

# COVID-19 Scientific Advisory Group Rapid Response Report

## Key Research Question: What are the highest priority indications for use of serologic testing for COVID-19 clinically and to inform public health efforts?

### Context

- Serologic testing will soon become available in Alberta and it is anticipated that the demand from clinicians, researchers and public health officials will be high.
- Once the SARS-CoV-2 panel is validated, it will be important to prioritize who can/should receive serologic testing so that lab capacity can meet the needs of the health system.
- Media stories from Germany and the United Kingdom suggest using proof of immunity (via serosurvey) to SARS-CoV-2 as a tool to determine eligibility for return to normal society (an “immunity passport”).

### Key Messages from the Evidence Summary

- No evidence was identified to inform the clinical or public health implications of serological testing in special populations such as immunocompromised people, critical care patients, or the organ transplantation community.
- There was no direct evidence for using serology to inform ‘return to work’ (RTW) policies. However, findings from the immunological and infection dynamics during infection suggest that a combination of RNA testing, IgG testing and IgM testing may help inform RTW decisions for healthcare personnel once a better understanding of the antibody response to infection is gained.
- This rapid review did not include an analysis of neutralizing antibody and its use in convalescent plasma therapy. This may be addressed in a future review.

### Committee Discussion

There was general consensus among committee members that current evidence does not support the routine use of serology for acute diagnostic purposes. However, a list of potential priority groups who would be appropriate candidates for serological testing was felt to be useful in addressing this question as evidence emerges which resulted in addition of the fourth recommendation. As well, it was requested that it be made clear in the text that this review does not address the use of neutralizing antibody directed against SARS-CoV-2 as therapy; this was added in the Key Messages. The use of convalescent plasma therapy may be appropriate for a separate rapid review, and it is understood trials are underway. A more in-depth discussion and evaluation around SARS-CoV-2 mutations and the impact on neutralizing antibody was also deferred.

### Recommendations

1. At this point in time, the dynamics of the COVID-19 serological response are not well understood and will be dependent on the assay used. Therefore, it is not recommended that serological testing be used to inform decisions around healthcare worker return to work policies or for acute care diagnostics. Additionally, there is currently insufficient evidence to support that primary infection leads to immunity in subsequent re-exposure.
2. A multi-disciplinary working group coordinated with Alberta Precision Laboratories and including public health should be formed to coordinate serologic priorities for clinical and public health purposes, establish and research requests and establish appropriate serum banking to meet these needs. The priorities identified should inform the selection of serologic assay chosen by APL.

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3. Before serology is adopted for routine use in Alberta for any purpose, testing platforms must undergo rigorous evaluation to determine analytical and clinical sensitivity and specificity. This should include validating tests across a broad range of well characterized samples (for example, from stored serum prior to pandemic onset acute blood at set times from acute presentation of proven infection, COVID-19 swab negative patients with clinically suspected infection).
4. Once a serological assay is available for use, the following will need to be determined: an outline of the evidence supporting that primary infection leads to immunity to reinfection (and its duration), operationalization/capacity of the testing program, priority lists of populations for testing, an analysis of the economic and health benefits, and an evaluation framework for the serological program. Groups to be considered as potential priorities for serological testing include those for whom it could facilitate return to work decisions (healthcare workers, essential services workers), those who present late in the course of illness when nucleic acid testing may be negative, those from whom convalescent plasma for therapeutic purposes could be collected, and participants in vaccine and surveillance studies. A reliable serological assay would contribute greatly to the understanding of the epidemiology of COVID-19.

### Summary of Evidence

Literature for this review was collected from a database search covering OVID MEDLINE, EMBASE, LitCovid, TRIP PRO, PubMed, WHO Global research on coronavirus (database), Google and Google Scholar. The search was limited to articles published after 2019. 88 articles were identified for title and abstract screening. Following screening and critical appraisal, 18 articles were included in the final evidence review. The quality of the evidence was mixed. Studies from the current pandemic were often case series or observational studies with poor comparators or controls. The limitations on publication date and the *de facto* language exclusion criteria limits the inclusion of studies published in Chinese, Italian, or from other countries that are further ahead in their epidemiologic curve.

### *Evidence from existing policies and guidelines*

There are few guidelines published that address serological testing. The United States Food and Drug Administration (FDA) merely dictates that any tests must be validated for cross-reactivity/analytical specificity, class specificity, and clinical agreement. They offer no comment on RTW policies, convalescent plasma or population-based serosurveys (United States Food and Drug Administration, 2020).

### *Have serological tests been used to inform healthcare worker (HCW) return to work in any jurisdiction?*

No direct evidence was identified that described a model of using serology to inform 'return to work' (RTW) policies in any jurisdiction. There was some evidence that could be used to inform an RTW policy in Alberta, however, it was of low quality and leaves too many questions unanswered.

There is evidence that serological testing can confirm viral exposure in the absence of respiratory sample RNA. In patients with undetectable RNA in their respiratory tract samples collected during day 1-3, day 4-7, day 8-14 and day 15-39 after symptom onset, 28.6% (2/7), 53.6% (15/28), 98.2% (56/57) and 100% (30/30) had detectable antibody in total Ab assay, respectively (Zhao et al., 2020).

In one study, SARS-CoV-2-specific antibodies were detectable as early as 1-3 days post-symptom onset but the median seroconversion time was 11 days (Zhao et al., 2020). Another study found that the median time to detection for IgM was 5 days after symptoms onset while that of IgG was 14 days (Guo et al., 2020). Testing for both immunoglobulin M (IgM) and immunoglobulin G (IgG) may indicate recent infection and recovery, respectively (Xia et al., 2020; Al Kahlout et al., 2019), however, the two studies have limited applicability due to study quality (Xia et al., 2020) and MERS context (Al Kahlout et al., 2019). The sensitivity of a test for both IgG and IgM, or total antibody, is higher than the sensitivity of a test for either antibody alone (Xia et al., 2020; Zhao et al., 2020). Because of the time required for a patient to seroconvert, the utility of serology as an acute diagnostic

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test may be limited. As well, the duration of IgM positivity has not yet been defined, which is critical to using it as an indication of acute infection.

A preprint study of 175 recovered COVID-19 patients found that the development of neutralizing antibodies (Nabs) generally occurred between days 10-15 after infection, but approximately 30% of patients were observed to have very low titres of SARS-CoV-2-specific antibodies (Wu et al., 2020). The NAb titres were significantly higher in elderly and middle-aged adult patients (40-85 yrs) compared to younger patients (15-39 yrs) ( $p < 0.0001$ ) and were negatively correlated with lymphocyte count, suggesting that the immunological response to SARS-CoV-2 may not be accurately represented by a serological assay (Wu et al., 2020). It also highlights that the immunological response to SARS-CoV-2 is still poorly understood.

A dual serological test could be used to confirm RNA results in asymptomatic people following exposure to confirmed COVID-19 patients (for example, in HCW), and the results used to inform quarantine decisions and further test regimens (Xia et al., 2020; Haveri et al., 2020). However, there is very limited evidence, if any, to show what cross-reactivity exists between SARS-CoV-2 and the human coronaviruses already in seasonal circulation. This would affect the analytical specificity of any serological test and has already been observed in serological testing for seasonal coronaviruses and would be a potential issue to address (Lehmann et al., 2008; Shao et al., 2007).

The use of serology to confirm infection in asymptomatic contacts of positive cases is supported by a serosurvey conducted in Qatar during the Middle East Respiratory Syndrome (MERS) outbreak in 2012-2016. Healthcare workers were considered as close contacts to four confirmed positive MERS-CoV cases and tested for exposure (presence of IgG) and infection (presence of IgM), although these results were not used to inform RTW decisions (Al Kahlout et al., 2019).

### *How has serology been used clinically or in research for special populations such as immunocompromised patients? Critical care patients? Organ donors/recipients?*

No evidence was identified with respect to the use of serological testing in special populations. Studies identified in the literature search were largely related to managing patients during the COVID-19 outbreak but did not address serological testing or the implications on these populations.

### *What testing models can be used to confirm immunity to COVID-19 in large populations?*

Population-based serosurveys have been used following MERS outbreaks and have been suggested from current experience with seroconversion following SARS-CoV-2 infection. Xia et al. (2020) suggests that a combination RNA/antibody test could be used to screen travelers or large populations who have been in areas with a high COVID-19 prevalence or use serological testing alone in a population-based serosurvey to determine the full extent of the COVID-19 pandemic.

A large-scale serosurvey was conducted following the MERS outbreak in Qatar using samples from blood donors, healthcare workers, and four confirmed positive cases (as controls). The initial test was an IgG test for Spike protein, followed by whole-virus and recombinant protein recognition as confirmatory tests (Al Kahlout et al., 2019). The study found 10/4719 positive in the blood donor population, 1/135 positive close contacts (HCW) and 3/4 positive among confirmed positive cases, suggesting high cross-reactivity between MERS and seasonal coronaviruses (Al Kahlout et al., 2019). The known cross-reactivity between MERS and the unknown cross-reactivity between seasonal coronaviruses and SARS-CoV-2 confirms the need for careful assay validation. A similar serosurvey was conducted at a women's university in Saudi Arabia following RNA confirmation of MERS-CoV in eight residents (Van Kerkhove et al., 2019). Out of 828 tests, an additional 11 cases were identified serologically but asymptomatic (Van Kerkhove et al., 2019). These two studies show that a population serosurvey is feasible, but the scale should be considered when starting any research projects.

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One review article summarizes COVID-19 serology as being of limited use for screening patients during the incubation/asymptomatic phase, for the diagnosis of symptomatic disease, and for screening for viral shedding during convalescence; however, the strength of serology was identified in its use in serosurveys to assess individual and population immunity (Cheng et al. 2020).

### Evolving Evidence

The evidence does not appear to be changing quickly on this topic. As the body of evidence regarding the serological dynamics of COVID-19 advances, it will be necessary to re-evaluate this review.

Date question received by advisory group: April 3, 2020

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Date of first assessment: April 15, 2020

Date of re-assessment: n/a

### Authorship & Committee Members

This review was written by Rachael Erdmann and scientifically reviewed by Nathan Zelyas, Alexander Doroshenko, and John Gill (external reviewer). The full Scientific Advisory Group was involved in discussion and revision of the document: Braden Manns (co-chair), Lynora Saxinger (co-chair), John Conly, Shelley Duggan, Nelson Lee, Elizabeth MacKay, Andrew McRae, Jeremy Slobodan, James Talbot, and Brandie Walker.

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## Appendix

### List of Abbreviations

AHS: Alberta Health Services

CoV: Coronavirus

COVID-19: Coronavirus Disease 2019

CPT: Convalescent Plasma Therapy

FDA: Food and Drug Administration

HCW: Healthcare Worker

IgG: Immunoglobulin G

IgM: Immunoglobulin M

KRS: Knowledge Resource Services

MERS: Middle East Respiratory Syndrome

RNA; Ribonucleic acid

RTW: Return to Work

SARS: Severe Acute Respiratory Syndrome

SCCM: Society for Critical Care Medicine

### Literature Search

The literature search was conducted by the Knowledge Resource Services (KRS) unit of Alberta Health Services (AHS). On April 3, 2020, the KRS librarian searched OVID MEDLINE, EMBASE, LitCovid, TRIP PRO, PubMed, WHO Global research on coronavirus (database), Google and Google Scholar for literature published between 2019 and 2020. In brief, the search strategy included MeSH terms and keyword related to:

- SARS-CoV-2 or COVID-19 or novel coronavirus
- Serologic testing or serology
- Immunocompromised populations
- Convalescent plasma

No language limits were placed on the search. 88 articles were retrieved from searching activities. 56 articles were excluded according to the exclusion criteria, 2 articles were discarded based on quality. 18 articles were included in this review.

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

Inclusion Criteria	Exclusion Criteria
<ul style="list-style-type: none"> <li>- Serology testing</li> <li>- Describes clinical or public health application of immunological/serological testing</li> <li>- Describes coordination of research efforts for COVID serological testing</li> <li>- Describes outcomes of serologically-based therapy (eg. convalescent plasma therapy)</li> <li>- Human study</li> <li>- Any population</li> <li>- SARS-CoV-2 (COVID-19), SARS, MERS</li> <li>- Any jurisdiction</li> <li>- Guidelines</li> <li>- Article is peer-reviewed, is from a reputable source, or has a described methodology</li> </ul>	<ul style="list-style-type: none"> <li>- Molecular or biochemical testing for SARS-CoV-2</li> <li>- Describes basic immunological findings without application to clinical or public health context</li> <li>- No outcomes described</li> <li>- Animal or <i>in vitro</i> study</li> <li>- Influenza, RSV, circulating coronavirus, or other contagious virus</li> <li>- Opinion, commentary or editorial</li> </ul>

### Critical Appraisal

Critical appraisal was conducted using an adapted Mixed Methods Appraisal Tool (MMAT) (Hong et al., 2018). References 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. This modified MMAT method allows for a quick appraisal of the evidence and provides a yes/no decision for inclusion based on quality. However, it does not provide a ranking of the studies or detailed analysis of the aspects of quality. The table below summarizes the results of the critical appraisal and includes sources flagged by SAG members as receiving public attention or determined by the writer/reviewers to be relevant to the question.

Table 2. Summary of quality assessment results for articles included in this review. Two studies were rejected on the basis of quality and are not included below.

	Reference	Quality Appraisal Criteria
1.	Zhang, Du, Li et al., 2020	1) <input checked="" type="checkbox"/> Peer-reviewed: Case series <input type="checkbox"/> Not peer-reviewed <input type="checkbox"/> Letter, commentary, editorial, preprint <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input type="checkbox"/> Other: <specify>  2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)  2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue?

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		<input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)
2.	Xia N., et al., 2020	<p>1) <input type="checkbox"/> Peer-reviewed: &lt;specify study type&gt;  <input checked="" type="checkbox"/> Not peer-reviewed  <input checked="" type="checkbox"/> Letter, commentary, editorial, <b>preprint</b>  <input type="checkbox"/> Guideline: &lt;Specify source &gt; (AHS, PHAC, WHO, Reputable research group, other)  <input type="checkbox"/> Other: &lt;specify&gt;</p> <p>2a) Are there clear research questions or a clearly identified issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p>
3.	Haveri et al., 2020	<p>1) <input checked="" type="checkbox"/> Peer-reviewed: Case study  <input type="checkbox"/> Not peer-reviewed  <input type="checkbox"/> Letter, commentary, editorial, preprint  <input type="checkbox"/> Guideline: &lt;Specify source &gt; (AHS, PHAC, WHO, Reputable research group, other)  <input type="checkbox"/> Other: &lt;specify&gt;</p> <p>2a) Are there clear research questions or a clearly identified issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p>
4.	Al Kahlout et al., 2019	<p>1) <input checked="" type="checkbox"/> Peer-reviewed: Serological surveillance study  <input type="checkbox"/> Not peer-reviewed  <input type="checkbox"/> Letter, commentary, editorial, preprint  <input type="checkbox"/> Guideline: &lt;Specify source &gt; (AHS, PHAC, WHO, Reputable research group, other)  <input type="checkbox"/> Other: &lt;specify&gt;</p> <p>2a) Are there clear research questions or a clearly identified issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p>
5.	Zhao et al., 2020	<p>1) <input checked="" type="checkbox"/> Peer-reviewed: Longitudinal cohort study  <input type="checkbox"/> Not peer-reviewed  <input type="checkbox"/> Letter, commentary, editorial, preprint  <input type="checkbox"/> Guideline: &lt;Specify source &gt; (AHS, PHAC, WHO, Reputable research group, other)  <input type="checkbox"/> Other: &lt;specify&gt;</p>

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		<p>2a) Are there clear research questions or a clearly identified issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p>
6.	Van Kerhove et al., 2015	<p>1) <input checked="" type="checkbox"/> Peer-reviewed: Epidemiological survey  <input type="checkbox"/> Not peer-reviewed  <input type="checkbox"/> Letter, commentary, editorial, preprint  <input type="checkbox"/> Guideline: &lt;Specify source &gt; (AHS, PHAC, WHO, Reputable research group, other)  <input type="checkbox"/> Other: &lt;specify&gt;</p> <p>2a) Are there clear research questions or a clearly identified issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p>
7.	Pang et al., 2020	<p>1) <input checked="" type="checkbox"/> Peer-reviewed: Systematic review  <input type="checkbox"/> Not peer-reviewed  <input type="checkbox"/> Letter, commentary, editorial, preprint  <input type="checkbox"/> Guideline: &lt;Specify source &gt; (AHS, PHAC, WHO, Reputable research group, other)  <input type="checkbox"/> Other: &lt;specify&gt;</p> <p>2a) Are there clear research questions or a clearly identified issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p>
8.	US Food and Drug Administration, 2020	<p>1) <input type="checkbox"/> Peer-reviewed: &lt;specify study type&gt;  <input checked="" type="checkbox"/> Not peer-reviewed  <input type="checkbox"/> Letter, commentary, editorial, preprint  <input checked="" type="checkbox"/> Guideline: &lt;Specify source &gt; (AHS, PHAC, WHO, Reputable research group, other)  <input type="checkbox"/> Other: &lt;specify&gt;</p> <p>2a) Are there clear research questions or a clearly identified issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p>



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9.	Zhou et al., 2020	<p>1) <input checked="" type="checkbox"/> Peer-reviewed: Review/clinical update  <input type="checkbox"/> Not peer-reviewed  <input type="checkbox"/> Letter, commentary, editorial, preprint  <input type="checkbox"/> Guideline: &lt;Specify source &gt; (AHS, PHAC, WHO, Reputable research group, other)  <input type="checkbox"/> Other: &lt;specify&gt;</p> <p>2a) Are there clear research questions or a clearly identified issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p>
10.	Guo et al., 2020	<p>1) <input checked="" type="checkbox"/> Peer-reviewed: Cohort study  <input type="checkbox"/> Not peer-reviewed  <input type="checkbox"/> Letter, commentary, editorial, preprint  <input type="checkbox"/> Guideline: &lt;Specify source &gt; (AHS, PHAC, WHO, Reputable research group, other)  <input type="checkbox"/> Other: &lt;specify&gt;</p> <p>2a) Are there clear research questions or a clearly identified issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p>
11.	Lehmann et al., 2008	<p>1) <input checked="" type="checkbox"/> Peer-reviewed: Assay development and validation  <input type="checkbox"/> Not peer-reviewed  <input type="checkbox"/> Letter, commentary, editorial, preprint  <input type="checkbox"/> Guideline: &lt;Specify source &gt; (AHS, PHAC, WHO, Reputable research group, other)  <input type="checkbox"/> Other: &lt;specify&gt;</p> <p>2a) Are there clear research questions or a clearly identified issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p> <p>2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue?  <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)</p>
12.	Shao et al., 2007	<p>1) <input checked="" type="checkbox"/> Peer-reviewed: Cohort study  <input type="checkbox"/> Not peer-reviewed  <input type="checkbox"/> Letter, commentary, editorial, preprint  <input type="checkbox"/> Guideline: &lt;Specify source &gt; (AHS, PHAC, WHO, Reputable research group, other)  <input type="checkbox"/> Other: &lt;specify&gt;</p> <p>2a) Are there clear research questions or a clearly identified issue?</p>

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		<input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard) 2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)
13.	Wu et al., 2020	1) <input type="checkbox"/> Peer-reviewed: <specify> <input checked="" type="checkbox"/> Not peer-reviewed <input checked="" type="checkbox"/> Letter, commentary, editorial, <b>preprint</b> <input type="checkbox"/> Guideline: <Specify source > (AHS, PHAC, WHO, Reputable research group, other) <input type="checkbox"/> Other: <specify> 2a) Are there clear research questions or a clearly identified issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard) 2b) Is the collected data or presented evidence (incl. expert opinion) appropriate to address the research questions or issue? <input checked="" type="checkbox"/> Yes   <input type="checkbox"/> No (discard)

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