Australian Government
National Health and Medical Research Council

NHMRC

National COVID-19 Health and Research Advisory Committee[a]

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Reinfection: what do we know and what are the implications for vaccines?

Question:

What do we know about SARS-CoV-2 reinfection? How common is it? And what are the implications for vaccines?

This paper focusses on natural- and vaccine-induced immunity as we currently understand these concepts. Establishing whether reinfection by SARS-CoV-2 is possible has important implications for considering the likelihood of achieving herd immunity against this virus.

Key points[b]

The following points provide a summary of the information emerging from published evidence and expert advice relevant to the above question. Some of the points are speculative, which is consistent with the recent nature of the COVID-19 pandemic. This advice is point in time and may need further review as more evidence is available.

This report was reviewed by Professor Sharon Lewin AO (co-Chair of NCHRAC) and Professor Michael Good AO (NCHRAC member).

Technical terms are explained in the Glossary (Attachment 1).

1. People with SARS-CoV-2 may continue to test positive for several months without being sick or infectious, although this is rare. Reinfection is confirmed when testing shows that each virus' genetic makeup is different.
2. Reinfection could occur if neutralising antibodies and/or cell-mediated immunity declines or the virus changes such that critical immunogenic epitopes are no longer recognised.
3. Antibodies to SARS-CoV-2 generally decrease after the first few months of infection. However, there is evidence that memory B and T-cells will contribute to long-lasting immunity to SARS-CoV-2. Their ability to respond quickly (an anamnestic response), together with pre-existing antibody, will underpin natural immunity.
4. The critical level of antibody to allow protection from infection has recently been defined in monkey models, but is not yet known in humans.

[a] NHMRC is providing secretariat and project support for the Committee, which was established to provide advice to the Commonwealth Chief Medical Officer on Australia's health response to the COVID-19 pandemic. The Committee is not established under the NHMRC Act and does not advise the NHMRC CEO.
[b] See Background section for definitions of key terms.

5. Cases of reinfection have been reported but remain rare. However, it is difficult to be quantitative because the number of people exposed twice to SARS-CoV-2 is likely to be low and reinfections will only be detected if patients are tested. Most people who are re-infected but asymptomatic will evade detection, but these people are likely to be infectious. The COVID-19 reinfection tracker is a useful resource.
6. Based on the responses to other coronaviruses, it is possible that long-term immunity will not follow infection. Data from a recent study in rhesus macaques (monkeys) showed that virus-specific antibodies could provide complete protection (sterile immunity) in the short term to reinfection. The antibody threshold level for protection was a neutralising antibody titre of ~ 50 and an ELISA titre to the receptor binding domain of the Spike protein of ~ 100.
7. The level of antibody response is generally higher in people with more severe infections. There is evidence that people with asymptomatic initial infections have lower antibody titres which are more likely to wane over time.
8. The overall picture of people's immune responses to SARS-CoV-2 may be mixed with varying levels of total antibody, neutralising antibody and T-cell responses in different individuals after an initial infection or vaccination.
9. The nature and duration of natural immunity and vaccine-induced immunity could be very different because of the different ways in which the critical antigens are vectored and delivered. There are examples in other viruses where vaccine-induced immunity is more potent and more durable than natural immunity
10. Whilst vaccines are crucial in the global response to COVID-19, it is likely that vaccines will not result in life-long immunity. Vaccines based on mRNA technology have not been used in humans before and as such we cannot speculate on the duration of immunity that they may induce. Similarly, adenoviral vaccines have not previously been licensed for human use.
11. The likelihood of successful herd immunity depends on the efficacy and duration of natural and vaccine immunity, and other factors. For a virus with a Ro value of 2.5, >60% of the population needs to be immune for herd immunity to extinguish the epidemic. This level of immunity can come from a vaccine or natural immunity but other non-pharmaceutical interventions can also contribute to protection.
12. Given the possibility of reinfection, it will be important to determine whether more severe disease can occur in vaccine failures (known as antibody-dependent enhancement). There is no evidence to date that this occurs in animal models. In human clinical Phase III trials of three effective COVID vaccines to date, there was reduced or no severe disease in vaccinated individuals. This theoretical concern will need to be assessed in large numbers of people in Phase IV trials, outside of Australia.
13. None of the current vaccines have shown sterilising immunity in animal models. This means that infection in the nose but not lung was demonstrated in vaccinated animals. If sterilising immunity is not achieved, then ongoing transmission would still be possible. This potential limitation of first generation vaccines will need to be considered in the context of international travel to Australia and quarantine procedures.
14. In one large Phase III vaccine study of the chimpanzee adenovirus vector (Oxford/Astra Zeneca), endpoint included symptomatic and severe disease as well as asymptomatic

infection (detected by weekly RT-PCR tests). Vaccine efficacy was lower for asymptomatic infection compared to symptomatic disease.

Background:

Below is an explanation of the main concepts that underpin the Key points above.

Technical terms are explained in the Glossary (Attachment 1).

Reinfection

Reinfection can be defined as either:

- when a person was infected and got sick once, recovered and cleared the virus, and then later became infected and got sick again, OR
- a virus enters cells in the body again (after the original virus has been cleared), regardless of whether symptoms develop for either the first or subsequent episodes of infection.

The first definition is more relevant to the individual, whereas reinfection that results in the person being infectious to others is important with respect to the transmission of the virus.

Since the scientific literature uses both definitions, both aspects of reinfection are considered in this paper.

Terms and concepts such as reactivation, relapse, inflammatory rebound and recurrence are also used in the literature. The distinction between these terms and reinfection is not always clear. This advice paper focusses on reinfection by a SARS-CoV-2 virus that is genetically distinct from the SARS-CoV-2 virus that caused the initial infection, which has been confirmed by genetic sequencing.

It is challenging to properly determine that reinfection has occurred. The US Centers for Disease Control and Prevention have published criteria for establishing SARS-CoV-2 reinfection.[c]

RT-PCR, a method which detects viral RNA, is often used to demonstrate that the original virus has been cleared. RT-PCR is also semi-quantitative and can distinguish high and low levels of virus. RT-PCR can detect down to very low levels which are likely not relevant for transmission. False positive or false negative results can also occur. RT-PCR can detect RNA of the "dead virus" that remains in the recovered patient's body.

Sterilising vs clinical immunity

Sterilising immunity means that there is no replication of the virus in the host as the result of an immune response. In the case of SARS-CoV-2, this means no virus in the nasal passages or lungs. The rhesus macaque study by McMahan et al. (ref #18) showed that it can be mediated solely by neutralising antibodies if the titre is sufficient. However, a sub class of T-cells (CD8+) can contribute to sterile protection when antibody titres decline.

[c] https://www.cdc.gov/coronavirus/2019-ncov/php/reinfection.html

For reinfection by SARS-CoV-2 to occur, there cannot be sterilising immunity as this would prevent infection.

Clinical immunity occurs when, as a result of an immune response, a person has no symptoms or signs of infection and therefore they are protected from developing disease. It does not imply sterile immunity and people with clinical immunity may still have virus identified in the nose and therefore could still be infectious. More work is needed to understand if the amount of virus identified in the nose is directly related to risk of transmission.

Many vaccines are primarily intended to prevent clinical disease (in animal models, this is measured as virus identified in the lungs) and do not necessarily protect against infection (in animals and humans identified as virus identified in the nose). In other words, not all vaccines produce a sterilising immune response.[d]

In humans, the outcomes of infection can be detected as:

1. Symptomatic infection – virus identified on a nasal swab and accompanied by a range of clinical symptoms that can be mild, moderate or severe
2. Asymptomatic infection – virus identified on a nasal swab but no symptoms, or
3. Transmission of virus to others – can only be quantified at a population level.

Herd immunity and vaccines

Herd immunity is population resistance to the spread of a virus. It is achieved when a high enough proportion of individuals have sterilising immunity to a virus, either through natural or vaccine-induced immunity. Herd immunity will be more challenging to achieve if a virus infection does not lead to sterilising immunity, since viral transmission will still be possible even if individuals have only clinical immunity.

An overview of vaccine development is out of scope for this paper. However, it should be noted that vaccines comprising different technologies for stimulating an immune response against SARS-CoV-2 are being utilised. This includes vaccines based on mRNA technology or using other viruses to deliver the SARS-CoV-2 antigens. These include human and chimpanzee adenoviruses. These have not been licensed previously for use in humans.

Context

Reinfection by SARS-CoV-2 and implications for vaccines is a particularly active area of research and much has been published on this topic since the start of the COVID-19 pandemic. Key reports are outlined below.

A rapid evidence report from the Alberta Health Services COVID-19 Scientific Advisory Group in November 2020 on the topic *Can people with previous COVID-19 infection be reinfected by the virus?* provides an excellent summary of the current evidence about reinfection (Attachment 2). The Albertan group published reports on the same topic in March and May

[d] https://thehill.com/changing-america/well-being/prevention-cures/501677-what-is-sterilizing-immunity-and-do-we-need-it

2020). The Albertan report includes a summary table (Table 1a) of reported cases as of 13 October 2020, which is based on a similar table in Iwasaki (2020) (ref #6).

A report from the Burnet Institute's Know-C19 Hub in September 2020 (Attachment 3) provides the following summary of what is known about the duration of immunity to SARS-CoV-2:

- Antibody responses to SARS-CoV-2 can be detected 10-15 days post symptom onset. One study looking at neutralising antibody titres post infection showed a decline at just 90 days post symptom onset. It was also found that there was a correlation between more severe disease symptoms and higher antibody titres.
- Clinical immunity involving B and T cells may play a vital role in immunity and subsequent reinfection.
- Further vaccine research needs to be conducted to understand whether a vaccine will confer sterilising immunity or, if it instead, mainly prevents severe COVID-19.

The Rapid Research Information Forum provided the report *Reinfection with SARS-CoV-2* to the Minister for Health on 19 April 2020 (Attachment 4). This report found that:

- The evidence for reinfection is based on anecdotal reports that may have flawed methodology.
- No direct evidence for immunity in patients exists, however it is likely that patients are protected from reinfection based on the changes detected in the blood cells and antibodies seen in most recovered patients.
- Population-level studies are needed to determine with greater certainty whether reinfection can occur in people who have developed antibodies to SARS-CoV-2.
- A decline in immunity or mutations in the virus could increase possibility of reinfection.

Approach

The Albertan report (Attachment 2) conducted a rapid review of evidence about SARS-CoV-2 reinfection published between 4 May 2020 and 13 October 2020. As such, the approach for this advice paper was to build on this evidence review and focus on evidence published after 13 October 2020.

The key search strategy was to search Pubmed using the search term "covid-19 reinfection". This search on 7 December 2020 resulted in the identification of 159 publications. Publications that met the following criteria were included in the evidence tables below:

1. Published after 13 October 2020 (exceptions noted in tables below)
2. Not included in Albertan report (Attachment 2)
3. Related to SARS-CoV-2 reinfection, which included aspects such as:
    a. likelihood and rate of reinfection
    b. mechanisms underlying reinfection
    c. how soon after the first infection reinfection can take place
    d. severity of reinfection cases
    e. immune response to SARS-CoV-2

f. implications of reinfection for vaccines.

4. Focus on humans or primates
5. Reinfection was established by genetic sequencing (where relevant)
6. Written in English.

Grey literature[e,f,g,h] was identified via newsletters, internet searches and email alerts and led to the identification of additional references that were included in the evidence tables below. Some references were provided directly by NCHRAC members.

Exceptions to the above search strategy are outlined in the evidence tables below.

The Key points were developed based on consideration of the three reports (Attachments 2–4) and the evidence published since 13 October 2020. The last three Key points are unique to this advice paper and are not reflected in the Albertan report.

Evidence about SARS-CoV-2 reinfection by SARS-CoV-2 and implications for vaccines

The references in Table 1 are relevant directly to reinfection or the implication of reinfection for vaccines. Table 1 provides the first author, date of publication, journal, title and a concise statement about the relevance of the reference to the topic.

The full abstract (or summary) and search strategy for each reference and is included in Table 3.

Table 1: References published since 13 October relevant directly to reinfection or the implication of reinfection for vaccines (or recent references not included in Albertan report at Attachment 2 that informed this advice paper, marked with a '*').

Ref #	First author	Date and journal	Title	Relevance
1	W. Deng	1 September 2020* Science	Primary exposure to SARS-CoV-2 protects against reinfection in rhesus macaques	*Included since only the preprint was included in Albertan report.* Primary SARS-CoV-2 exposure protects against subsequent reinfection in rhesus macaques.

[e] https://www.scientificamerican.com/article/what-covid-19-reinfection-means-for-vaccines/

[f] https://theconversation.com/coronavirus-reinfection-what-it-actually-means-and-why-you-shouldnt-panic-144965

[g] https://www.smh.com.au/national/a-man-was-reinfected-with-covid-what-does-that-mean-for-immunity-20200902-p55rlq.html

[h] https://www.statnews.com/2020/08/25/four-scenarios-on-how-we-might-develop-immunity-to-covid-19/

Ref #	First author	Date and journal	Title	Relevance
2	A. A. Osman	September 2020* New Microbes and New Infections	Re-positive coronavirus disease 2019 PCR test: could it be a reinfection? [mini-review]	*Not included in Albertan report.* Positive RT-qPCR assays after previous negative results due to false-negative laboratory results and prolonged viral shedding, rather than to reinfection.
3	M.F. Good and M.T. Hawkes	October 2020* mBio	The Interaction of Natural and Vaccine-Induced Immunity with Social Distancing Predicts the Evolution of the COVID-19 Pandemic	Examines relationship between immunity and vaccine effectiveness based on modelling.
4	J. M. Coish	October 2020* Microbes and Infection	Out of the frying pan and into the fire? Due diligence warranted for ADE in COVID-19 [commentary]	*Not included in Albertan report.* Discusses antibody-dependent enhancement in context of vaccine development and the importance of in vitro experiments.
5	A. Gidari	10 October 2020* European Journal of Clinical Microbiology & Infectious Diseases	Is recurrence possible in coronavirus disease 2019 (COVID-19)? Case series and systematic review of literature	*Not included in Albertan report.* Shows difficulty in delineating recurrence and reinfection. Recurrence mostly due to prolonged viral RNA persistence in the respiratory tract.

Ref #	First author	Date and journal	Title	Relevance
6	A. Iwasaki	12 October 2020 The Lancet Infectious Diseases	What reinfections mean for COVID-19.	*This report was included in Albertan report at Attachment 2 and is included here because of its relevance to this advice paper.*
7	A. Ghali	13 October 2020 Qatar Medical Journal	Cases and etiologies of suspected COVID-19 reactivation [editorial]	Suggests that reinfection or reactivation of the virus is actually a result of prolonged shedding of the virus complemented with occasional false positives/negatives and lab errors.
8	W. F. Garcia-Beltran	20 October 2020 medRxiv	COVID-19 neutralizing antibodies predict disease severity and survival [preprint]	Shows importance of neutralising humoral immunity on disease progression. Evidence for protection against wild type and mutant SARS-CoV-2 reinfection.
9	A. Addetia	21 October 2020 Journal of Clinical Microbiology	Neutralizing Antibodies Correlate with Protection from SARS-CoV-2 in Humans during a Fishery Vessel Outbreak with a High Attack Rate	Presence of neutralising antibodies from prior infection was significantly associated with protection against reinfection.

Ref #	First author	Date and journal	Title	Relevance
10	J. Overbaugh	22 October 2020 Nature Medicine	Understanding protection from SARS-CoV-2 by studying reinfection [news and views]	Implication of reinfection for vaccines.
11	P. Colson	15 November 2020 Journal of Infection [letter to the editor]	Evidence of SARS-CoV-2 reinfection with a different genotype	Case studies of early reinfection.
12	J-S. Lee	21 November 2020 Clinical Infectious Diseases	Evidence of Severe Acute Respiratory Syndrome Coronavirus 2 Reinfection After Recovery from Mild Coronavirus Disease 2019	A case study of reinfection shortly after recovery from mild initial infection in Korea, confirmed by genomic sequencing (not included in Table 1a of Albertan report).
13	B. Prado-Vivar	23 November 2020 Lancet Infectious Diseases	A case of SARS-CoV-2 reinfection in Ecuador	Case was included in Table 1a of Albertan report; however only preprint was available at the time.
14	B. Spellberg	24 November 2020 JAMA Internal Medicine	Antibodies, Immunity, and COVID-19 [invited commentary]	Overview of immunity and reinfection in the context of US seroprevalence study.
15	S. Falahi	November 2020 New Microbes and New Infections	COVID-19 reinfection: prolonged shedding or true reinfection	Reviews difficulties in establishing true cases of reinfection.
16	C. Woolsey	24 November 2020	Establishment of an African green monkey model for	Evidence for protection against

Ref #	First author	Date and journal	Title	Relevance
		Nature Immunology	COVID-19 and protection against reinfection	reinfection in monkey model.
17	K-H. Song	25 November 2020 Korean Journal of Internal Medicine	Dynamics of viral load and anti-SARS-CoV-2 antibodies in patients with positive RT-PCR results after recovery from COVID-19 [rapid communication]	Show detection of RNA particles more likely than reinfection in four patients.
18	K. McMahan	4 December 2020 Nature	Correlates of protection against SARS-CoV-2 in rhesus macaques	Shows in monkeys that sterilising immunity is directly related to titre of total and neutralising antibodies. CD8 T-cells also play a role but are only partially protective.
19	C. Yang	December 2020 Emerging Microbes and Infections	Viral RNA level, serum antibody responses, and transmission risk in recovered COVID-19 patients with recurrent positive SARS-CoV-2 RNA test results: a population-based observational cohort study.	Recurrence more likely than reinfection.

Other relevant evidence or reviews

The articles in Table 2 provide background information and have informed the development of this report. Most articles examine the immune response to SARS-CoV-2 infection (sero-prevalence). These types of studies do not provide evidence about the likelihood of reinfection since the relationship between antibodies/immune cells and immunity is not known (the "correlates of protection"). In particular, articles related to memory B- or T-cells have been included.

Table 2 provides the first author, date of publication, journal, title and a concise statement about the relevance of the reference to the topic. The full abstract (or summary) and search strategy for each reference and is included in Table 3.

Table 2: References not related directly to reinfection and the implication of reinfection for vaccines. Most references were published since 13 October, however other references that were also informed this advice paper (not included in Albertan report at Attachment 2), marked with a '*', have been included.

Ref #	First author	Date and journal	Title	Relevance/key finding
20	Z. Chen	29 July 2020* Nature Reviews Immunology	T cell responses in patients with COVID-19 [review]	*Not included in Albertan report.* Likely role for T cells in COVID-19 pathology and immunological memory
21	D. F. Gudbjartsson	1 September 2020* New England Journal of Medicine	Humoral Immune Response to SARS-CoV-2 in Iceland	*Not included in Albertan report.* Antiviral antibodies against SARS-CoV-2 did not decline within 4 months after diagnosis by RNA test.
22	Y. Peng	4 September 2020* Nature Immunology	Broad and strong memory CD4+ and CD8+ T cells induced by SARS-CoV-2 in UK convalescent individuals following COVID-19	*Not included in Albertan report.* Evidence for memory T cells against SARS-CoV-2.
23	A.W.D. Edridge	14 September 2020* Nature Medicine	Seasonal coronavirus protective immunity is short-lasting	*Not included in Albertan report.* Reinfection with the same seasonal coronavirus occurred frequently at 12 months after infection.
24	Y. Tan	5 October 2020* Frontiers in Medicine	Durability of neutralizing antibodies and T-cell response post SARS-CoV-2 infection	*Not included in Albertan report.* Evidence for humoral and cellular immunity persisting over a relatively longer period,

Ref #	First author	Date and journal	Title	Relevance/key finding
				including to a SARS-CoV-2 variants.
25	T. Wu	5 October 2020* Frontiers in Medicine	Persistence of humoral and cellular immune response after SARS-CoV-2 infection: opportunities and challenges [Comment]	*Not included in Albertan report.* Overview of immune response to SARS-CoV-2, emphasising that it is still not well understood.
26	A. Plüddemann	19 October 2020 Centre for Evidence-Based Medicine article	What is the role of T cells in COVID-19 infection? Why immunity is about more than antibodies	Likely role for T cells in COVID-19 pathology and immunological memory.
27	J. Seow	26 October 2020 Nature Microbiology	Longitudinal observation and decline of neutralizing antibody responses in the three months following SARS-CoV-2 infection in humans	Neutralising antibody response declines after initial infection and is related to disease severity.
28	C.O. Ogega	30 October 2020 medRxiv	Durable SARS-CoV-2 B cell immunity after mild or severe disease [preprint]	Evidence for B cell-mediated immunity against SARS-CoV-2 after recovery from mild or severe COVID-19 disease.
29	C. Gaebler	5 November 2020 bioRxiv	Evolution of Antibody Immunity to SARS-CoV-2 [preprint]	Memory B cell response to SARS-CoV-2 evolves between 1.3 and 6.2 months after infection.
30	J. M. Dan	16 November 2020 bioRxiv	Immunological memory to SARS-CoV-2 assessed for greater than six months after infection [preprint]	Detection of memory B cells six months after infection.

Ref #	First author	Date and journal	Title	Relevance/key finding
31	Z. Li	16 November 2020 bioRxiv	SARS-CoV-2-specific T cell memory is long-lasting in the majority of convalsecent COVID-19 individuals [preprint]	T cell memory responses present nine months after infection.
32	G. E. Hartley	20 November 2020 MedRxiv	Rapid and lasting generation of B-cell memory to SARS-CoV-2 spike and nucleocapsid proteins in COVID-19 disease and convalescence [preprint]	Detection of memory B cells eight months after infection.
33	L. B. Rodda	23 November 2020 Cell	Functional SARS-CoV-2-specific immune memory persists after mild COVID-19 (in press; journal pre-proof)	Mild COVID-19 elicits memory lymphocytes that persist and display functional hallmarks of antiviral immunity.
34	C. Horner	30 November 2020 Proceedings of the National Academy of Sciences of the USA	A highly immunogenic and effective measles virus-based Th1-biased COVID-19 vaccine	Demonstrates the important of how antigens are vectored and delivered for the nature and duration of immunity.
35	M. Voysey	8 December 2020 The Lancet	Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK	Vaccine efficacy for symptomatic and asymptomatic infection.

Abstracts

Each box contains the reference number, title, first author, date, source, search strategy, and the abstract (if available) and/or summary of the key findings.

Table 3: The full abstract (or summary) and search strategy for references in Tables 1 and 2.

#1 Primary exposure to SARS-CoV-2 protects against reinfection in rhesus macaques W. Deng | 1 September 2020 | Science	Search strategy: Pubmed search using term [covid-19 reinfection]
Coronavirus disease 2019 (COVID-19), which is caused by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global pandemic. It is unclear whether convalescing patients have a risk of reinfection. We generated a rhesus macaque model of SARS-CoV-2 infection that was characterised by interstitial pneumonia and systemic viral dissemination mainly in the respiratory and gastrointestinal tracts. Rhesus macaques reinfected with the identical SARS-CoV-2 strain during the early recovery phase of the initial SARS-CoV-2 infection did not show detectable viral dissemination, clinical manifestations of viral disease, or histopathological changes. Comparing the humoral and cellular immunity between primary infection and rechallenge revealed notably enhanced neutralising antibody and immune responses. Our results suggest that primary SARS-CoV-2 exposure protects against subsequent reinfection in rhesus macaques.	

#2 Re-positive coronavirus disease 2019 PCR test: could it be a reinfection? [mini-review] A. A. Osman| September 2020 | New Microbes and New Infections	Search strategy: Pubmed search using term [covid-19 reinfection]
Abstract: The coronavirus disease 2019 (COVID-19) outbreak started in December 2019 and rapidly spread around the globe as a major health threat. Several reports on re-positive cases subsequent to discharge from hospitals caught our attention. We aimed to highlight RT-qPCR positivity re-detection after discharge from isolation, with special consideration of the possible reasons behind it. We found that re-positive RT-qPCR assays for severe acute respiratory syndrome coronavirus 2 after previous negative results might be attributed to false-negative laboratory results and prolonged viral shedding, rather than to reinfection. These findings are encouraging and should be validated in a larger cohort. Table presents an overview of the reports on PCR re-positive COVID-19 cases and conclusions, including suspected reactivation. Provides a summary of the limitations of RT-qPCR.	

#3 The Interaction of Natural and Vaccine-Induced Immunity with Social Distancing Predicts the Evolution of the COVID-19 Pandemic M.F. Good and M.T. Hawkes | Oct 2020 | mBio	Search strategy: Provided by NCHRAC member.
The existence and nature of immunity to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are currently unknown; however, neutralising antibodies are thought to play the major role and data from studying other coronaviruses suggest that partial clinical immunity lasting up to 1 year will occur postinfection. We show how immunity, depending on its durability, may work with current social practices to limit the spread of the virus. We further show that a vaccine that is 50% effective and taken by 50% of the population will prevent further loss of life, providing that social distancing is still practiced and that immunity does not wane quickly. The ability of our society to function effectively moving forward will depend on how the spread of the SARS-CoV-2 virus is contained. Immunity to the virus will be critical to this equation.	

#4 Out of the frying pan and into the fire? Due diligence warranted for ADE in COVID-19 [commentary] J. M. Coish | October 2020 | Microbes and Infection	Search strategy: Pubmed search using term [covid-19 reinfection]
Antibody-dependent enhancement (ADE) is an atypical immunological paradox commonly associated with dengue virus reinfection. However, various research models have demonstrated this phenomenon with other viral families, including *Coronaviridae*. Recently, ADE in SARS-CoV-2 has emerged as one hypothesis to explain severe clinical manifestations. Whether SARS-CoV-2 is augmented by ADE remains undetermined and has therefore garnered criticism for the improper attribution of the phenomenon to the pandemic. Thus, critical evaluation of ADE in SARS-CoV-2 vaccine development will be indispensable to avoid a global setback and the erosion of public trust.	

#5 Is recurrence possible in coronavirus disease 2019 (COVID-19)? Case series and systematic review of literature A. Gidari| 10 October 2020 | European Journal of Clinical Microbiology & Infectious Diseases	Search strategy: Pubmed search using term [covid-19 reinfection]
Abstract: Can a patient diagnosed with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) be infected again? This question is still unsolved. We tried to analyse local and literature cases with a positive respiratory swab after recovery. We collected data from symptomatic patients diagnosed with SARS-CoV-2 infection in the Italian Umbria Region that, after recovery, were again positive for SARS-CoV-2 in respiratory tract	

specimens. Samples were also assessed for infectivity in vitro. A systematic review of similar cases reported in the literature was performed. The study population was composed of 9 patients during a 4-month study period. Among the new positive samples, six were inoculated in Vero-E6 cells and showed no growth and negative molecular test in culture supernatants. All patients were positive for IgG against SARS-CoV-2 nucleoprotein and/or S protein. Conducting a review of the literature, 1350 similar cases have been found. The presumptive reactivation occurred in 34.5 days on average (standard deviation, SD, 18.7 days) after COVID-19 onset, when the 5.6% of patients presented fever and the 27.6% symptoms. The outcome was favourable in 96.7% of patients, while the 1.1% of them were still hospitalised at the time of data collection and the 2.1% died. Several hypotheses have been formulated to explain new positive respiratory samples after confirmed negativity. According to this study, the phenomenon seems to be due to the prolonged detection of SARS-CoV-2 RNA traces in respiratory samples of recovered patients. The failure of the virus to replicate in vitro suggests its inability to replicate in vivo.

#6 What reinfections mean for COVID-19 A. Iwasaki | 12 October 2020 | The Lancet Infectious Diseases	Search strategy: Pubmed search using term [covid-19 reinfection]
[first paragraph of article] One of the key questions in predicting the course of the COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is how well and how long the immune responses protect the host from reinfection. For some viruses, the first infection can provide lifelong immunity; for seasonal coronaviruses, protective immunity is short-lived. Table 1 in this article provides a summary of the characteristics associated with reinfection with SARS-CoV-2. This table provides the basis for Table 1a in the Albertan report at Attachment 2.	

#7 Cases and etiologies of suspected COVID-19 reactivation A. Ghali| 13 October 2020 | Qatar Medical Journal	Search strategy: Pubmed search using term [covid-19 reinfection]
Our article outlines a perspective on COVID-19 reactivation with considerations of implored commentary on behalf of the medical community regarding open discourse about this subject. Such a topic is paramount in elucidating parameters that pertain to testing, and subsequent public health population dynamics once uneventful cases pass. We argue that what some may refer to as a reinfection or reactivation of the virus, is actually a result of prolonged shedding of the virus complemented with occasional false	

positives/negatives and lab errors. This article was written with the perspective of informing in addition to engage discussions that distill salient, evidence-based characterisation of COVID-19. We hope to recruit fellow academics in medicine who see trends in their own respective communities about people who re-test, and to explore their clinical outcomes.

#8 COVID-19 neutralizing antibodies predict disease severity and survival [preprint] W. F. Garcia-Beltran | 20 October 2020 | medRxiv	Search strategy: Pubmed search using term [covid-19 reinfection]
COVID-19 exhibits variable symptom severity ranging from asymptomatic to life-threatening, yet the relationship between severity and the humoral immune response is poorly understood. We examined antibody responses in 113 COVID-19 patients and found that severe cases resulting in intubation or death exhibited increased inflammatory markers, lymphopenia, and high anti-RBD antibody levels. While anti-RBD IgG levels generally correlated with neutralisation titer, quantitation of neutralisation potency revealed that high potency was a predictor of survival. In addition to neutralisation of wild-type SARS-CoV-2, patient sera were also able to neutralise the recently emerged SARS-CoV-2 mutant D614G, suggesting protection from reinfection by this strain. However, SARS-CoV-2 sera was unable to cross-neutralise a highly-homologous pre-emergent bat coronavirus, WIV1-CoV, that has not yet crossed the species barrier. These results highlight the importance of neutralising humoral immunity on disease progression and the need to develop broadly protective interventions to prevent future coronavirus pandemics.	

#9 Neutralizing Antibodies Correlate with Protection from SARS-CoV-2 in Humans during a Fishery Vessel Outbreak with a High Attack Rate A. Addetia | 21 October 2020 | J Clin Microbiol.	Search strategy: Pubmed search using term [covid-19 reinfection]
The development of vaccines against SARS-CoV-2 would be greatly facilitated by the identification of immunological correlates of protection in humans. However, to date, studies on protective immunity have been performed only in animal models and correlates of protection have not been established in humans. Here, we describe an outbreak of SARS-CoV-2 on a fishing vessel associated with a high attack rate. Predeparture serological and viral reverse transcription-PCR (RT-PCR) testing along with repeat testing after return to shore was available for 120 of the 122 persons on board over a median follow-up of 32.5 days (range, 18.8 to 50.5 days). A total of 104 individuals had an RT-PCR-positive viral test with a cycle threshold (CT) of <35 or seroconverted during the follow-up period, yielding an attack rate on board of 85.2% (104/122	

individuals). Metagenomic sequencing of 39 viral genomes suggested that the outbreak originated largely from a single viral clade. Only three crew members tested seropositive prior to the boat's departure in initial serological screening and also had neutralising and spike-reactive antibodies in follow-up assays. None of the crew members with neutralising antibody titers showed evidence of bona fide viral infection or experienced any symptoms during the viral outbreak. Therefore, the presence of neutralising antibodies from prior infection was significantly associated with protection against reinfection (Fisher's exact test, P = 0.002).

#10 Understanding protection from SARS-CoV-2 by studying reinfection [news and views] J. Overbaugh | 22 October 2020 | Nature Medicine	Search strategy: Pubmed search using term [covid-19 reinfection]
There are numerous additional points that should be understood about reinfection with SARS-CoV-2. Is such reinfection a rare phenomenon that occurs in people with notably weak immune responses? If so, what is limited about these responses? Is there evidence that neutralising antibodies are especially poor in these patients, and can cases of reinfection shed light on the titer of antibody and/or other immune measures that are no longer protective? Do people who are reinfected have little disease and are their viral loads lower than those typical of first infections? This would suggest that even though the immune response to infection is not adequate to provide sterilising immunity, it may provide therapeutic benefit, which could still be useful for a vaccine approach, at least initially, until better vaccine concepts emerge. The study of reinfection with SARS-CoV-2 is critical because if neutralising antibody responses are robust in people who are reinfected, this suggests that the vaccine concepts need to be diversified. This could include considering diverse antibody epitopes, both neutralising and non-neutralising, and optimising the effector function of antibodies and enhancing cellular responses. It is critical to understand how infection with SARS-CoV-2 affects reinfection risk and to use these studies of naturally exposed populations, working in concert with vaccine efforts, to understand correlates of immunity. Studies of naturally HIV-exposed populations and vaccine trials have also taught that researchers need to look beyond neutralising antibodies and consider other measures of antibody function and such a broad approach to studies of reinfection seems equally prudent for SARS-CoV-2.	

#11 Evidence of SARS-CoV-2 reinfection with a different genotype P. Colson | 15 November 2020 | Journal of Infection [letter to the editor]	Search strategy: Pubmed search using term [covid-19 reinfection]

We report here a patient with two infections at a 105 days interval despite seroconversion. We demonstrated by genotypic analyses that the two successive infections involved distinct viral variants and that samples tested were collected from the same individual. Such early reinfections with SARS-CoV-2 is surprising, as we are used with a majority of respiratory viruses to observe a single, annual epidemic episode. This atypical epidemiological pattern is particularly relevant in our geographical area (France) where the second outbreak that started during the summer was linked to multiple distinct variants having accumulated mutations that differed from viral mutants that circulated during the first outbreak. This deserves conducting further studies to figure out whether or not this would make sense to include several viral variants in future vaccines.

Contains updated version of Table 1a from Albertan report (Attachment 2).

#12 Evidence of Severe Acute Respiratory Syndrome Coronavirus 2 Reinfection After Recovery from Mild Coronavirus Disease 2019 J-S. Lee | 21 November 2020 | Clinical Infectious Diseases	Search strategy: Pubmed search using term [covid-19 reinfection]
We conducted whole-genome sequencing of the viral RNA from clinical specimens at the initial infection and at the positive retest from 6 patients who recovered from COVID-19 and retested positive for SARS-CoV-2 via rRT-PCR after recovery. A total of 13 viral RNAs from the patients' respiratory specimens were consecutively obtained, which enabled us to characterise the difference in viral genomes between initial infection and positive retest. At the time of the positive retest, we were able to acquire a complete genome sequence from patient 1, a 21-year-old previously healthy woman. In this patient, through the phylogenetic analysis, we confirmed that the viral RNA of positive retest was clustered into a subgroup distinct from that of the initial infection, suggesting that there was a reinfection of SARS-CoV-2 with a subtype that was different from that of the primary strain. The spike protein D614G substitution that defines the clade "G" emerged in reinfection, while mutations that characterise the clade "V" (ie, nsp6 L37F and ORF3a G251V) were present at initial infection. Reinfection with a genetically distinct SARS-CoV-2 strain may occur in an immunocompetent patient shortly after recovery from mild COVID-19. SARS-CoV-2 infection may not confer immunity against a different SARS-CoV-2 strain.	

#13 A case of SARS-CoV-2 reinfection in Ecuador B. Prado-Vivar | 23 November 2020 | Lancet Infectious Diseases	Search strategy:

	Pubmed search using term [covid-19 reinfection]
Here we report the first confirmed case of SARS-CoV-2 reinfection in Ecuador and South America. SARS-CoV-2 genome sequencing was done. No shared mutations were observed between the two sequences, further suggesting that both variants resulted from distinct evolutionary trajectories. It was therefore surprising that our patient showed more severe disease with the second infection than with the first, especially because the patient did not have any additional clinical conditions that could explain it.	

#14 Antibodies, Immunity, and COVID-19 B. Spellberg | 24 November 2020 | JAMA Internal Medicine	Search strategy: Identified in regular JAMA Internal medicine email alert
From the article: In summary, a robust and well-designed seroprevalence study using residual serum samples from across the US has found that herd immunity to SARS-Cov-2 is nowhere in sight, even as the COVID-19 pandemic has raged on for a year. The good news is that the limited number of reinfections of SARS-CoV-2 to date, and the experience with natural infections with other viruses, suggests that protective immunity to COVID-19 should result, a harbinger for the success of vaccines. The bad news is that, like the 1918 influenza pandemic, achieving herd immunity through natural infections will take years of painful sacrifice that are tallied in numerous deaths, severe long-term health sequelae, and widespread economic disruption and hardship. Let us hope that safe and effective vaccines help avoid the consequences of naturally developing herd immunity to COVID-19, as they have reliably done for so many other respiratory viruses. Key references provided within include Klein et al., who show that most individuals with symptomatic COVID-19 mount neutralising antibody responses to SARS-CoV-2 based on the analysis of convalescent plasma.	

#15 COVID-19 reinfection: prolonged shedding or true reinfection? S. Falahi | November 2020 | New Microbes and New Infections	Search strategy: Pubmed search using term [covid-19 reinfection]
The SARS-CoV-2 pandemic is underway and millions of people have been infected. A large number of patients with COVID-19 have recovered and been discharged. While a number	

of recovered patients test positive again or even have a recurrence of clinical symptoms. Some researchers believe that a positive retest is related to the long-term persistence of the virus in the body, although there is some evidence in favor of reinfection. In this study, we focus more on the possible reasons for positive retesting, antibody responses, and review of possible reinfection case reports.

Summarises:

- Possible reasons for positive retest and challenges in distinguishing between prolonged shedding/reactivation and true reinfection.
- Dynamics of antibody responses in patients with COVID-19
- Reinfection studies.

#16 Establishment of an African green monkey model for COVID-19 and protection against reinfection C. Woolsey | 24 November 2020 | Nature Immunology	Search strategy: Pubmed search using term [covid-19 reinfection]
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for an unprecedented global pandemic of COVID-19. Animal models are urgently needed to study the pathogenesis of COVID-19 and to screen vaccines and treatments. We show that African green monkeys (AGMs) support robust SARS-CoV-2 replication and develop pronounced respiratory disease, which may more accurately reflect human COVID-19 cases than other nonhuman primate species. SARS-CoV-2 was detected in mucosal samples, including rectal swabs, as late as 15 days after exposure. Marked inflammation and coagulopathy in blood and tissues were prominent features. Transcriptome analysis demonstrated stimulation of interferon and interleukin-6 pathways in bronchoalveolar lavage samples and repression of natural killer cell- and T cell–associated transcripts in peripheral blood. Despite a slight waning in antibody titers after primary challenge, enhanced antibody and cellular responses contributed to rapid clearance after re-challenge with an identical strain. These data support the utility of AGM for studying COVID-19 pathogenesis and testing medical countermeasures.	

#17 Dynamics of viral load and anti-SARS-CoV-2 antibodies in patients with positive RT-PCR results after recovery from COVID-19 [rapid communication] K-H. Song | 25 November 2020 | Korean Journal of Internal Medicine	Search strategy: Pubmed search using term [covid-19 reinfection]
Recently, the number of patients with coronavirus disease 2019 (COVID-19) who have tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), via the reverse transcription polymerase chain reaction (RT-PCR) test, after recovery has	

increased; this has caused a dilemma regarding the medical measures and policies. We evaluated the dynamics of viral load and anti-SARS-CoV-2 antibodies in four patients with positive RT-PCR results after recovery. In all patients, the highest levels of immunoglobulin G (IgG) and IgM antibodies were reached after about a month of the onset of the initial symptoms. Then, the IgG titers plateaued, and the IgM titers decreased, regardless of RT-PCR results. The IgG and IgM levels did not increase after the post-negative positive RT-PCR results in any of the patients. Our results reinforced that the post-negative positive RT-PCR results may be due to the detection of RNA particles rather than reinfection in individuals who have recovered from COVID-19.

#18 Correlates of protection against SARS-CoV-2 in rhesus macaques K. McMahan | 4 December 2020 | Nature	Search strategy: Provided by NCHRAC Chair
Recent studies have reported protective efficacy of both natural immunity1 and vaccine-induced immunity2–7 against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) challenge in rhesus macaques. However, the importance of humoral and cellular immunity for protection against SARS-CoV-2 infection remains to be determined. Here we show that adoptive transfer of purified IgG from convalescent macaques protects naïve recipient rhesus macaques against SARS-CoV-2 challenge in a dose dependent fashion. Depletion of CD8+ T cells in convalescent animals partially abrogated the protective efficacy of natural immunity against SARS-CoV-2 re-challenge, suggesting the importance of cellular immunity in the context of waning or subprotective antibody titers. These data demonstrate that relatively low antibody titers are sufficient for protection against SARS-CoV-2 in rhesus macaques, and that cellular immune responses may also contribute to protection if antibody responses are suboptimal. We also show that higher antibody titers are required for therapy of SARS-CoV-2 infection in macaques. These findings have important implications for the development of SARS-CoV-2 vaccines and immune-based therapeutics.	

#19 Viral RNA level, serum antibody responses, and transmission risk in recovered COVID-19 patients with recurrent positive SARS-CoV-2 RNA test results: a population-based observational cohort study. C. Yang | December 2020 | Emerging Microbes and Infections	Search strategy: Pubmed search using term [covid-19 reinfection]
Managing recovered COVID-19 patients with recurrent-positive SARS-CoV-2 RNA test results is challenging. We performed a population-based observational study to characterise the viral RNA level and serum antibody responses in recurrent-positive patients and evaluate their viral transmission risk. Of 479 recovered COVID-19 patients, 93 (19%) recurrent-positive patients were identified, characterised by younger age, with a	

median discharge-to-recurrent-positive length of 8 days. After readmission, recurrent-positive patients exhibited mild (28%) or absent (72%) symptoms, with no disease progression. The viral RNA level in recurrent-positive patients ranged from 1.8 to 5.7 log10 copies/mL (median: 3.2), which was significantly lower than the corresponding values at disease onset. There are generally no significant differences in antibody levels between recurrent-positive and non-recurrent-positive patients, or in recurrent-positive patients over time (before, during, or after recurrent-positive detection). Virus isolation of nine representative specimens returned negative results. Whole genome sequencing of six specimens yielded only genomic fragments. 96 close contacts and 1,200 candidate contacts of 23 recurrent-positive patients showed no clinical symptoms; their viral RNA (1,296/1,296) and antibody (20/20) tests were negative. After full recovery (no longer/never recurrent-positive), 60% (98/162) patients had neutralising antibody titers of ≥1:32. Our findings suggested that an intermittent, non-stable excretion of low-level viral RNA may result in recurrent-positive occurrence, rather than reinfection. Recurrent-positive patients pose a low transmission risk, a relatively relaxed management of recovered COVID-19 patients is recommended.

#20 T cell responses in patients with COVID-19 Z. Chen | 29 July 2020 | Nature Reviews Immunology	Search strategy: Pubmed search using term [covid-19 reinfection]
The role of T cells in the resolution or exacerbation of COVID-19, as well as their potential to provide long-term protection from reinfection with SARS-CoV-2, remains debated. Nevertheless, recent studies have highlighted various aspects of T cell responses to SARS-CoV-2 infection that are starting to enable some general concepts to emerge.	

#21 Humoral Immune Response to SARS-CoV-2 in Iceland D. F. Gudbjartsson | 1 September 2020 | New England Journal of Medicine	Search strategy: Referenced in Tan et al. (ref #24)
Little is known about the nature and durability of the humoral immune response to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We measured antibodies in serum samples from 30,576 persons in Iceland, using six assays (including two pan-immunoglobulin [pan-Ig] assays), and we determined that the appropriate measure of seropositivity was a positive result with both pan-Ig assays. We tested 2102 samples collected from 1237 persons up to 4 months after diagnosis by a quantitative polymerase-chain-reaction (qPCR) assay. We measured antibodies in 4222 quarantined persons who had been exposed to SARS-CoV-2 and in 23,452 persons not known to have been exposed. Of the 1797 persons who had recovered from SARS-CoV-2 infection, 1107 of the 1215 who were tested (91.1%) were seropositive; antiviral antibody	

titers assayed by two pan-Ig assays increased during 2 months after diagnosis by qPCR and remained on a plateau for the remainder of the study. Of quarantined persons, 2.3% were seropositive; of those with unknown exposure, 0.3% were positive. We estimate that 0.9% of Icelanders were infected with SARS-CoV-2 and that the infection was fatal in 0.3%. We also estimate that 56% of all SARS-CoV-2 infections in Iceland had been diagnosed with qPCR, 14% had occurred in quarantined persons who had not been tested with qPCR (or who had not received a positive result, if tested), and 30% had occurred in persons outside quarantine and not tested with qPCR. Our results indicate that antiviral antibodies against SARS-CoV-2 did not decline within 4 months after diagnosis. We estimate that the risk of death from infection was 0.3% and that 44% of persons infected with SARS-CoV-2 in Iceland were not diagnosed by qPCR.

#22 Broad and strong memory CD4+ and CD8+ T cells induced by SARS-CoV-2 in UK convalescent individuals following COVID-19 Y. Peng | 4 September 2020 | Nature Immunology	Search strategy: Referenced in ABC news article on 26 November 2020
The development of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines and therapeutics will depend on understanding viral immunity. We studied T cell memory in 42 patients following recovery from COVID-19 (28 with mild disease and 14 with severe disease) and 16 unexposed donors, using interferon-γ-based assays with peptides spanning SARS-CoV-2 except ORF1. The breadth and magnitude of T cell responses were significantly higher in severe as compared with mild cases. Total and spike-specific T cell responses correlated with spike-specific antibody responses. We identified 41 peptides containing CD4+ and/or CD8+ epitopes, including six immunodominant regions. Six optimised CD8+ epitopes were defined, with peptide–MHC pentamer-positive cells displaying the central and effector memory phenotype. In mild cases, higher proportions of SARS-CoV-2-specific CD8+ T cells were observed. The identification of T cell responses associated with milder disease will support an understanding of protective immunity and highlights the potential of including non-spike proteins within future COVID-19 vaccine design.	

#23 Seasonal coronavirus protective immunity is short-lasting A.W.D. Edridge | 14 September 2020 | Nature Medicine	Search strategy: Pubmed search using term [covid-19 reinfection]
Abstract: A key unsolved question in the current coronavirus disease 2019 (COVID-19) pandemic is the duration of acquired immunity. Insights from infections with the four seasonal human coronaviruses might reveal common characteristics applicable to all human coronaviruses. We monitored healthy individuals for more than 35 years and	

determined that reinfection with the same seasonal coronavirus occurred frequently at 12 months after infection.

#24 Durability of neutralizing antibodies and T-cell response post SARS-CoV-2 infection Y. Tan | 5 October 2020 | Frontiers in Medicine	Search strategy: Cited in this article in The Conversation published on 1 December 2020
The ongoing pandemic of Coronavirus disease 19 (COVID-19) is caused by a newly discovered β Coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). How long the adaptive immunity triggered by SARS-CoV-2 can last is of critical clinical relevance in assessing the probability of second infection and efficacy of vaccination. Here we examined, using ELISA, the IgG antibodies in serum specimens collected from 17 COVID-19 patients at 6–7 months after diagnosis and the results were compared to those from cases investigated 2 weeks to 2 months post-infection. All samples were positive for IgGs against the S- and N-proteins of SARS-CoV-2. Notably, 14 samples available at 6–7 months post-infection all showed significant neutralising activities in a pseudovirus assay, with no difference in blocking the cell-entry of the 614D and 614G variants of SARS-CoV-2. Furthermore, in 10 blood samples from cases at 6–7 months post-infection used for memory T-cell tests, we found that interferon γ-producing CD4+ and CD8+ cells were increased upon SARS-CoV-2 antigen stimulation. Together, these results indicate that durable anti-SARS-CoV-2 immunity is common in convalescent population, and vaccines developed from 614D variant may offer protection from the currently predominant 614D variant of SARS-CoV-2.	

#25 Persistence of humoral and cellular immune response after SARS-CoV-2 infection: opportunities and challenges [Comments] T. Wu | 5 October 2020 | Frontiers in Medicine	Search strategy: Referenced in Tan et al. (ref #24)
Table 1 provides a summary of studies on the dynamics of antibody response after SARS-CoV-2 infection. Provides an overview of humoral and cellular immune responses after SARS-CoV-2 infection including references to reports that observed decay in IgG or neutralising antibodies among the recovered patients during 2–3 months after infection, particularly among the asymptomatic participants.	

#26 What is the role of T cells in COVID-19 infection? Why immunity is about more than antibodies	Search strategy: Google search

A. Plüddemann | 19 October 2020 | Centre for Evidence-Based Medicine article	

Summary:

- CD4+ T cells help B cells to produce antibodies and help CD8+ T cells to kill virus-infected cells.
- One of the dominant cytokines produced by T cells is interferon gamma, a key player in controlling viral infection.
- Lymphopenia is a main feature of COVID-19 infection, affecting CD4+ T cells, CD8+ T cells, and B cells, and is more pronounced in severely ill patients.
- T cell responses in severely ill patients may be impaired, over-activated, or inappropriate, and further research is required to elucidate this and inform treatment strategies.
- There is some evidence of cross-reactivity with seasonal/endemic coronaviruses.
- Emerging studies suggest that all or a majority of people with COVID-19 develop a strong and broad T cell response, both CD4 and CD8, and some have a memory phenotype, which bodes well for potential longer-term immunity.
- Understanding the roles of different subsets of T cells in protection or pathogenesis is crucial for preventing and treating COVID-19.

#27 Longitudinal observation and decline of neutralizing antibody responses in the three months following SARS-CoV-2 infection in humans J. Seow | 26 October 2020 | Nature Microbiology	Search strategy: Pubmed search using term [covid-19 reinfection]

Antibody responses to SARS-CoV-2 can be detected in most infected individuals 10–15 d after the onset of COVID-19 symptoms. However, due to the recent emergence of SARS-CoV-2 in the human population, it is not known how long antibody responses will be maintained or whether they will provide protection from reinfection. Using sequential serum samples collected up to 94 d post onset of symptoms (POS) from 65 individuals with real-time quantitative PCR-confirmed SARS-CoV-2 infection, we show seroconversion (immunoglobulin (Ig)M, IgA, IgG) in >95% of cases and neutralising antibody responses when sampled beyond 8 d POS. We show that the kinetics of the neutralising antibody response is typical of an acute viral infection, with declining neutralising antibody titres observed after an initial peak, and that the magnitude of this peak is dependent on disease severity. Although some individuals with high peak infective dose (ID50 > 10,000) maintained neutralising antibody titres >1,000 at >60 d POS, some with lower peak ID50 had neutralising antibody titres approaching baseline within the follow-up period. A similar decline in neutralising antibody titres was observed in a cohort of 31 seropositive healthcare workers. The present study has important implications when considering widespread serological testing and antibody protection against reinfection with SARS-CoV-2, and may suggest that vaccine boosters are required to provide long-lasting protection.

#28 Durable SARS-CoV-2 B cell immunity after mild or severe disease [preprint] C.O. Ogega | 30 October 2020 | medRxiv	Search strategy: Pubmed search using term [covid-19 reinfection]
Multiple studies have shown loss of SARS-CoV-2 specific antibodies over time after infection, raising concern that humoral immunity against the virus is not durable. If immunity wanes quickly, millions of people may be at risk for reinfection after recovery from COVID-19. However, memory B cells (MBC) could provide durable humoral immunity even if serum neutralising antibody titers decline. We performed multi-dimensional flow cytometric analysis of S protein receptor binding domain (S-RBD)-specific MBC in cohorts of ambulatory COVID-19 patients with mild disease, and hospitalised patients with moderate to severe disease, at a median of 54 (39-104) days after onset of symptoms. We detected S-RBD-specific class-switched MBC in 13 out of 14 participants, including 4 of the 5 participants with lowest plasma levels of anti-S-RBD IgG and neutralising antibodies. Resting MBC (rMBC) made up the largest proportion of S-RBD-specific class-switched MBC in both cohorts. FCRL5, a marker of functional memory when expressed on rMBC, was dramatically upregulated on S-RBD-specific rMBC. These data indicate that most SARS-CoV-2-infected individuals develop S-RBD-specific, class-switched MBC that phenotypically resemble germinal center-derived B cells induced by effective vaccination against other pathogens, providing evidence for durable B cell-mediated immunity against SARS-CoV-2 after recovery from mild or severe COVID-19 disease.	

#29 Evolution of Antibody Immunity to SARS-CoV-2 C. Gaebler | 5 November 2020 | bioRxiv [preprint]	Search strategy: Pubmed search using term [covid-19 reinfection]
SARS-CoV-2 has infected 47 million individuals and is responsible for over 1.2 million deaths to date. Infection is associated with development of variable levels of antibodies with neutralising activity that can protect against infection in animal models. Antibody levels decrease with time, but the nature and quality of the memory B cells that would be called upon to produce antibodies upon reinfection has not been examined. Here we report on the humoral memory response in a cohort of 87 individuals assessed at 1.3 and 6.2 months after infection. We find that IgM, and IgG anti-SARS-CoV-2 spike protein receptor binding domain (RBD) antibody titers decrease significantly with IgA being less affected. Concurrently, neutralising activity in plasma decreases by five-fold in pseudotype virus assays. In contrast, the number of RBD-specific memory B cells is unchanged. Memory B cells display clonal turnover after 6.2 months, and the antibodies they express have greater somatic hypermutation, increased potency and resistance to RBD mutations, indicative of continued evolution of the humoral response. Analysis of intestinal biopsies	

obtained from asymptomatic individuals 3 months after COVID-19 onset, using immunofluorescence, electron tomography or polymerase chain reaction, revealed persistence of SARS-CoV-2 in the small bowel of 7 out of 14 volunteers. We conclude that the memory B cell response to SARS-CoV-2 evolves between 1.3 and 6.2 months after infection in a manner that is consistent with antigen persistence.

#30 Immunological memory to SARS-CoV-2 assessed for greater than six months after infection [preprint] J. M. Dan | 16 November 2020 | bioRxiv	Search strategy: Referenced in ABC news article on 26 November 2020
Understanding immune memory to SARS-CoV-2 is critical for improving diagnostics and vaccines, and for assessing the likely future course of the pandemic. We analysed multiple compartments of circulating immune memory to SARS-CoV-2 in 185 COVID-19 cases, including 41 cases at ≥6 months post-infection. Spike IgG was relatively stable over 6+ months. Spike-specific memory B cells were more abundant at 6 months than at 1 month. SARS-CoV-2-specific CD4+ T cells and CD8+ T cells declined with a half-life of 3-5 months. By studying antibody, memory B cell, CD4+ T cell, and CD8+ T cell memory to SARS-CoV-2 in an integrated manner, we observed that each component of SARS-CoV-2 immune memory exhibited distinct kinetics.	

#31 SARS-CoV-2-specific T cell memory is long-lasting in the majority of convalsecent COVID-19 individuals [preprint] Z. Li | 16 November 2020 | bioRxiv	Search strategy: Referenced in ABC news article on 26 November 2020
An unaddressed key question in the current coronavirus disease 2019 (COVID-19) pandemic is the duration of immunity for which specific T cell responses against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are an indispensable element. Being situated in Wuhan where the pandemic initiated enables us to conduct the longest analyses of memory T cell responses against SARS-CoV-2 in COVID-19 convalescent individuals (CIs). Magnitude and breadth of SARS-CoV-2 memory CD4 and CD8 T cell responses were heterogeneous between patients but robust responses could be detected up to 9 months post disease onset in most CIs. Loss of memory CD4 and CD8 T cell responses were observed in only 16.13% and 25.81% of CIs, respectively. Thus, the overall magnitude and breadth of memory CD4 and CD8 T cell responses were quite stable and not inversely correlated with the time from disease onset. Interestingly, the only significant decrease in the response was found for memory CD4 T cells in the first 6-month post COVID-19 disease onset. Longitudinal analyses revealed that the kinetics of SARS-CoV-2 memory CD4 and CD8 T cell responses were quite heterogenous between patients. Loss of memory CD4 T cell responses was observed more frequently in asymptomatic	

cases than after symptomatic COVID-19. Interestingly, the few CIs in which SARS-CoV-2-specific IgG responses disappeared showed more durable memory CD4 T cell responses than CIs who remained IgG-positive for month. Collectively, we provide the first comprehensive characterisation of the long-term memory T cell response in CIs, suggesting that SARS-CoV-2-specific T cell immunity is long-lasting in the majority of individuals.

#32 Rapid and lasting generation of B-cell memory to SARS-CoV-2 spike and nucleocapsid proteins in COVID-19 disease and convalescence [preprint] G. E. Hartley | 20 November 2020 | MedRxiv	Search strategy: Referenced in ABC news article on 26 November 2020
(Background) Lasting immunity to SARS-CoV-2 following infection is questioned because serum antibodies decline in convalescence. However, functional immunity is mediated by long-lived memory T and B (Bmem) cells. (Objective) To determine the longevity and immunophenotype of SARS-CoV-2-specific Bmem cells in COVID-19 patients. (Methods) Recombinant spike receptor binding domain (RBD) and nucleocapsid protein (NCP) were produced for ELISA-based serology, and biotinylated for fluorescent tetramer generation to identify SARS-CoV-2-specific Bmem cells by flow cytometry with a panel of 13 mAbs. 36 blood samples were obtained from 25 COVID-19 patients (11 paired) between 4-242 days post-symptom onset for detection of neutralising antibodies, IgG serology and flow cytometry. (Results) The recombinant RBD and NCP were specifically recognised by serum IgG in all patients and reactivity declined >20 days post-symptom onset. All patients had detectable RBD- and NCP-specific Bmem cells at 8.23-267.6 cells/ml of blood (0.004-0.13% of B cells) regardless of sampling time. RBD- and NCP-specific Bmem cells predominantly expressed IgM or IgG1, with the latter formed slightly later than the former. RBD-specific IgG+ Bmem were predominantly CD27+, and numbers significantly correlated with circulating follicular helper T cell numbers. (Conclusion) RBD- and NCP-specific Bmem cells persisted for 8 months, indicating that the decline in serum antibodies after 1 month does not indicate waning of immunity but a contraction of the immune response. Flowcytometric detection of SARS-CoV-2-specific Bmem cells enables detection of long-term functional immunity following infection or vaccination for COVID-19.	

#33 Functional SARS-CoV-2-specific immune memory persists after mild COVID-19 L. B. Rodda | 23 November 2020; | Cell (in press; journal pre-proof)	Search strategy: Pre-print identified in Centre for Evidence-Based Medicine article published on 19 October 2020
We performed a longitudinal assessment of individuals recovered from mild COVID-19 to determine if they develop and sustain multifaceted SARS-CoV-2-specific immunological	

memory. Recovered individuals developed SARS-CoV-2-specific IgG antibodies, neutralising plasma, memory B and memory T cells that persisted for at least three months. Our data further reveal that SARS-CoV-2-specific IgG memory B cells increased over time. Additionally, SARS-CoV-2-specific memory lymphocytes exhibited characteristics associated with potent antiviral function: memory T cells secreted cytokines and expanded upon antigen re-encounter, while memory B cells expressed receptors capable of neutralising virus when expressed as monoclonal antibodies. Therefore, mild COVID-19 elicits memory lymphocytes that persist and display functional hallmarks of antiviral immunity.

#34 A highly immunogenic and effective measles virus-based Th1-biased COVID-19 vaccine C. Horner| 30 November 2020 | Proceedings of the National Academy of Sciences of the USA	Search strategy: Provided by NCHRAC committee member
Abstract: The COVID-19 pandemic has already caused over 1 million deaths. Therefore, effective vaccine concepts are urgently needed. In search of such a concept, we have analysed a measles virus-based vaccine candidate targeting SARS-CoV-2. Using this well-known, safe vaccine backbone, we demonstrate here induction of functional immune responses in both arms of adaptive immunity, yielding antiviral efficacy in vivo with the desired immune bias. Consequently, no immunopathologies became evident during challenge experiments. Moreover, the candidate still induces immunity against the measles, recognised as a looming second menace, when countries are forced to stop routine vaccination campaigns in the face of COVID-19. Thus, a bivalent measles-based COVID-19 vaccine could be the solution for two significant public health threats. The study shows that a COVID-19 recombinant measles virus can give significantly longer protection against COVID-19 than SARS-CoV-2 infection does.	

#35 Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK M. Voysey| 8 December 2020 | The Lancet	Search strategy: Provided by NCHRAC committee member
(Background) A safe and efficacious vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), if deployed with high coverage, could contribute to the control of the COVID-19 pandemic. We evaluated the safety and efficacy of the ChAdOx1 nCoV-19 vaccine in a pooled interim analysis of four trials. (Findings) Between April 23 and Nov 4, 2020, 23 848 participants were enrolled and 11 636 participants (7548 in the UK, 4088 in Brazil) were included in the interim primary efficacy analysis. In participants who received two standard doses, vaccine efficacy was 62·1% (95% CI 41·0–75·7; 27 [0·6%] of 4440 in the ChAdOx1 nCoV-19 group vs71 [1·6%] of 4455 in the control group) and in	

participants who received a low dose followed by a standard dose, efficacy was 90·0% (67·4–97·0; three [0·2%] of 1367 vs 30 [2·2%] of 1374; pinteraction=0·010). Overall vaccine efficacy across both groups was 70·4% (95·8% CI 54·8–80·6; 30 [0·5%] of 5807 vs 101 [1·7%] of 5829). From 21 days after the first dose, there were ten cases hospitalised for COVID-19, all in the control arm; two were classified as severe COVID-19, including one death. There were 74 341 person-months of safety follow-up (median 3·4 months, IQR 1·3–4·8): 175 severe adverse events occurred in 168 participants, 84 events in the ChAdOx1 nCoV-19 group and 91 in the control group. Three events were classified as possibly related to a vaccine: one in the ChAdOx1 nCoV-19 group, one in the control group, and one in a participant who remains masked to group allocation. (Interpretation) ChAdOx1 nCoV-19 has an acceptable safety profile and has been found to be efficacious against symptomatic COVID-19 in this interim analysis of ongoing clinical trials.

Attachments

Attachment 1: Glossary

Attachment 2: Alberta Health Services COVID-19 Scientific Advisory Group Rapid Evidence Report '*Can people with previous COVID-19 infection be reinfected by the virus?*', 6 November 2020.

Glossary

adaptive immune response (or total antibody response)	Takes place after a pathogen such as a virus enters the body. It is virus specific and long lasting. It is characterised by a rapid increase in T and B cells numbers. It involves helper and killer T-cells, plasma B-cells memory B-cells and serum antibodies, including neutralising antibodies. Cell-mediated immunity is achieved by cytotoxic T-cells that are able to bind to an infected cell and cause cell lysis.
anamnestic response	The rapid reappearance of antibody in the blood following introduction of an antigen to which the subject had previously developed a primary immune response. It requires the presence of memory B-cell (MBCs). While in a resting state these cells do not secrete antibody but they can be rapidly activated to multiply and to become antibody-secreting cells when virus enters the host. A critical question is whether MBCs can respond rapidly enough to prevent clinical disease following exposure to the virus. Pre-existing antibody and memory T-cells will contribute to protection.
antigen	A molecule that is recognised by an antibody or a cell of the immune system (T-cells, B-cells). It might typically be a protein.
clinical immunity	This occurs when, as a result of an immune response, a person has no symptoms or signs of infection and therefore they are protected from developing disease.
correlates of immunity or protection	The measurable signs that a person is protected against becoming reinfected with a virus. Measurable signs are commonly antibodies. It is important to know the correlates of immunity to assess the effectiveness of a vaccine's immune response. If the correlates of immunity are not known, the only method of assessing vaccine effectiveness will be through large phase III trials with clinical outcomes (i.e. infection and/or disease, not just laboratory markers).
epitope	The smallest part of a molecule that is recognised by antibodies or cells or the immune system. It may consist of amino acids, sugars or lipids and may be formed by different parts of a molecule coming together.
neutralising antibodies	These antibodies bind to antigens and prevent viral entry into cells.
R and Ro	The basic reproduction number (Ro) for an infection is the expected number of cases directly generated by one case in a population where all individuals are susceptible to infection. This is different to the Effective Reproductive Number (R). R is the average number of secondary cases per infectious case in a population where there are both immune and non-immune individuals. It will differ between different populations. R is the product of Ro and the fraction of the population that is susceptible. To achieve herd immunity, R needs to be less than one. This can be achieved when a percentage of the population is immune to infection, either through natural or vaccine-induced immunity, or through other measures that render individuals protected (e.g. social distancing). For SARS-CoV-2, Ro is thought to be ~2.5. Therefore, for R to be <1 (required to extinguish the epidemic), 60% of the population needs to be resistant to infection. It is unlikely that this will be achieved by a vaccine alone because vaccines may not give rise to sterilising immunity and because of vaccine hesitancy.

sterilising immunity	This occurs when there is no replication of the virus in the host as the result of an immune response. In the case of SARS-CoV-2, this means no virus in the nasal passages or lungs.

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 sgmRNA 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)	1st infection		2nd infection		Time between infections: positive RT-PCR (days)	Genome sequencing	Ab detected after 1st infection	Ab detected after 2nd 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 1st and 2nd 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	1st and 2nd 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

Location (Reference)	Sex	Age (years)	1st infection		2nd infection		Time between infections: positive RT-PCR (days)	Genome sequencing	Ab detected after 1st infection	Ab detected after 2nd 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)	1st infection		2nd infection		Time between infections: positive RT-PCR (days)	Genome sequencing	Ab detected after 1st infection	Ab detected after 2nd 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 buy 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 sgmRNA 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 epid emiologic 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 sgmRNA, 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 sgmRNA, 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.

Date question received by advisory group: March 2020

Date of first assessment: March 18, 2020

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.

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)

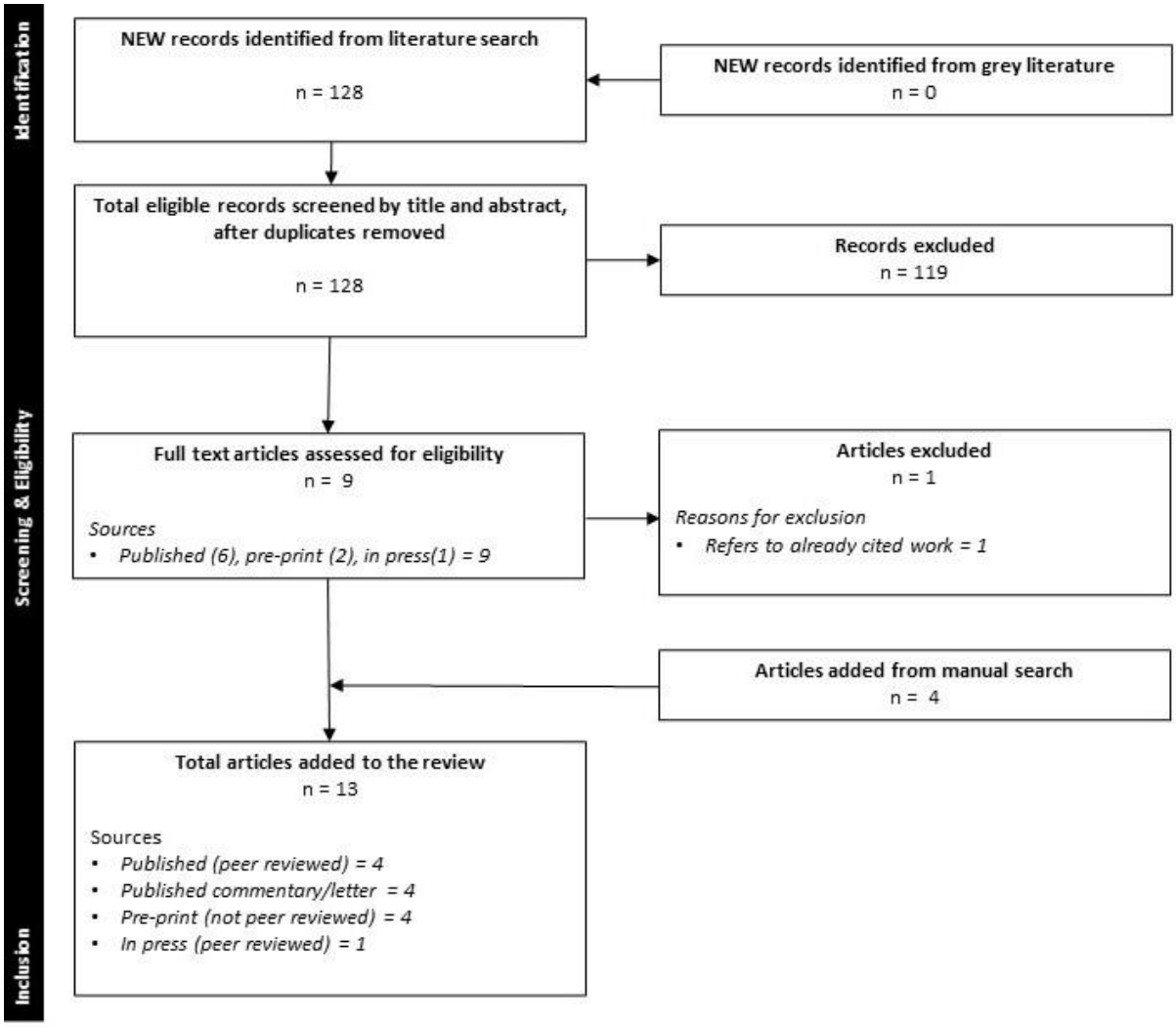

Table 2. Inclusion and exclusion criteria for results of the literature search

Inclusion Criteria	Exclusion Criteria
- 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	- 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) - 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

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	• 12 articles
	  ○ 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-occurence" 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-occurence" 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-occurence" 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-occurence" OR relapse OR recrudescence)

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