (SNVs) can accumulate during a single infection is unclear, and the variability in time elapsed and occasionally very high cycle threshold (Ct) values make assessment of reinfection challenging in some of these cases.

Characterization of optimal serologic testing methodologies, correlations of antibody titres with the likelihood of immunity, and further analysis of shedding of transmissible virus in an expanded group of patients (including immunocompromised patients) were highlighted as evolving areas. Key gaps in knowledge of antibody kinetics include the antibody response in asymptomatic or paucisymptomatic infection, and differential antibody responses by infection severity. Serological surveys to describe the extent of infection in particular populations should account for the dynamics of antibody and the potential for infections associated with different severities of illness to have different antibody responses in their analysis.

Strength of evidence and limitations of this review

While some cases of SARS-CoV-2 reinfection have occurred, not enough time has passed since the introduction of SARS-CoV-2 to the human population to determine whether reinfection is idiosyncratic and rare or will become increasingly common over time.

In addition, the information and literature related to COVID-19 is rapidly changing. The current literature on COVID-19, and particularly reinfection by SARS-CoV-2, is limited primarily to cohort studies, case reports and published letters about identified cases.

Evidence Included

Evidence was collected from a structured and pragmatic search of literature on coronaviruses. This topic required reliance on observational studies in peer-reviewed and non-peer-reviewed publications. As well, the evidence is from preprint, published correspondence, or observational studies, with lower rigor than formal studies (epidemiological or clinical trials). This review updates the previous review from May 4, 2020 to October 13, 2020.

The evidence included in this review was obtained by a literature search performed by AHS Knowledge Resource Services (KRS) and literature collected from internet searches. Thirteen relevant references were identified after screening for inclusion/exclusion criteria. Any duplicate articles from the previous update (May 12, 2020) were excluded, and this review focused on descriptions of reported cases of reinfection confirmed by genetic sequencing.

Evidence from secondary and grey literature

No grey literature was found for this update.

Evidence from the primary literature

To date, 17 specific cases provide evidence that reinfection with SARS-CoV-2 has occurred after recovery from COVID-19 disease. This raises the possibility that immunity to SARS-CoV-2 may be of limited duration (similar to human endemic coronaviruses) and reinfection is possible after recovery from COVID-19.

Background

To prove reinfection after recovering from COVID-19 disease, genomes of the SARS-CoV-2 virus from initial and subsequent infection need to be sequenced to show evidence of different genetic backgrounds, indicating a discrete reinfection. Following this criterion, 17 cases of reinfection after recovery from the COVID-19 disease are reported here, each confirmed by viral genome sequencing. Two sets of researchers (To et al. [2020b] and Larson et al. [2020]) attempted to cultivate viable virus from the reinfection cases but were not successful.

In earlier reviews (March 18, 2020 and May 12, 2020) about the possibility of SARS-CoV-2 reinfection, articles reported on cases using a variety of terms: recurrence, re-positive, relapse, reactivation, and/or reinfection (without genetic sequencing). These terms also appeared in publications reviewed for this update. Most of the early literature described repeat positive RT-PCR, which was ultimately considered related to prolonged viral shedding around the limits of detection, resulting in intermittent positive test results.

A more recent paper by Chen et al, (2020) described the clinical features of patients with shorter-term repeat positive tests, which were documented in (14.74%) of patients admitted during 28-day follow-up. Reassuringly, this repeat positive group had normalized blood counts, improved CT scans, no new symptoms, and did not transmit infection to their traced contacts around the repeat positive test. Similarly, Zheng et al. (2020) did a prospective cohort study on recurrent positive tests and noted that the repeat positive cases in their cohort occurred in nearly 10% of COVID-19 patients, were not associated with worsening symptoms, and were unlikely to be cases of reinfection.

The duration of positive RT-PCR can be prolonged after infection. Wajnberg et al. (2020) found that a positive RT-PCR can occur up to 28 days after symptom resolution, and Xiao et al. (2020) found positive RT-PCR up to three months after symptom resolution.

As noted in the previous update (May 12, 2020), there are no conclusive studies of the kinetics of population-based antibody responses with correlation of antibody titres with protection against reinfection. To et al. (2020a) also noted that an insufficient antibody response after COVID-19 infection could impact both the susceptibility to reinfection and potentially the severity of infection.

Summary of Evidence

This update, which reviews 17 well-documented cases of reinfection, provides preliminary evidence to suggest that prolonged protective immunity after recovery from COVID-19 is not guaranteed, even though the number of reinfection cases reported in the literature is small.

Table 1a summarizes reported cases following the example of Iwasaki (2020). Given that some cases of reinfection are asymptomatic, there may be more reinfections that have not been reported due to (1) a lack of significant symptoms (and thus no repeat testing) and also (2) the occurrence of symptomatic reinfections where virologic studies have not been done. It should be noted that the description of the genetic analyses of the purported new strains was not always detailed enough to identify the evidence as poor, moderate, or best evidence of reinfection by the CDC laboratory criteria (listed later in the document), although clade differences where noted constitute best evidence.

In these cases, repeat positive PCR with a genetically different virus occurred anywhere from 19 days up to 142 days after the start of the first infection (positive RT-PCR test). Eleven of the individually documented cases of reinfection were male and six were female. Almost all cases in Qatar were male, and researchers note this is due to the epidemic mostly affecting craft and manual workers (Raddad et al., 2020). The authors concluded that reinfections were rare in relation to inferred numbers of possible multiple exposures (Raddad et al., 2020).

Two of the cases in India (Gupta et al., 2020) were in healthcare workers who were asymptomatic for both infections, detected through routine screening of healthcare workers. The first case of reinfection in Hong Kong (To et al., 2020a) was found through routine returned traveler screening. This highlights the point made by Iwasaki (2020) that without routine community testing or screening, asymptomatic cases of reinfection would not be found. The significance of asymptomatic reinfections is difficult to gauge - asymptomatic cases are a modest percentage of overall cases but may be associated with some transmission ([Scientific Advisory Group rapid review](#)). It is unknown whether this incidence carries over to cases of reinfection.

Following the investigative criteria set out by the CDC for possible cases of reinfection (CDC, 2020), we identified two additional possible cases of reinfection from the literature (Table 1b). Evidence of reinfection in the form of genetic sequencing was not included, but the authors state “we are the most confident of [these] being true cases of SARS-CoV-2 reinfection, as they exhibited the largest interval (87 and 84 days, respectively) between their two COVID-19 episodes. Also, their two positive SARS-CoV-2 IgG antibody tests showed that antibodies were present after the first and persisted through to the second COVID-19 episode, and were therefore less likely to be a false positive finding” (Tomassini et al., 2020). This aligns closely with the rationale used by the US CDC of considering cases that fit the following three criteria: 1) persons with detection of SARS-CoV-2 RNA ≥ 45 days after the first detection of SARS-CoV-2 RNA (include if Ct value < 33 or not available), 2) with a symptomatic second episode and no obvious alternate etiology for COVID-19–like symptoms OR close contact with a person known to have laboratory-confirmed COVID-19 (we included the asymptomatic HCW), and 3) paired respiratory specimens (one from each infection episode) are available.

Table 1a: Characteristics of reinfections with SARS-CoV-2, confirmed by genetic sequencing (as per Iwasaki, 2020)

Location (Reference)	Sex	Age (years)	1 st infection		2 nd infection		Time between infections: positive RT-PCR (days)	Genome sequencing	Ab detected after 1 st infection	Ab detected after 2 nd infection
			Ct value of RT-PCR	Symptoms	Ct value of RT-PCR	Symptoms				
Hong Kong (To et al., 2020a and To et al. 2020b)	Male	33	n/a	Mild-cough and sputum, sore throat, fever, and headache	27	Asymptomatic	142	-2 strains from 1 st and 2 nd episode from different clades/lineages with 24 nucleotide differences	IgG+ and IgM-	IgG+
Nevada, USA (Tillet et al., 2020)	Male	25	35	Mild	35	Hospitalized	48	1 st and 2 nd specimens from f clade 20C. Sample 1 had 4 SNVs different from Sample 2, which had an additional unique 7 SNVs	n/a	IgM+ and IgG+
Seattle, USA (Goldman et al., 2020)	Female	60-69	22.8	Hospitalized with fever, chills, productive cough, dyspnea and chest pain	43.3	Less severe symptoms even though still hospitalized (Presented to ER with dyspnea, reporting 2 weeks of dry cough and weakness)	140	Samples differed by 10x (iSNVs first typed as clade 19B, second 20A.)	n/a	IgG+, IgM+, and IgA+
Belgium (Van Elslande et al., 2020)	Female	51	26-27	Mild-headache, fever, myalgia, coughing, chest pain and dyspnea	33	Milder-headache, cough, fatigue, and rhinitis	93	One sample was lineage B.1.1 SARS-CoV-2 virus and 2nd infection by lineage A. 11 mutations with 99.7% identity).	n/a	IgG+
Ecuador (Prado-Vivar et al., 2020)	Male	46	n/a	Worse-intense headache and drowsiness	n/a	Worse- odynophagia, nasal congestion, fever of 38.5°C, strong back pain, productive cough, and dyspnea	63	First sample from 20A clade and the B1.p9 lineage Second sample from the 19B clade and the A.1.1 lineage. No shared mutations between the two sequences.	IgM+ and IgG-	IgM+ and IgG+
India (Gupta et al., 2020)	Male	25	36	Asymptomatic	16.6	Asymptomatic	108	9 unique variant differences between the virus isolates from the two episodes of infection	n/a	n/a
India (Gupta et al., 2020)	Female	28	28.16	Asymptomatic	16.92	Asymptomatic	115	10 unique variant differences between the virus isolates from the two episodes of infection	n/a	n/a
India (Shastri et al., 2020)	Male	27	32	Sore throat, nasal congestion and rhinitis	23-25	Myalgia, fever, non-productive cough, fatigue	66	Comparative analyses revealed differences in the presence and absence of specific mutations in the virus	n/a	Negative
India (Shastri et al., 2020)	Male	31	32-33	Asymptomatic	36-38	Myalgia, malaise	65		n/a	Negative

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Location (Reference)	Sex	Age (years)	1 st infection		2 nd infection		Time between infections: positive RT-PCR (days)	Genome sequencing	Ab detected after 1 st infection	Ab detected after 2 nd infection
			Ct value of RT-PCR	Symptoms	Ct value of RT-PCR	Symptoms				
India (Shastri et al., 2020)	Male	27	35-36	Asymptomatic	20-21	Fever, headache, myalgia and a non-productive cough	19 (atypically short but low Ct value)	sequences from the 1st and 2nd episode in all four paired samples. See Table 2 in Shastri et al. (2020) for details	n/a	n/a
India (Shastri et al., 2020)	Female	24	32-35	Sore throat, rhinitis and myalgia	17-21	Fever, myalgia, rhinitis, sore throat, non productive cough and fatigue	55		n/a	Negative
Virginia, USA (Larson et al., 2020)	Male	42	n/a	Cough, subjective fever, myalgias	n/a	Worse-fevers, cough, shortness of breath and GI symptoms	51	Phylogenetics Same lineage, with B.1.26 and the genome encoded the D614G variation several potential variations between the first and second strains, including one high confidence variation.	n/a	IgG+
Netherlands (Mulder et al., 2020)	Female	89	n/a	Fever, severe cough, and lymphocyte count of 0.4x10 ⁹ /L	n/a	More severe- fever, cough, dyspnea - resulted in death	59	The two strains differed at 10 nucleotide positions and sequences did not cluster in the phylogenetic tree.	n/a	negative
Qatar (Raddad et al., 2020) 4 confirmed via genetic sequencing	Female	45-49	36	Severity (symptoms) not assessed, not hospitalized	25	Severity (symptoms) not assessed, not hospitalized	88	One genome of inferior quality, but differences included the D614G mutation (supporting evidence of reinfection)	n/a	negative
Qatar (Raddad et al., 2020)	Male	25-29	36	Severity (symptoms) not assessed, not hospitalized	28	Severity (symptoms) not assessed, not hospitalized	46	Multiple changes of allele frequency and D614G mutation (conclusive evidence for reinfection)	n/a	n/a
Qatar (Raddad et al., 2020)	Male	40-44	17	Severity (symptoms) not assessed, not hospitalized	29	Severity (symptoms) not assessed, not hospitalized	71	Multiple changes of allele frequency and D614G mutation (conclusive evidence for reinfection)	n/a	n/a
Qatar (Raddad et al., 2020)	Male	25-29	30	Severity (symptoms) not assessed, not hospitalized	32	Severity (symptoms) not assessed, not hospitalized	55	One genome of inferior quality, but differences included the D614G mutation (supporting evidence of reinfection)	n/a	n/a

Shaded cells – less robust evidence of reinfection as high Ct value, and/or same clade. See CDC reinfection laboratory methods and levels of evidence section below.

Table 1b: Characteristics of cases of reinfections with SARS-CoV-2 to be considered (US CDC criteria), not confirmed by genetic sequencing

Location (Reference)	Sex	Age (years)	1 st infection		2 nd infection		Time between infections: positive RT-PCR (days)	Genome sequencing	Ab detected after 1 st infection	Ab detected after 2 nd infection
			Ct value of RT-PCR	Symptoms	Ct value of RT-PCR	Symptoms				
UK (Tomassini et al., 2020)	Male	82	n/a	Cough, fever, sore throat, dyspnoea, new oxygen demand, haemoptysis	n/a	Fever, cough, dyspnoea	87	Not done	n/a	IgG+ (days 88, 92)
UK (Tomassini et al., 2020)	Female	62	n/a	Cough, fever, dyspnoea	n/a	Asymptomatic (HCW on immunocompromised unit, routine screening)	84	Not done	n/a	IgG+ (days 62, 85)

Discussion

Virologic findings in reinfection cases

The viral load also varies as shown by the Ct values (lower number = higher viral load) reported for first infections and reinfections (Table 1a). No clear pattern is apparent, and the small number of cases makes any generalization challenging. The Ct count for reinfections was lower in two cases, indicating a higher viral load than the first infection and may indicate infectiousness (Iwasaki, 2020). None of the case reports of reinfections provided information on whether viable virus was collected and could be cultivated.

The degree of sequence difference put forth as supporting reinfection in these studies varied from multiple SNVs found corresponding to different lineages and clades, to “a single high certainty variation”. The natural history of viral mutation over the course of infection has not been fully clarified, so it is unclear whether a single high confidence variation in a 51-day proposed reinfection (without Ct values reported; as reported by Larson et al. [2020]) truly constitutes a reinfection. See below for the levels of evidence suggested by the CDC in assessing reinfections.

Serologic findings in reinfection cases, and coronavirus immunity

Serology results were not always available in the described reinfection cases, and in those where it was done, antibodies against SARS-CoV-2 could be absent in the reinfection sample, even when present in the first infection sample (Table 1a). There were two cases with paired serology, the first case both samples were positive for IgG, the second both were positive for IgM but the IgG only was positive on the second assay. There were 11 cases with serology after the second respiratory sample was positive, with 5/11 negative, 4/11 showing IgG only, and one case with IgM, IgG and IgA positive, and one with IgM and IgG positive. It should be noted that a variety of serologic assays are in use with different operating characteristics, so these data are not directly comparable and the number of samples (cases) is small.

Brief overview: coronavirus immunity

The volume of publications on the topic of immunity and immune responses to infection by SARS-CoV-2 has expanded significantly over the past few months, so a brief overview only is included in this targeted rapid review. Previous reviews (March 18, 2020 and May 12, 2020) referenced pre-print studies that have since been published in high quality, peer-reviewed journals and warrant being included again. For example, Wajnberg et al. (2020) showed that more than 99% of patients with mild to moderate symptoms (none were hospitalized) who self-reported or had laboratory-documented SARS-CoV-2 infection developed IgG antibodies. Wu et al. (2020) showed 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 could make these patients more prone to recurrence (and possibly reinfection).

At this time, it is unknown whether the few cases of reinfection are a result of (1) individual weak or absent immune responses to the initial infection, (2) individual immune characteristics that prevent durable immunity, or (3) if long term protective immunity is not possible. Wajnberg et al. (2020) suggest a level of immunity after infection may be anticipated based on what is known about antibody responses to other coronaviruses (SARS-CoV, MERS-CoV, and human coronaviruses [HCoV]), but it is still unknown how long this immunity may last.

Although a full literature search was not done to address this question, a review of key reference articles around immunity was performed to frame this discussion. Key findings are summarized below:

- Human antibody responses to coronaviruses have been summarized in a review by Huang et al. (2020). In this review, the median time to detection of an antibody response was the shortest for SARS-CoV-2 (11.0 days; IQR 7.0–14.0 days), followed by SARS-CoV (13.5 days; IQR 10.0–18.0 days) and MERS-CoV (15.0 days; IQR 12.0–18.0 days).
- Most long-term studies found that SARS-CoV and MERS-CoV IgG waned over time (typically detectable up to at least a year), while others found detectable levels of IgG three years post symptom onset. Antibody kinetics varied across the severity gradient, with antibodies remaining detectable longer after illness with more severe symptoms.

- Human challenge studies with HCoV indicate that serum and mucosal immune responses (serum IgG, IgA, neutralizing titer, and mucosal IgA) provide possible correlates of protection from infection and disease, but response to HCoV229E, an alphacoronavirus, has been assessed in human challenge studies and appears to wane after 6-12 months.
- In a review of adaptive and innate immunity to coronaviruses, Sariol et al. (2020) describe a variable duration of immunity to other human coronaviruses. SARS-CoV and MERS-CoV betacoronavirus infections appear to induce neutralizing antibody responses for a period of time and longer lived (3-6 year) T cell responses. These T cell responses appear to confer partial protection and could also play a role in reducing pathologic innate immune responses involved in cytokine release syndromes. These responses may last longer than neutralizing antibody responses and could be important in longevity of immunity induced by vaccination. However, T cells have also been observed to play possible immunopathogenic roles in some coronavirus infections, including Th2-skewed responses to SARS-CoV.

Based on current literature, it remains unknown whether a neutralizing antibody response, SARSCoV-2-specific T cell response, or both are required, and there is a distinction between preventing infection and transmission (which may be more dependent of neutralizing antibody) and preventing clinical disease (which may be related to T cell responses). Correlates of protection would need to be determined. Longitudinal studies are needed to evaluate the duration of responses after infection (or vaccination), as the current data are inconclusive and we only < 12 months of data since the pandemic started. It should be noted that T cell-mediated responses might minimize disease severity, but might not prevent infection subsequent viral transmission (Sariol et al., 2020).

SARS-CoV Reinfection: impact on the prospect of herd immunity and implications for public health guidance

There has been much public attention to the prospect of natural, population-based immunity (or “herd immunity”) as a potential control method for COVID-19 in populations. Proponents of this approach suggest that allowing spread of infection in lower-risk populations by reducing public health restrictions would reduce the likelihood of repeated epidemic surges. Confining discussion to the available immunologic data around other human coronaviruses does not support this a possibility, and current antibody, T cell immunity and reinfection data for the SARS-CoV-2 virus raises the possibility that natural immunity might not be long lasting. Thus, the prospect of natural, infection-induced durable immunity remains speculative.

Permitting widespread SARS-CoV-2 infection as means of preventing future epidemics in a population should not be considered unless durable natural immunity is proven. These cases of reinfection (though small in number) further support that it is premature to consider this feasible even before considering any other aspects before such as epidemiologic and value based considerations. The occurrence of reinfections also calls into question the possibility of immunity “passports”, at least until the durability of natural immune responses and the relative rarity or commonness of reinfection is further delineated.

Population immunity through the use of vaccines remain a feasible goal because vaccines might be more effective at creating a tailored, durable immune response to the SARS-CoV-2 virus, may be more efficient at reducing viral circulation compared to natural immunity, especially if any acquired immunity requires boosts (a routine part of many vaccines) (Fontanet & Cauchemez, 2020), and vaccine booster series may augment duration of protection of protection wanes.

Reference Information from the US CDC Protocol for investigation of reinfection (CDC, 2020):

Investigative criteria:

1. **Prioritize** persons with detected SARS-CoV-2 RNA ≥ 90 days since first SARS-CoV-2 infection:

Persons with detected SARS-CoV-2 RNA* ≥ 90 days after the first detection of SARS-CoV-2 RNA, whether or not symptoms were present

AND

Paired respiratory specimens (one from each infection episode) are available

*If detected by RT-PCR, only include if Ct value < 33 or if Ct value unavailable

2. **Consider** persons with COVID-19–like symptoms and detection of SARS-CoV-2 RNA 45–89 days since first SARS-CoV-2 infection:

Persons with detection of SARS-CoV-2 RNA* ≥ 45 days after the first detection of SARS-CoV-2 RNA

AND

With a symptomatic second episode and no obvious alternate etiology for COVID-19–like symptoms OR close contact with a person known to have laboratory-confirmed COVID-19

AND

Paired respiratory specimens (one from each infection episode) are available

*If detected by RT-PCR, only include if Ct value < 33 or if Ct value unavailable

Adaptation considerations:

If resources are limited, further prioritize the sampling of persons in high-risk groups (e.g. healthcare workers).

If investigating suspected reinfection cases among severely immunocompromised persons, consider a prospective study dedicated to this population, as results will not be generalizable to the general population.

Participant exclusion criteria:

Laboratory specimen from either first or second illness episode is unavailable.

Estimated number of participants: The estimated monthly enrollment is expected to vary by jurisdiction, duration of local outbreak intensity, and referral testing operational factors. Consider taking these factors, as well as prior number of suspected SARS-CoV-2 cases reported, into account during local protocol adaptation.

Sampling: No a priori sampling will be undertaken; instead all suspected cases reported will be investigated per protocol. When necessary, eligibility criteria may be narrowed per adaptation considerations provided in this common investigation protocol.

LABORATORY TESTING & INTERPRETATION: Reinfection Protocol**Laboratory testing:**

Respiratory specimens should be tested by RT-PCR or other nucleic acid amplification tests to detect viral RNA (Ct values reported) and genomic sequencing to compare strains across episodes. Viral culture and sgRNA can be used to determine the presence or absence of replication-competent virus. If serum is available, also consider serologic testing to determine the immunologic response to initial infection and to suspected reinfection.

If interested in investigating cases in which the initial illness specimen is not available, consider the same laboratory testing, with the exception of genomic sequencing. Genomic sequencing of the suspected reinfection specimen, in the absence of a paired respiratory specimen or detailed knowledge of the circulating SARS-CoV-2 strains during the first SARS-CoV-2 illness or infection, is not recommended.

Genomic sequencing of paired specimens—that meet the quality criteria below—is needed to investigate reinfection. Single nucleotide polymorphism analysis alone might not be sufficient to distinguish reinfection from long-term shedding, as intra-host variation in the mutation rate of SARS-CoV-2 is poorly understood. However, identification of paired specimens from distinct lineages (as defined in Nextstrain or GISAID) serves as higher quality evidence for SARS-CoV-2 reinfection. The quality criteria for testing and levels of evidence are described in more detail below.

Genomic testing should meet the following quality criteria for investigation for reinfection with SARS-CoV-2:

Genome coverage >100/per base position is recommended for consensus generation

Q score of consensus >30 with 99% of the genome covered

1000x average genome coverage recommended for analysis of minor variation

Removal of amplicon primer contamination from assembly

Use of high-fidelity sequencing platforms (Q score per read >30) preferred for consensus generation

If low fidelity sequencing platforms (Q score per read <30) are used, verification of SNPs via alternate sequencing method is encouraged

Support for but not definitive evidence of reinfection can be provided by other information, such as culture or sub-genomic mRNA analysis (to detect the presence of replication-competent virus) or serology, which could be useful to document a serologic response to SARS-CoV-2. Aside from laboratory evidence, other supporting evidence for reinfection could include clinical course (COVID-19–like symptoms) and epidemiologic links to a confirmed case.

Laboratory evidence:

Levels of evidence for reinfections using genomic data are as follows:

Best evidence

Differing clades as defined in Nextstrain and GISAID of SARS-CoV-2 between the first and second infection, ideally coupled with other evidence of actual infection (e.g., high viral titers in each sample or positive for sgRNA, and culture)

Moderate evidence

>2 nucleotide differences per month* in consensus between sequences that meet quality metrics above, ideally coupled with other evidence of actual infection (e.g., high viral titers in each sample or positive for sgRNA, and culture)

Poor evidence but possible

≤2 nucleotide differences per month* in consensus between sequences that meet quality metrics above or >2 nucleotide differences per month* in consensus between sequences that do not meet quality metrics above, ideally coupled with other evidence of actual infection (e.g., high viral titers in each sample or positive for sgRNA, and culture)

* The mutation rate of SARS-CoV-2 is estimated at 2 nucleotide differences per month, therefore if suspected reinfection occurs 90 days after initial infection, moderate evidence would require >6 nucleotide differences.

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Date report submitted to committee: March 18, 2020

Date of re-assessment: May 11, 2020

Date of second re-assessment: November 25, 2020

Authorship and Committee Members

This review was written by Seija Kromm, Lyne Bourassa, and Lynora Saxinger (co-chair, plus primary reviewer), with Alexander Doroshenko, Michael Parkins (external reviewer), and Susanne Benseler (external reviewer) as additional reviewers. The full Scientific Advisory Group was involved in discussion and revision of the document: Braden Manns (co-chair), Lynora Saxinger (co-chair), John Conly, Alexander Doroshenko, Shelley Duggan, Nelson Lee, Elizabeth MacKay, Andrew McRae, Melissa Potestio, 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

COVID-19: Coronavirus Disease-2019

Ct: Cycle threshold value

CDC: US Centers for Disease Control and Prevention

HCoV: Human coronavirus

HCW: Healthcare worker

IQR: Interquartile range

RT-PCR: Reverse transcription polymerase chain reaction

SAG: Scientific Advisory Group

SARS: Severe Acute Respiratory Syndrome

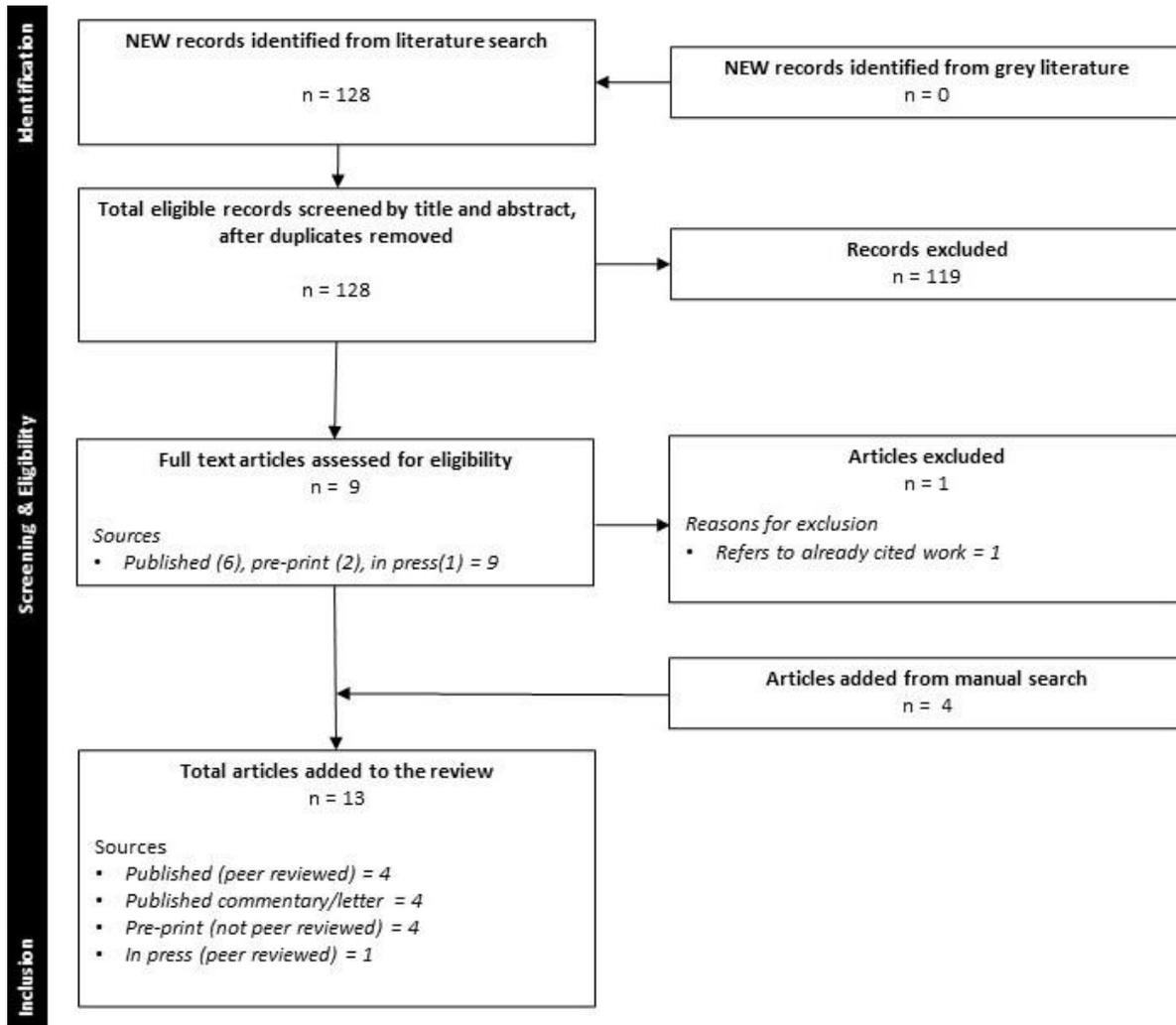
SNV: Single nucleotide variant

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 May 1, 2020 to date of search (October 13, 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 2 below. The PRISMA diagram in Figure 1 provides the flowchart for the newly added literature review evidence.

Figure 1. Flowchart of literature focused on reinfection with SARS-CoV-2 (with genetic sequencing)**Table 2.** 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 (confirmed by genetic sequencing) - Human only - Timeline: May 1, 2020 to October 13, 2020 - All methods - 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 discussion)

	articles, letters to the editor, newspaper articles and other media publications) <ul style="list-style-type: none"> - Not about re-infection - Focus is on immune response, reactivation, recurrence, relapse, and/or re-positive - Focus is on human/seasonal coronavirus with no apparent linkage to the novel coronavirus(es) - Animal models/studies - Modelling studies - SARS-CoV and MERS-CoV - Reinfection without genetic sequencing
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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 3 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 3. Narrative overview of the NEW literature included in this review.

	Description
Volume	<ul style="list-style-type: none"> • 12 articles <ul style="list-style-type: none"> ○ 1 retrospective cohort study (pre-print) from Qatar ○ 1 prospective cohort study (peer-reviewed) from China ○ 5 case reports (3 peer-reviewed, 2 pre-print) from USA, Ecuador, and China ○ 4 Letters to the Editor (peer-reviewed with 1 in press) from India, USA, Netherlands and Belgium ○ 1 commentary (peer-reviewed) from USA
Quality	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, with articles reporting individual cases besides Raddad et al (2020) who reports four cases. The available study designs are potentially biased given they are observational – but this is difficult to avoid given the novel nature of the subject matter and the small number of cases of reinfection worldwide.
Applicability	The current evidence are reports from various countries While public health controls may be different than in Alberta, this does not impact the applicability of the currently available evidence to Alberta.
Consistency	N/A

*Search Strategy***Database: Medline/PubMed****Date search conducted: Sep 8, 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. (51113)
- 2 exp Recurrence/ (184128)
- 3 reinfect*.mp. (9238)
- 4 recurren*.mp. (679274)
- 5 relaps*.mp. (182595)
- 6 recrudescence*.mp. (2904)
- 7 reoccur*.mp. (2683)
- 8 exp Immunity/ (341381)
- 9 immunity.mp. (289827)
- 10 immune.mp. (713213)
- 11 exp Antibodies, Viral/ (105676)
- 12 exp Antibodies, Neutralizing/ (11042)
- 13 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (1840799)
- 14 1 and 13 (6388)
- 15 limit 14 to yr="2020" (2478) – Did not use this search strategy because it pulled up too much extraneous, unrelated information due to keywords immunity and the Antibody/Immunity subject headings. Ran search below, removing these terms, and had a much more manageable and relevant set of results.

- 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. (51113)
- 2 exp Recurrence/ (184128)
- 3 reinfect*.mp. (9238)
- 4 recurren*.mp. (679274)
- 5 relaps*.mp. (182595)
- 6 recrudescence*.mp. (2904)
- 7 reoccur*.mp. (2683)
- 8 exp Antibodies, Viral/ (105676)
- 9 exp Antibodies, Neutralizing/ (11042)
- 10 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (917420)
- 11 1 and 10 (2910)
- 12 limit 11 to yr="2020" (662)

Database: CINAHL**Date search conducted: Sep 8, 2020****Search terms used/Strategy:**

- S1 (MH "Coronavirus+") OR (MH "Coronavirus Infections+") OR coronaviru* OR "corona virus" OR ncov* OR n-cov* OR ("2019 ncov" OR 2019ncov OR Hcov*)
16,166
- S2 COVID-19 OR COVID19 OR COVID-2019 OR COVID2019 15,458

- S3 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 1,810
- S4 (MH "Severe Acute Respiratory Syndrome") 2,213
- S5 ("severe acute respiratory syndrome cov 2" OR "severe acute respiratory syndrome coronavirus*") OR "severe acute respiratory syndrome" OR "severe acute respiratory disease*" 3,470
- S6 S1 OR S2 OR S3 OR S4 OR S5 20,341
- S7 (MH "Recurrence") 48,452
- S8 reinfect* OR reccur* OR relaps* OR reoccur* OR recrudescence 35,122
- S9 (MH "Antibodies+") OR antibod* 103,999
- S10 S7 OR S8 OR S9 173,821
- S11 S6 AND S10 515
- S12 S6 AND S10 Limiters - Published Date: 20200401- 306

Database: Grey literature**Date search conducted: Sep 8, 2020****Search terms used/Strategy:****TRIP Pro/Google Scholar/Google/**

("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) from:2020

LitCovid/CEBM/ WHO/CDC/Stanford Medicine NEJM/CochraneLibrary/covidevidence.org/medRxiv

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

Database: Medline/PubMed**Date search conducted: Oct 13, 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. (66975)
- 2 "severe acute respiratory syndrome*".mp. (33727)
- 3 "severe acute respiratory disease*".mp. (55)
- 4 exp Severe Acute Respiratory Syndrome/ (5079)
- 5 1 or 2 or 3 or 4 (67704)
- 6 exp Recurrence/ (184697)
- 7 reinfect*.mp. (9568)
- 8 recurren*.mp. (720825)
- 9 relaps*.mp. (193946)
- 10 recrudescence*.mp. (2984)
- 11 reoccur*.mp. (2957)
- 12 exp Antibodies, Viral/ (106248)
- 13 exp Antibodies, Neutralizing/ (11273)

- 14 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (969439)
 15 5 and 14 (3241)
 16 limit 15 to dt=20200901-20201013 (115)

CINAHL

- S1 (MH "Coronavirus+") OR (MH "Coronavirus Infections+") OR coronaviru* OR "corona virus" OR ncov* OR n-cov* OR ("2019 ncov" OR 2019ncov OR Hcov*) 16,166
 S2 COVID-19 OR COVID19 OR COVID-2019 OR COVID2019 15,458
 S3 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 1,810
 S4 (MH "Severe Acute Respiratory Syndrome") 2,213
 S5 ("severe acute respiratory syndrome cov 2" OR "severe acute respiratory syndrome coronavirus*") OR "severe acute respiratory syndrome" OR "severe acute respiratory disease*" 3,470
 S6 S1 OR S2 OR S3 OR S4 OR S5 20,341
 S7 (MH "Recurrence") 48,452
 S8 reinfect* OR reccur* OR relaps* OR reoccur* OR recrudescence 35,122
 S9 (MH "Antibodies+") OR antibod* 103,999
 S10 S7 OR S8 OR S9 173,821
 S11 S6 AND S10 515
 S12 S6 AND S10 Limiters - Published Date: 20200401- 306

Database: Grey literature**Date search conducted: Oct 13, 2020****Search terms used/Strategy:****TRIP Pro/Google Scholar/Google**

("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) from:2020

LitCovid/CEBM/ WHO/CDC/Stanford Medicine NEJM/CochraneLibrary/covidevidence.org/medRxiv

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

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