

4 June 2020

IMPORTANT NOTICE: COVID-19 research is developing rapidly. Rapid Research Information Forum (RRIF) briefings summarise the best available evidence at the time of writing and each is clearly marked with the relevant submission date. This update expands on the content of the briefing dated 30 April 2020 and should be read in conjunction with that document. Further updates may be published. Consultation with the Australian Academy of Science is possible if the reader has questions.

The original brief, provided at the end of this update, responded to the request for advice on: The predictive value of serological antibody tests and the comparability of point-of-care (POC) tests to laboratory tests.

The original report noted that both point-of-care and laboratory-based serological antibody tests for COVID-19 were not yet sensitive or specific enough for widespread deployment. At the time, laboratory-based tests designed to run on specialised equipment in hospitals and reference labs were being produced by companies such as Roche and Abbott. Abbott's serological antibody test has since been independently validated and two more reputable institutions have advertised additional laboratory-based serological antibody tests for COVID-19. This update provides an overview of the above COVID-19 serological antibody tests.

Abbott, USA, on 15 April 2020 announced their laboratory-based serological antibody test for use on their ARCHITECT sample analysers.^{1,2} The test is a Chemiluminescent microparticle immunoassay, which is a modified and advanced form of the Enzyme Linked Immunosorbent Assay (ELISA) technique and provides qualitative results indicating a presence or absence of SARS-CoV-2 specific antibodies. It has received USA Food and Drug Administration Emergency Use Authorisation (EUA) and European Conformité Européene (CE) approval.³ Abbott states that the ARCHITECT instruments can run up to 100 to 200 tests per hour. The test has been independently validated, results published on 7 May 2020, by researchers at the University of Washington School of Medicine and the Fred Hutchinson Cancer Research Centre. They found the test to have 99.9% specificity and 100% sensitivity 17 days after symptom onset.⁴ The researchers noted that a vast majority of their test samples were obtained from hospitalised COVID-19 patients who may have higher antibody concentrations than patients with less severe disease and asymptomatic infected individuals. Some laboratories in Australia with access to Abbott's ARCHITECT analyser are undertaking evaluation of this test.

Roche, a Swiss multinational, on 3 May 2020 announced that it has received EUA and CE approval for its COVID-19 laboratory-based serological antibody test, Elecsys.⁵ Elecsys is an electrochemiluminescence immunoassay "ECLIA" also based on a modified and advanced ELISA technique and provides qualitative results.⁶ Roche reported that Elecsys is 99.81% specific, showing no cross-reactivity to the other human coronaviruses that cause the common cold, and 100% sensitive in samples taken 14 days after PCR

diagnostic testing was performed. Information is not available on whether these COVID-19 patient samples were obtained from hospitalised patients, with a potentially higher antibody concentration, or those with less severe disease symptoms. Similar to Abbott's test, Elecsys requires specific machinery and must be used on Roche's sample analyser, *cobas e*, which can provide test results within 18 minutes and has a potential throughput of 300 tests per hour. Elecsys has not yet been independently validated.

A partnership between GenScript Biotech Corporation, USA, Duke-NUS Medical School, Singapore, and Singapore's Agency for Science, Technology and Research (A*STAR) on 15 May 2020 announced that they have developed a laboratory-based COVID-19 serological test, cPass.^{7,8} They stated that this is the first commercially available test that can specifically measure neutralising antibodies and can do so within an hour. Neutralising antibodies are those that can interfere with the virus's ability to infect host cells and provide protection against an invading pathogen. This surrogate virus neutralisation test (sVNT) specifically detects antibodies that bind to the spike protein of SARS-CoV-2, an essential protein involved in virus host cell entry. This test has a reported specificity of 100% and sensitivity of 95.6% for samples collected between 14 and 61 days after symptom onset.^{9,10} cPass is undergoing independent validation in Australia at the Doherty Institute and has received CE and Singapore Health Sciences Authority (HSA) approval.

Bio-Techne Corporation, USA, and the Mount Sinai Health System's commercial branch, Kantaro Biosciences LLC, USA, on 19 May 2020 announced their partnership for large-scale manufacturing and distribution of Mount Sinai's COVID-19 serological antibody test.¹¹ The test is based on the ELISA technique and has also been designed to qualitatively detect antibodies that bind to the virus's spike protein. Notably, the test consists of two ELISA steps that enables a reported specificity value of 100% and 92.5% sensitivity with samples taken 10 to 14 days post infection.^{12,13} Mount Sinai's test has already been performed on 30,000 patient samples and received EUA approval on 15 April 2020. Bio-technie and Kantaro Biosciences are currently undertaking validation studies. Distribution of this test in Australia is unlikely to occur until July 2020.

Although highly sensitive and specific tests are ideal, antibody neutralisation tests that are close to 100% specific but do not reach 100% sensitivity are likely to still be useful to identify individuals who have protective antibodies once immunity against SARS-CoV-2 reinfection is better understood. A highly sensitive serological test, if used within the correct timeframe after disease onset, could compensate for the false negative rate of nucleic acid diagnostic tests. The combination of both methods may greatly assist sero-surveillance by increasing detection rates of both acute and previous infection.

Importantly, in a circumstance like Australia where the number of people having been infected with COVID-19 is fewer than one in a thousand, a test must be more than 99.9% specific to be useful for population-level sero-surveillance studies; otherwise a high proportion of positive readings will be false.¹⁴ To arrive at that

figure, validation needs to involve negative serum samples (pre-November 2019) in the order of 10,000 samples. A test that has, at least, 90% sensitivity could still be informative for sero-surveillance if the observed results are calibrated accordingly.

This is a rapidly moving area of research and commercial serological testing for COVID-19, if independently validated, may be ready for widespread deployment in the near future.

APPENDIX

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Australian Government

Chief Scientist

30 April 2020

The Hon Greg Hunt MP
Minister for Health
Parliament House
CANBERRA ACT 2600

CC:

The Hon Karen Andrews MP, Minister for Industry, Science and Technology
Dr Brendan Murphy, Chief Medical Officer

Dear Minister

Please find attached a response to your request for advice on the predictive value of serological antibody tests and the comparability of point-of-care tests to laboratory tests.

This rapid response has been prepared by the Rapid Research Information Forum that I Chair. The report synthesises the evidence base on this matter and has been informed by relevant experts and has been peer reviewed. Details of the authors and peer reviewers can be found in the Appendix.

I hope this document proves useful to you and your colleagues.

Yours sincerely,

A handwritten signature in purple ink, appearing to read 'Alan Finkel'.

Dr Alan Finkel AO FAA FTSE FAHMS
Australia's Chief Scientist

30 April 2020

This rapid research brief responds to the request for advice on the predictive value of serological antibody tests and the comparability of point-of-care (POC) tests to laboratory tests.

- Point-of-care (POC) and laboratory-based serological tests can be used to detect antibodies against SARS-CoV-2. Globally, health authorities are evaluating their use to determine individual immunity, the prevalence of infection in the population, to aid in diagnosis, to aid in contact tracing, and to inform when restrictions can be eased.
- Laboratory-based tests are both quantitative and qualitative. POC tests deliver only a positive or negative result; or a semi-quantitative result at best.
- Neither type of serological test is currently ready for widespread deployment. However rapid advances can be expected.
- With respect to immunity, the interpretation of serological antibody tests relies on a clear understanding of the immune response to SARS-CoV-2, which currently remains undefined.
- For as long as the prevalence of COVID-19 is low in Australia and available serological tests are not approaching 100% specificity, serological testing to measure the prevalence of COVID-19 will not be meaningful. However, if highly accurate serological techniques operating in some academic labs are validated against national standards, they could offer a means for predicting prevalence at the population level.
- Laboratory-based serological testing is being used to identify donors of convalescent plasma that could be used to treat critically ill COVID-19 patients.

Laboratory testing is a key tool to detect the presence and spread of COVID-19 in the community. Nucleic acid tests use polymerase chain reaction (PCR) to directly detect the presence of SARS-CoV-2 nucleic acid (RNA) from respiratory samples and saliva.¹ These tests are usually used to diagnose COVID-19 patients. Serological tests, which use blood plasma or serum as the starting material, detect whether antibodies have been produced in response to previous SARS-CoV-2 infection.

Although both PCR diagnostic testing and serological antibody testing for previous SARS-CoV-2 infection methods can be conducted at point-of-care (POC) or in specialised laboratories, the POC options for both tests have not proven reliable for widespread deployment. Encouragingly, this is an area of rapid research and it is likely that accurate and validated tests may become available soon.

This brief's focus is on the value of serological testing and its POC and laboratory testing options.

Laboratory-based serological tests for SARS-CoV-2 antibody detection

Laboratory-based antibody tests are considered more accurate compared to POC options. However, they require sophisticated equipment and are conducted in accredited facilities by specialist trained staff. As such, laboratory tests are more costly and time consuming, are usually not widely accessible and are difficult to scale.

A common laboratory technique used to detect antibodies against a particular pathogen is an enzyme-linked immunosorbent assay (ELISA), which is generally highly sensitive and specific compared to POC antibody tests.

In addition, specialised laboratory techniques can specifically detect neutralising antibodies. Neutralising antibodies are those that can bind and protect against an invading pathogen. They do this by interfering with the virus's ability to infect host cells. Binding antibodies that are not neutralising do not offer the same protective ability.²⁻⁴ In papers awaiting peer review, putative neutralising antibodies against SARS-CoV-2 in COVID-19 patients have been reported.⁵⁻⁷ However, in addition to being pre-print papers, these studies have small sample sizes and so generalisations about SARS-CoV-2 neutralising antibodies are difficult to apply to the broader population. Current serological tests and neutralisation assays can therefore, at best, provide an 'estimate of immunity'.

Specific laboratory-based methods can also be used to detect and differentiate between antibody subtypes (IgM and IgG) that are indicative of timing of virus exposure and active or past infections.^{8,9}

Point-of-care serological tests for SARS-CoV-2 antibody detection

The value of POC tests is that they provide rapid results, are relatively easy to use and can be made widely accessible with testing often carried out by the patient or near the patient by a medical practitioner.^{10,11}

Examples include the standard over-the-counter pregnancy test or blood glucose monitors. As testing regimes for COVID-19 expand, there is an increasing demand for POC testing.

To detect antibodies using POC tests, a lateral flow immunoassay is used, in which the sample is placed into a paper-based test device and the non-quantitative results are displayed within 5 to 30 minutes. Although this technique is based on the same principles as an ELISA, it generally has lower sensitivity and specificity.¹² Furthermore, neutralisation assays are not available for POC testing and must be conducted in a laboratory.

High quality POC serological tests have transformed the diagnosis of HIV, hepatitis C, hepatitis B and syphilis. Importantly, these tests have been subject to extensive independent validation, which has not yet been possible with SARS-CoV-2.

Although it is possible to detect antibodies using POC tests or laboratory methods, the two are not the same. POC tests only detect the presence or absence of antibodies against a virus, whereas laboratory tests can

indicate the amount and type of antibody, although thresholds are often established and results are reported in a qualitative manner.

Further research is needed to strengthen the specificity and sensitivity for detection of SARS-CoV-2 antibodies for both POC and laboratory-based methods.

The value of serological testing during the COVID-19 pandemic

The predictive value of serological testing is inversely proportional to disease prevalence.¹³ This is particularly important in the Australian COVID-19 context given the low number of cases and the presumed low prevalence. The consequence of this is a high false positive rate. For example, if a test is 99% accurate (sensitivity and specificity are each 99%) but the disease prevalence is only 1% of the population, then the false positive rate will be 50%. That is, of 100 positive tests, 50 will be inaccurate. This creates a significant challenge in identifying immunity within populations in a country with a low rate of infection.

In Singapore, laboratory-based serological testing was used to support contact tracing and surveillance measures.¹⁴ The researchers could identify the missing link between three infection clusters: an individual who was infected but had tested negative twice for the virus by PCR, then positive for antibodies against SARS-CoV-2. Contact tracing using serological testing has also been reported in Cairns, Queensland.¹⁵ These examples highlight that serological testing is particularly useful in this context as, unlike PCR,¹⁶ it measures prior infection, not just current presence of virus.

In addition to supplementing acute diagnoses, serological tests can have an important role in disease surveillance and control. They can provide answers to questions on the extent of undiagnosed community infection including asymptomatic spread and allow public health experts to better model public health interventions and direct specific movement restrictions.

Serological testing also has value in determining how strong and long-lasting the human immune response to SARS-CoV-2 is likely to be. A recent report of COVID-19 patients, awaiting peer review, has described that SARS-CoV-2 antibody concentrations began to fall 8 weeks post-symptom onset.¹⁷ This information would inform the timing of serological testing.

Serological testing could provide estimates of who has had an immune response. This could assist in the clearance for returning to work, particularly of front line health workers, and the distribution of a future vaccine giving priority to those who are susceptible.¹⁸ However, there are insufficient data to definitively say if the presence of SARS-CoV-2 antibodies, and at what level, might be considered protective.

In the later stages of an outbreak, epidemiologists can use serological testing data to refine key parameters of the pandemic such as the fatality rate of a disease. Early in a pandemic, the fatality rate often appears higher than it actually is because only sick or symptomatic people are tested and the fatality rate is

calculated as the total number of deaths divided by the total number of known cases.^{19,20} The information may be useful in monitoring the effect of physical distancing measures and other non-pharmaceutical interventions at the population level.

Laboratory-based serological testing is also being used to identify donors of convalescent plasma – plasma that may contain high concentration of neutralising antibodies derived from recovered COVID-19 patients. Convalescent plasma can be used to treat COVID-19 patients requiring acute care.^{21,22} Recent small-scale studies suggest that convalescent plasma therapy may significantly improve outcomes for COVID-19 patients.^{23–26}

Limitations of serological testing for SARS-CoV-2 antibodies

The development and impact of serological tests rely on a clear understanding of the full immune response to SARS-CoV-2,²⁷ which currently remains undefined. Validation is also required for the population where the test will be deployed.²⁸

It can take 7 to 14 days for most COVID-19 patients to produce detectable SARS-CoV-2 specific antibodies. The intensity of the immune response varies greatly from person to person, with some individuals producing either none or an undetectable concentration of antibody.^{7,27,29–34} Due to the delayed antibody response, serological testing does not have a major diagnostic role during the acute phase of disease.²⁷ It may contribute to COVID-19 diagnosis where PCR testing has been negative or in asymptomatic and mild cases. As such, serological testing can be used as an adjunct to PCR testing.¹⁶

Serological testing does not have value in predicting how infectious a COVID-19 patient is. It has been argued, based on SARS-CoV and MERS, that patients become less infectious as an antibody response is elicited.³⁵ It is unclear if this is true for SARS-CoV-2 infection. In a small study by Wölfel *et al.*, all COVID-19 patients had detectable levels of neutralising antibody but the levels did not suggest close correlation with viral load in sputum or faecal samples or symptom severity, which in some patients persisted for several months.⁶

As for all pathology tests, serological testing can deliver false positives and negatives. A positive SARS-CoV-2 antibody test may be found in people not infected with this virus but infected with other human coronaviruses that cause the common cold.³² This example reinforces the need for highly accurate and validated tests.

POC testing cannot yet replace laboratory-based methods

The application of POC testing in diverse environments means that they lack the rigorous quality controls of laboratory-based testing and participation in quality assurance programs. In addition, specific training and restricted locations may be required for handling serum from COVID-19 patients. Although independent and

post-market evaluations are in progress for POC COVID-19 tests, they have not yet been validated for individual use.

The UK's National COVID Testing Scientific Advisory Panel, led by Professor Crook at the University of Oxford, has just released the results of its evaluation of nine commercial POC serological tests being considered by the UK government.¹⁷ The researchers compared these with their in-house academic laboratory ELISA and concluded that the performance of these POC tests was inadequate for individual patient applications and population prevalence studies. Notably, the in-house ELISA was able to achieve 100% specificity, demonstrating that non-commercial techniques could be implemented if validated against national and international standards. Lassaunière *et al.* also evaluated commercially available COVID-19 serological tests, which included POC lateral flow and laboratory-based ELISA test kits, and observed that POC tests varied more than laboratory-based methods.³⁶ In another study, Whitman *et al.* also demonstrated that POC serological tests produce variable results.³⁷ These three studies are all awaiting peer review.

Cellex, a POC lateral flow immunoassay for screening COVID-19, has obtained Emergency Use Authorisation by the USA's Food and Drug Administration. However, the instructions for use specify that it is only to be used as an aid in diagnosis of previous infection.³⁸ The standard diagnostic test for COVID-19 is laboratory-based nucleic acid testing via PCR.^{39–42}

Importantly, if POC serological tests are implemented using kits that are not yet fully validated, there is a risk that they will not provide public health officials with the information that they need and, worse still, that they may provide an incorrect answer. Poor specificity will typically overestimate the number of people who have been infected and poor sensitivity may lead people who have been infected to believe they have not been infected.

Before deploying POC serological testing for SARS-CoV-2, it is important to validate the test's reliability and, if deployed, establish confirmation services at specialised laboratories to maintain quality control and assurance.

An important note on available COVID-19 research

Although current COVID-19 research is available through pre-print servers, many of these articles have not yet been peer reviewed (an imperative pillar of the scientific method) and the relatively short duration of the current outbreak has resulted in variable testing and reporting practices in different countries. As such, conclusions drawn need to be interpreted with caution. Pre-prints are marked with a § in the reference list.

Serological testing in relation to SARS-CoV-2 infection is a rapidly developing area of research with almost daily updates. This brief is accurate at the time of writing and may become out of date at a later time of reading. Consultation with the Australian Academy of Science is possible if the reader has questions.

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APPENDIX

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RAPID RESEARCH INFORMATION FORUM

The predictive value of serological testing during the COVID-19 pandemic

The Rapid Research Information Forum (RRIF), is a forum for rapid information sharing and collaboration within the Australian research and innovation sector. It is convened by the Australia's Chief Scientist, Dr Alan Finkel AO FTSE FAA FAHMS, and its operations are led by the Australian Academy of Science.

RRIF provides a mechanism to rapidly bring together relevant multidisciplinary research expertise to address pressing questions about Australia's response to COVID-19, as they emerge.

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