CADTH COVID-19 PANDEMIC

COVID-19 CADTH HORIZON SCAN

Serological Tests for COVID-19

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To produce this report, CADTH used a modified approach to the selection, appraisal, and synthesis of the evidence to meet decision-making needs during the COVID-19 pandemic. Care has been taken to ensure the information is accurate and complete, but it should be noted that international scientific evidence about COVID-19 is changing and growing rapidly.

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Table 1: Revision History

Version	Date	Section	Description of changes made	Reason for change
1	May 6, 2020		—	—
2	May 28, 2020	Key Messages	Addition of authorized tests	Tests authorized by Health Canada
		Context	Addition of authorized tests	Tests authorized by Health Canada
		The Technology	Table 1: Changes to the length of time for results of CLIA and ELISA tests	Additional and revised guidance available
		Evidence	Addition of two authorized tests	Tests authorized by Health Canada
3	July 9, 2020	Key Messages and Availability	Amendment of number of authorized tests in Canada and/or the US	Tests authorized by Health Canada and the FDA
		Evidence	Added reference to performance data available online for tests granted EUA	Tests authorized by the FDA
		Evidence	Added reference to living Cochrane systematic review	Recently published Cochrane review
		Evidence	Using two antibody-based serological tests detecting different viral proteins may help improve overall test accuracy	FDA statement on test accuracy
4	December 18, 2020	Key Messages	Amendment of number of authorized tests in Canada	Tests authorized by Health Canada
		Key Messages	Removed: Serological tests may be used to indicate who could be prioritized to return to work or serve as a frontline health worker.	No longer relevant
		Key Messages	Added: Current evidence does not support the role of serological testing in routine clinical care.	Review article co-authored by member of COVID-19 Immunity Task Force
		Availability	Amendment of number of authorized tests in Canada and/or the US	Tests authorized by Health Canada and the FDA
		Evidence	Added reference to performance data for tests approved by Health Canada	Tests authorized by Health Canada
		Overall Evidence Conclusion	Added: In a rapid systematic review, which included 10 studies with diagnostic accuracy outcomes for antibody-based tests, test sensitivities and specificities ranged from 18.4% to 96.1% and 88.9% to 100%, respectively. Additionally, the authors conducted a pooled analysis of 16 studies that resulted in a sensitivity of 87.8%	Rapid systematic review available

Version	Date	Section	Description of changes made	Reason for change
			for an initial RT-PCR test. Thus, the lack of a true reference standard for COVID-19 diagnosis should be taken into consideration when interpreting the findings of diagnostic accuracy studies on antibody-based tests.	
		Overall Evidence Conclusion	Removed: As not all test developers have published their data, and with some making unfounded claims regarding their tests, there may also be a lack of transparency in the accuracy and performance of serology tests in clinical settings.	No longer relevant
		Context	Removed: There is concern that inadequate testing may fail to identify individuals with the infection or may mislabel individuals as having recovered from the disease when they have never been infected. Validation ensures test accuracy and reliability, and helps prevent the further spread of the disease.	No longer relevant
		Context	Added as fourth paragraph: At this time, there is still uncertainty around the nature, extent, and duration of immunity to COVID-19, as well as concerns about the accuracy of some serological tests. For this reason, in Canada, the role of serology tests in clinical care is limited. The current focus of serology tests is on research on immunity and population-based studies to guide public health policies.	New data available
		Context	Removed as beginning of sixth paragraph: At least three provinces are considering using serology tests as a means of easing COVID-19 restrictions and social distancing measures.	No longer relevant
		Context	Added to last paragraph: Currently, 28 research projects have been funded through the task force.	New data available
		The Technology	Changes to the second paragraph: In the early days of COVID-19, serology-based tests were used in some hospitals to complement molecular-based	New data available

Version	Date	Section	Description of changes made	Reason for change
			testing as part of the recovery criteria and as a discharge requirement. This may be important because the sensitivity of some PCR-based tests may be compromised if specimens are taken too early in the disease process or if the specimen collection is inadequate. Findings from a review article co-authored by a lead member of the Canadian COVID-19 Immunity Task Force suggested that serological testing currently does not have a role in routine clinical care.	
		Implications	Amendment to second paragraph of Public Health heading to refer to waves of infection rather than a second wave of infection	No longer relevant
		Implications	Amendment to first paragraph to clarify that there is uncertainty about the appropriate roll out of serological testing due to uncertainties about immune response and COVID-19	New data available
		Implications	Amendment to first and second paragraph of Societal heading to remove text that was out-dated as the role of serology testing and thinking around its usefulness has changed	No longer relevant

CLIA = chemiluminescence immunoassays; ELISA = enzyme-linked immunosorbent assay; EUA = Emergency Use Authorization; RT-PCR = reverse transcriptase-polymerase chain reaction.

Key Messages

- Current evidence does not support a role for serological testing in routine clinical care.
- If accurate, antibody-based serological tests may provide information on the transmission of COVID-19.
- Rapid point-of-care serological tests may provide results in approximately 10 to 15 minutes.
- Health Canada is reviewing serological COVID-19 tests through the expedited access route. Currently, 12 antibody-based serological tests have been authorized in Canada under the priority review process.
- Based on the available literature, the performance and role of these tests in clinical settings have not been completely demonstrated.
- Evidence to confirm that individuals have immunity to COVID-19 or are protected from reinfection is lacking.

Context

The early diagnosis of coronavirus disease 2019 (COVID-19) plays a critical role in optimizing supportive care for individuals with severe illness[1] and in containing the transmission of the infection through case identification, isolation, and contact tracing.[2] The primary method used in Canada for identifying COVID-19 is the laboratory-based polymerase chain reaction (PCR) test using a nose-throat swab. This test identifies the presence of antigens expressed early in infections.[3]

Serological testing measures the level of antibodies present in the blood. Antibodies are proteins produced by the immune system to protect the body from infection.[4] Unlike the deep nasal or throat swab detection methods, serological tests are intended to confirm suspected cases of COVID-19 after individuals have recovered and developed antibodies that may protect them from future infection and to identify asymptomatic carriers of the virus.[5]

In Canada, serological tests for COVID-19 first became available in May of 2020.[6] Currently, 12 serological tests have been authorized by Health Canada via the expedited access pathway to determine their validity.[7] Similarly, in the European Union[8] and some other countries, including the US[9] and Australia,[10] some serology tests are available and have been officially approved by their regulatory bodies with conditional use.[8,9,10]

At this time there is still uncertainty about the nature, extent, and duration of immunity to COVID-19, as well as concerns about the accuracy of some serological tests. For this reason, in Canada, the role of serology tests in clinical care is limited.[11] The current focus of serology tests is on research on immunity and population-based studies to guide public health policies.[11]

Information from the test, if accurate, could provide insight into the transmission of COVID-19 and may inform policy decisions on return to work, the use of personal protective equipment, the continuation of social distancing practices, and attendance at large gatherings.[12] The loosening of restrictions put into place due to the COVID-19 pandemic will be influenced by the characteristics of different community populations and will be linked to their vulnerability and immunity to the infection.[13]

There may be significant medical, public health, societal, and economic policy implications related to the deployment of these tests.

A government-funded COVID-19 immunity task force has been established to oversee the coordination of a series of country-wide serological test surveys. Data from these surveys will provide insight into the extent of the spread of the virus, its impact on populations at higher risk, and potential immunity.[14] Currently, 28 research projects have been funded through the task force. [15]

About This Document

This rapid Horizon Scan summarizes information identified through a limited literature search. It is not a systematic review, it was not peer-reviewed, and a critical appraisal of studies was not undertaken. It is not intended to provide recommendations. Care has been taken to ensure the information is accurate and complete, but it should be noted that international scientific evidence about COVID-19 is changing and growing rapidly.

The Technology

Serological testing measures antibodies — specifically immunoglobulin M and immunoglobulin G — present in the blood when the body responds to a specific infection. Serology tests for COVID-19 are not designed to detect the virus in newly infected individuals; instead, they are intended to detect the virus after the infection has matured and mounted an antibody response.[5] Current knowledge suggests that antibodies become detectable in blood somewhere between seven and 14 days after exposure to the virus, although some patients may develop antibodies sooner.[16]

In the early days of COVID-19, serology-based tests were used in some hospitals to complement molecular-based testing as part of the recovery criteria and as a discharge requirement.[17] This may be important because the sensitivity of some PCR-based tests may be compromised if specimens are taken too early in the disease process or if the specimen collection is inadequate.[17] Findings from a review article co-authored by a lead member of the Canadian COVID-19 Immunity Task Force suggested that serological testing currently does not have a role in routine clinical care.[11]

The strength of antibody response depends on several factors, including age, nutritional status, severity of disease, and certain medications or infections like HIV that suppress the immune system.[18]

Scientific understanding on COVID-19 immunity after infection is limited and evolving. It is unclear how long antibodies last (and if it will be the same for everyone), how much antibody is required to protect the immune system, the role of immunity in interrupting transmission, and if individuals who have recovered from the virus can be reinfected.[19] Data from China, South Korea, and Japan suggest that reinfection may be possible. However, these cases may not be well-substantiated and the issue may be influenced more by testing inadequacies than by genuine reinfections.[20]

Antibody-Based Serological Testing Techniques

The various types of antibody-based serological tests include rapid diagnostic tests (e.g., lateral flow immunoassay [LFIA]), chemiluminescence immunoassay (CLIA), enzyme-linked immunosorbent assay (ELISA), and neutralization assay. Commonly using colloidal gold as a label, LFIAs are rapid tests that can be used at the point of care to yield qualitative readings (i.e., positive or negative readings as indicated by coloured lines).[21] As a lab-based test requiring venipuncture samples, ELISA can yield qualitative or quantitative readings (i.e., colour or fluorescence-based), which can detect the amount of viral protein and patient antibody complexes.[21] Being a technique that more closely resembles ELISA than LFIA, CLIAs require a lab-based analyzer to yield quantitative readings proportional to the amount of antibodies detected.[5,22] Finally, neutralization assays rely on cell cultures of the virus, with blood samples to determine if patients have active antibodies to help prevent reinfections.[21] Further test details are presented in Table 2.

Table 2: Antibody-Based Serological Testing Techniques

Type of immunoassay	Antibody assessment	Sampling method	Length of time for results	Setting
Rapid diagnostic test (e.g., LFIA with colloidal gold)	IgG, IgM, IgA	Finger prick or venipuncture (i.e., whole blood, serum, or plasma)	10 to 30 minutes	Point-of-care testing
CLIA	IgG, IgM, IgA	Venipuncture	1 to 2 hours	Lab
ELISA	IgG, IgM, IgA	Venipuncture	2 to 5 hours	Lab
Neutralization assay	Active neutralizing antibodies	Venipuncture	3 to 5 days	Lab

CLIA = chemiluminescence immunoassays; ELISA = enzyme-linked immunosorbent assay; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; LFIA = lateral flow immunoassay.

Availability

Twelve COVID-19 antibody-based serological tests — rapid laboratory-based immunoassay tests — were approved by Health Canada from May 2020 through October 2020 following priority scientific review. Health Canada is collaborating with the National Microbiology Laboratory to validate testing and research, and consulting with national and international experts to guide the regulation of serological tests.[23]

In the US, the FDA has approved 57 serological tests intended for use in clinical laboratories under the Emergency Use Authorization (EUA).[9] Initially, serology tests did not require an EUA submission. Instead, the FDA required that manufacturers validate tests themselves and notify the FDA of this action. The FDA also required manufacturers to label tests or test reports. The labelling was to indicate that the serology test has not been reviewed by the FDA, that negative results do not rule out COVID-19 infection, that follow-up molecular testing should be considered, and that serological testing should not be used as the sole basis for diagnosing COVID-19.[24]

The FDA has acknowledged some concerns about the quality of some of these tests that did not require FDA approval.[25] Since the issuance of the new FDA policy, more than 100 test manufacturers have notified the FDA that they have serology tests available that are intended for the diagnosis of COVID-19. The FDA is aware that some manufacturers have made false claims that their tests are FDA-approved or -authorized.[26] As well, some test

providers have been exposed for making fraudulent claims that their tests diagnose COVID-19 antibodies when they do not.[26]

The FDA has subsequently revised its policy on serology tests. As of May 4, 2020, manufacturers already marketing serology tests will be required to prepare and submit an EUA with their validation data within 10 business days from the date they notified the FDA of their validation testing. As well, the FDA has outlined recommendations for performance thresholds for test accuracy.[27]

The WHO currently recommends against the use of point-of-care immunodiagnostic tests for COVID-19 in the clinical setting.[28]

Cost

A rapid serological test developed in Canada by BTNX Inc. sells for approximately US$10.00 per test.[29]

Evidence

The list of antibody-based serological tests authorized by Health Canada is available online.[6] Relevant articles with clinical data and available datasheets from suppliers are summarized in this report. Additional test performance data are available online for serological tests granted EUA by the FDA.[30]

Lateral Flow Immunoassay

Literature on the use of LFIA for the detection of antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in one supplier-provided datasheet[31,32] and three articles.[33-35] As of November 3, 2020, no LFIA test has been approved by Health Canada.[6] Granted EUA by the FDA,[36] the Cellex qSARS-CoV-2 IgG/IgM Rapid Test[32] detects IgG and IgM against the nucleocapsid protein of SARS-CoV-2. Tested in 128 reverse transcription PCR (RT-PCR)-confirmed SARS-CoV-2 patients and 250 negative patients, the Cellex-supplied datasheet stated a positive percent agreement and negative percent agreement of 93.75% (95% confidence interval [CI], 88.06% to 97.26%) and 96.40% (95% CI, 92.26% to 97.78%), respectively.[32] Two primary studies involving the use of LFIAs included 397 and 128,[34] and 38 and 12,[35] hospital-based patients who tested positive and negative by RT-PCR, respectively. The IgM/IgG test developed by Li et al.[34] resulted in a sensitivity of 88.66% and a specificity of 90.63%, while the VivaDiag COVID-19 IgM/IgG Rapid Test[35] resulted in a sensitivity of 18.4% and a specificity of 91.7%. The IgM/IgG test supplied by Zhuhai Livzon Diagnostics Inc. was tested in 76 RT-PCR–positive patients and 37 negative patients with a clinical diagnosis of SARS-CoV-2 in the hospital setting.[33] At one to seven, eight to 14, and 15 days or more after the onset of symptoms, this IgM/IgG test resulted in sensitivities of 11.1%, 92.9%, and 96.8%, respectively.[33]

Chemiluminescence Immunoassay

Authorized by Health Canada under the interim order[6] and granted EUA by the FDA,[36] the DiaSorin LIAISON SARS-CoV-2 S1/S2 IgG test detects IgG against S1 and S2 antigens of SARS-CoV-2 with a specificity of approximately 98%.[37] At up to five, five to 15, and more than 15 days after the onset of symptoms, this IgG test resulted in sensitivities of 25.0%, 90.4%, and 97.4%, respectively.[37] Concordance with plaque reduction neutralization testing for neutralizing antibodies was assessed with 304 samples, which resulted in a positive agreement of 94.4% and negative agreement of 97.8%.[37] Twelve additional clinical studies

evaluating the accuracy of the DiaSorin LIAISON test had sensitivities ranging from 56.3% to 95.5% and specificities ranging from 90.5% to 100%.[38-48]

Also authorized by Health Canada[6] and the FDA,[36] the Abbott Architect SARS-CoV-2 IgG Assay is a chemiluminescent microparticle immunoassay for the qualitative detection of IgG against the SARS-CoV-2 nucleoprotein.[49] As per the supplier-provided instruction sheet, the Abbott Architect SARS-CoV-2 IgG Assay detected seroconversion rates of 25.00%, 86.36%, and 100.00% at three to seven, eight to 13, and 14 or more days after the onset of symptoms, respectively.[50] Tested in 689 and 1,020 confirmed positive and negative serum samples, respectively, the Abbott Architect SARS-CoV-2 IgG Assay resulted in a sensitivity of 100% and a specificity of 99.90% at day 17 after symptom onset.[49] Seven additional clinical studies evaluating the accuracy of the Abbott SARS-CoV-2 IgG test had sensitivities ranging from 62.5% to 97.9% and specificities ranging from 94.7% to 100%.[40,43,45,47,51-53]

Furthermore, authorized by Health Canada[6] and the FDA,[36] studies evaluating the Elecsys Anti-SARS-CoV-2 (Roche) and Sars-CoV-2 Total Antibody (Siemens) tests were identified. Eleven clinical studies evaluating the accuracy of the Elecsys Anti-SARS-CoV-2 (Roche) test had sensitivities ranging from 68.8% to 98.3% and specificities ranging from 96.2% to 100%.[38-45,47,48,53] Four clinical studies evaluating the accuracy of the Sars-CoV-2 Total Antibody (Siemens) test had sensitivities ranging from 73.3% to 98.1% and specificities ranging from 99.9% to 100%.[42-45]

Tested in 43 RT-PCR–confirmed patients and 33 suspected patients, the CLIA provided by Shenzhen YHLO Biotech Co., Ltd. resulted in sensitivities of 48.1% and 88.9%, and specificities of 100% and 90.9%, to IgM and IgG, respectively.[22] Tested in 37 RT-PCR–confirmed patients and showing a rapid increase in IgM and IgG six days after the onset of symptoms, the MAGLUMI 2000 Plus CLIA system resulted in sensitivities of 100% and 88% for IgG and IgM, respectively, on day 12.[54] Additionally, a review article included data for the Caris 200 Automatic Chemiluminescence Analyzer, which resulted in a sensitivity of 94.8% and specificity of 99.7% for the total antibody level (IgM, IgG, and IgA).[55]

Enzyme-Linked Immunosorbent Assay

Literature on the use of ELISA for the detection of antibodies against SARS-CoV-2 was identified in two supplier-provided datasheets[56,57] and three articles.[58-60] Granted EUA by the FDA,[36] the Mount Sinai COVID-19 ELISA IgG Antibody Test[56] and VITROS Immunodiagnostic Products Anti-SARSCoV-2 Total Reagent Pack[57] detects the presence of IgG and total IgM and IgG, respectively. The sensitivity and specificity data were not available for the Mount Sinai COVID-19 ELISA IgG Antibody Test.[21,56] Tested in 36 and 400 confirmed positive and negative samples, respectively, the Health Canada—approved[6] VITROS Immunodiagnostic Products Anti-SARSCoV-2 Total Reagent Pack resulted in a sensitivity of 83% and a specificity of 100%.[57] Furthermore, authorized by Health Canada[6] and the FDA,[36] the Euroimmun Anti-SARS-CoV-2 IgG test had sensitivities ranging from 72.2% to 100% and specificities ranging from 91.1% to 100%.[39,42,44,46-48,51-53,61]

Tested in 173 SARS-CoV-2–confirmed patients, the ELISA provided by Beijing Wantai Biological Pharmacy Enterprise Co., Ltd. showed seroconversion rates of 93.1%, 82.7%, and 64.7% for total antibody, IgM, and IgG, respectively.[58] Furthermore, the median times for seroconversion were 11, 12, and 14 days for total antibody, IgM, and IgG, respectively.[58] Tested in 82 RT-PCR–confirmed patients and 58 probable patients (i.e., RT-PCR–negative but symptomatic), the ELISA protocol developed by Guo et al. (2020)[60] showed seroconversion rates of 75.6% and 93.1% for IgM in the confirmed and probable groups,

respectively. Tested in serum samples collected at least 14 days after the onset of symptoms in 16 RT-PCR–confirmed patients, the ELISA test developed by To et al. (2020)[59] showed seroconversion rates of 94% for anti-nucleoprotein (NP) IgG, 88% for anti-NP IgM, 100% for anti-surface spike protein receptor binding domain (RBD) IgG, and 94% for anti-RBD IgM.

Additional Studies and Ongoing Trials

In March 2020, approximately 100 immunoassay submissions were received by the Foundation for Innovative New Diagnostics (FIND).[62] As of November 3, 2020, independent evaluation results from FIND are available for a growing number of antibody-based tests; however, results for the Health Canada—approved Euroimmun Anti-SARS-CoV-2 IgG are pending.[62] In a Cochrane living systematic review, the authors concluded that because of the low sensitivity of antibody-based serological tests in the first week following the onset of symptoms, these tests may be useful for the detection of previous infections when used 15 or more days post-symptom onset.[63] Nonetheless, due to the current paucity of study data beyond 35 days post-symptom onset, the utility of antibody-based serological tests for public health seroprevalence surveys is unclear.[63] As part of a multi-pronged approach to determine the true COVID-19 infection rate, the Canadian COVID-19 Immunity Task Force began testing for antibodies to SARS-CoV-2 in 40,000 samples from blood donors to the Canadian Blood Services and Héma-Québec.[64] Additionally, numerous non-peer–reviewed preliminary reports and ongoing clinical trials on serological tests have been registered on the medRxiv and ClinicalTrials.gov websites, respectively.

Overall Evidence Conclusion

Due to the scarcity of published large clinical studies and the standardization of performance testing of antibody-based serology tests against SARS-CoV-2, there remains uncertainty regarding the accuracy and role of the use of these tools. The identified literature suggested a wide range of test sensitivity and specificity across different antibody-based serological techniques. In a rapid systematic review including 10 studies with diagnostic accuracy outcomes for antibody-based tests, test sensitivities and specificities ranged from 18.4% to 96.1% and 88.9% to 100%, respectively.[65] Additionally, the authors conducted a pooled analysis of 16 studies, which resulted in a sensitivity of 87.8% for an initial RT-PCR test.[65] The lack of a true reference standard for COVID-19 diagnosis should be taken into consideration when interpreting the findings of diagnostic accuracy studies on antibody-based tests.[65] As not all test developers have published their data, and with some making unfounded claims regarding their tests, there may also be a lack of transparency in the accuracy and performance of serology tests in clinical settings.[5,66]

In addition to variable sensitivities and specificities, the clinical performance (i.e., positive and negative predictive value) of different antibody-based serological tests is likely lower because of the low presumed prevalence of SARS-CoV-2 infections.[67] Thus, the interpretation of test results should take into consideration the prevalence of SARS-CoV-2 infections in different settings (e.g., long-term care versus overall population).[68] In the general population, results from a single antibody-based serological test may not be sufficiently accurate to indicate if a patient has had a prior infection.[30] To help improve overall testing accuracy, a second test is needed to detect antibodies to a different viral protein.[30] Furthermore, as an antibody response against SARS-CoV-2 may take several days after infection to develop, antibody-based serological test accuracy is dependent on the time of sampling and may not be useful in the early days of infection because of the risk of false-negative results.[16,69] There is also the risk of false-positive results due to cross-

reactivity from a previous or current infection with other non-SARS-CoV-2 human coronaviruses.[70] Additionally, evidence is lacking for immunity from reinfection in those who have antibodies after recovering from COVID-19.[71]

With the current available evidence, the WHO does not recommend the use of rapid antibody-based serological tests for patient care.[72] The FDA's recommendations to health care providers state that an antibody-based serological test may be used to help determine if a patient may have been exposed to SARS-CoV-2, but it should not be used on its own for the diagnosis of COVID-19.[73] Nonetheless, antibody-based serological testing may have a role to play in contact tracing, therapeutic studies, return-to-work decisions, and serological surveillance.[16,74,75] The combination of RT-PCR and antibody-based serological tests may enhance the accuracy of infection detection.[34,60] The Alberta Health Services COVID-19 Scientific Advisory Group acknowledges that the development of and access to validated serological tests may help in the testing of priority groups such as health care providers.[20] Further research investigating the analytical and clinical accuracy of antibody-based serological tests, especially with standardized validation protocols and large clinical studies, would provide an additional knowledge base for clinicians, researchers, and decision-makers.

Implications

The deployment of validated serological tests across Canada may have medical, public health, societal, and socioeconomic implications. Although serological testing may be beneficial for informing decisions about easing the COVID-19 restrictions and social isolation, there is concern that their rollout (if they are rolled out after uncertainties about immune response to COVID-19 have been clarified and the accuracy of tests confirmed),[76] could also exacerbate inequalities and may compromise some individual liberties.[77]

Medical

There are several medical-related implications of serological tests for COVID-19 that extend beyond their immediate diagnostic capabilities. Some of the uses of these tests may include:

- These tests may identify fully recovered individuals who are willing to donate their antibodies for transfusion into patients who are critically ill from COVID-19 as part of studies investigating the use of convalescent plasma therapy as a treatment.[78]
- Data from serological surveillance programs may help to develop vaccines[79] by establishing optimal antigens[80] and checking vaccine efficacy.[81]
- Vaccination policies may use serology test data to identify who does not have COVID-19 antibodies and should be prioritized for vaccination,[82] and to help establish a "globally fair vaccine-allocation" policy.[83]

Public Health

Serological testing may provide answers to important epidemiological questions about the scope of the infection, including its transmissibility, virulence, actual fatality rates,[16,84] and to validate if measures put in place to stop the spread were effective.[85]

Epidemiologists may be able to use the serology results to determine the resistance of a population to waves of infection and prepare a response that is tailored to protect those in high-risk groups.[84]

Societal

There are some broad societal implications related to serology-based testing. If evidence emerges to confirm their use in clinical care, the tests may be used to ease physical distancing directives for different populations based on vulnerability and immunity to the infection.[13,86] The tests may be used to inform strategies on the closure and reopening of schools,[87] to identify requirements for personal protective equipment,[12] and to determine populations considered safe to travel.[88]

Some countries, such as the US, the UK, Italy, and Germany, have considered using serology-based tests as the basis for developing "immunity certificates" to loosen physical distancing measures during periods of lock down[89,90] to provide individuals with conditional access to society. These types of certificates may have implications related to the stigmatization and marginalization of some populations.[90] As well, these types of certificates may have some broader privacy-related issues, including those related to the protection of medical data.[77]

Socioeconomic

Serological testing, if effective, may be used to inform strategic staffing decisions about the return to work of essential workers, such as health care professionals, who are presumed to be immune and may not require certain types of protective equipment. If effective, the test may also help to overcome people's fears of contracting the virus from co-workers.[91]

Once priority groups have been tested, serological tests may be used to stimulate sectors of the economy that are contingent on the gathering of people.[92] Since individuals who do not have immunity may require regular PCR testing to prove that they are not infected, there is concern that they may be classified less favourably than those with immunity by employers.[77] As well, there are concerns that some people may deliberately attempt to expose themselves to COVID-19, with the hope that they will experience mild symptoms, so that they can return to work more quickly.[77]

Final Thoughts

Rigorous testing to determine analytical and clinical sensitivity and specificity is required before serological testing can be considered for widespread population-based use. As the utility of serological testing for COVID-19 immunity is predicated on the fact that immunity will last for some time and that reinfection is not possible, emerging evidence on immunity duration and reinfection will have to be reviewed and updated as new evidence becomes available. If serology tests prove to have clinical utility, initially, while production ramps up, there may not be enough serology tests for everyone; to ensure the most judicious distribution of these tests, policy-makers may want to consider priority group-based rollout of the test.

Literature Search Methods

A limited literature search was originally conducted on April 17, 2020, on the concepts of serology and COVID-19 using the following bibliographic databases: MEDLINE and Embase via Ovid, Scopus, and the Cochrane Library. Grey literature was identified by searching relevant sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters). No filters were applied to limit the retrieval by study type. The search was also limited to English-language documents published between January 1, 2017 and April 17, 2020.

After the initial literature search was completed, literature search results from MEDLINE and Embase via Ovid and from Scopus was updated on a monthly basis. Search results from websites of Canadian and international health technology agencies and a focused internet search were updated every six months. Relevant publications were also identified between regular alerts (e.g., via handsearching). Regular alerts updated the search until project completion; only citations retrieved before October 15, 2020, were incorporated into the analysis.

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