Title:

RAPID REVIEW: Testing for COVID-19

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Testing for COVID-19 – the current state of laboratory tests and recommendations within the context of New Zealand's pandemic response
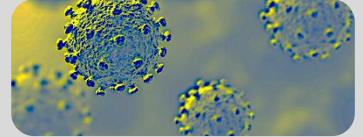
Report Date: 26-29th March 2020.

Report Recommendations:

- *Recommendation#1*: As much resource as possible should be targeted at monitoring and executing testing capabilities. This all-of-government response should include: (i) a COVID-19 PCR taskforce and; (ii) a COVID-19 'antibody/antigen' taskforce. These groups should urgently coordinate purchasing, validation, funding requests, timelines, priorities, adoption and scope local (New Zealand-based) capabilities and expertise.

- *Recommendation#2*: New Zealand should continue to prioritise its PCR testing capabilities. Securing supply lines, scalability and speed of testing should be the country's primary diagnostic focus at this point in time. Other countries are ahead of New Zealand on the infection curve and we are behind them in the queue for already scarce material for the test.

- *Recommendation#3*: New Zealand should actively engage with the rapidly developing 'Point-of-care' (POC) lateral flow diagnostic space for virus antigen and patient antibody (see inset image as an example). Purchasing decisions may need to be separated from adoption decisions to preserve optionality. There are risks in adopting the 'wrong' test that performs poorly – valuable resources may be expended if poor decisions are made. Conversely, there are risks of delaying decisions and missing out. The role and utility of new POC tests must be carefully explained to the public to avoid unrealistic expectations and perverse outcomes (e.g. patients who think they are immune, but are not, as the result of a false positive test for antibodies).

▲ Components of a coronavirus blood test that a company based in Derby claims gives a result in 10 minutes. Photograph: Christopher Furlong/Getty Images

- *Recommendation#4*: New Zealand should rapidly pursue testing capability to detect antibodies in a laboratory setting. Tests for antibodies in New Zealand's diagnostic laboratories (a test called 'ELISA') should also be considered for large scale serological testing in the coming weeks. It is likely these tests will be deployed with only partial validation. These tests can be purchased from overseas suppliers but New Zealand laboratories are already working on generating viral proteins and antibodies needed for these tests. Coordination, funding and support for these New Zealand-based initiatives should be mobilised to prevent fragmentation and duplication.

Report Key Messages:
- Reliable and rapid testing for SARS-CoV-2 is a vital part of New Zealand's pandemic response.

- The primary method for virus detection is a testing method called the Polymerase Chain Reaction (PCR). As the World Health Organisation notes, this test is still the best way to track and trace virus. New Zealand must do everything possible to maintain (and optimise) this testing capability. Securing supply chains of reagents must remain a top priority.

- Losing our PCR testing capability would have catastrophic consequences. The volume of tests required now, and in the future, needs to be constantly monitored.

- Testing can perform two vital roles in this pandemic:

    - (i) diagnosis of COVID-19 early in infection; this is undertaken using either PCR tests (current standard) or direct tests for virus particles (that are in rapid development but unproven)

- o (ii) population antibody tests: identification of patients who have been infected for some time or have recovered (and can possibly return to work) - antibody tests are new to market but are commercially available.

- Advances in diagnostic testing are rapidly evolving - companies are developing tests and are pushing for adoption (and market share). Many of the tests are unproven. A watching brief on testing development should remain a priority so that New Zealand can respond and pivot if/when needed.

- Recent articles in the media highlight a POC tests (akin to a pregnancy 'stick' test – called a lateral flow test – see image above) that can either (i) detect viral particles (called antigens) or (ii) detect antibodies that patients form in their bodies between 4-20 days after COVID-19 symptoms are first observed.

- Tests to directly detect viral particles (called antigen tests) could be a replacement for our PCR testing. They are currently being validated prior to being deployed in the UK. However, such a test recently failed in Spain where, anecdotally, the test was only 30% accurate. While these tests are 'in development' they are <u>not</u> market ready (as of 29th March) and so have unknown specificity or precision. Adopting a poor test would have a very detrimental outcome during the track & trace pandemic phase.

- Antibody testing (POC or laboratory based) will become increasingly useful in the New Zealand pandemic response, with antibody testing becoming a crucial part of testing hospitalised patients. There is a high chance that accurate antibody data generated in laboratories will enable us to better predict disease progression (and demand on hospitals).

- It is vital that antibody tests (in contrast to antigen tests) should <u>never</u> be regarded as a replacement for PCR tests – they are complementary and serve a different purpose. The false positive/negative rates of these POC tests remain uncertain.

- Antibody POC tests that identify past exposure are not very useful at this point in New Zealand's current track & trace phase because of the time it takes for our bodies to mount an antibody response to COVID-19. This 'time-lag' makes these kinds of test a poor proxy for infection relative to current PCR tests. However, securing these tests for later phases of the pandemic should be considered a priority.

- Testing for antibodies will almost certainly require the purchase and import of testing kits. There is an inherent risk that supply chains may become compromised and some companies may not be able to keep up with global demand. Events mean that procurement decisions will likely need to be rushed with multiple choices pursued to create a hedge strategy, but they must still be carefully considered and weighed against the risk of missing the window of availability. New Zealand should also mobilise its internal capabilities to develop and validate reagents used in COVID-19 testing reagents.

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Glossary of key terms and acronyms as they relate to COVID-19 and its testing:

Antibody – A protein made by your body to combat infection by virus. Antibodies to COVID-19 protect the body from re-infection as they can neutralise the virus.

Antibody test: Is a test to see if a patient has generated antibodies (see IgG and IgM) to the COVID-19 virus.

Antigen test: Is a test for the SARS-CoV-2 virus that detects surface proteins of the virus rather than the viral RNA (see PCR).

B-cells: Cells in the immune system that are responsible for antibody production.

COVID-19: The name given to the disease pandemic caused by the SARS-CoV-2 virus which arose in the Wuhan Provence in China in late 2019.

ELISA: Enzyme-linked immunosorbent assay. In the context of COVID-19 this is a test conducted inside a diagnostic laboratory to as test for antibodies (see IgG and IgM) to coronavirus. It could be used as a barometer of immune response to the virus.

False positive: When a test for COVID-19 comes up as positive when in fact the patient is not carrying the virus or been previously exposed.

False negative: When a test for COVID-19 comes up as negative when in fact the patient is carrying virus.

IgG: A type of antibody that is typically generated late in the COVID-19 infection

IgM: A type of antibody that is typically generated early in the COVID-19 infection

Lateral flow: A type of 'dipstick' point-of-care test akin to a pregnancy test, where body fluids are deposited on the device, which will (in 10-20 mins) reveal if antigen or antibodies to the virus are present.

Monoclonal antibody: This is a single 'type' of antibody that can detect Virus proteins. Making monoclonal antibodies is complex and finding one that is precise and can be produced at scale is time consuming. Monoclonal antibodies will ultimately be used as basis for point-of-care antigen tests.

PCR: 'Polymerase Chain Reaction'; a test by which RNA (or DNA) is photocopied. This is the core test for COVID-19 virus as it is very sensitive and specific.

POC: 'Point-Of-Care' a test that is typically a 'yes/no' answer that is conducted rapidly at the patient's bedside or their home.

RNA: The form of genetic material that the COVID-19 virus and related viruses use as opposed to many other viruses that use DNA.

RNA extraction kit: A kit purchased commercially that contains all the 'ingredients' needed to isolate viral RNA which is used in PCR tests.

SARS-CoV-2: The virus that is responsible for the COVID-19 epidemic.

Serological: A term used to describe how our body fluids respond to the virus, for example the formation of antibodies.

Validation: The process by which a test for COVID-19 is assessed to see how reliable it is. Test validation takes many forms but centres around how well a test performs in terms of sensitivity and precision. When products are rushed to market validation may be poor.

Background Summary and Document Scope:

Reliable and fast testing for COVID-19 is a vital part of New Zealand's pandemic response. New Zealand must do everything possible to maintain (and optimise) this testing capability. Supply chains of reagents must remain a top priority. There is an unknown risk that our reagent supply may begin to limit testing in some/all of our diagnostic laboratories.

The purpose of this document is to provide a rapid point-in-time evaluation of the different testing strategies for COVID-19 and recommend some possible options, scenarios and tests that may benefit New Zealand's pandemic response. Relevant to this document, is that COVID-19 testing is a rapidly moving field and the testing scenarios can change quickly.

In the face of the current COVID-19 pandemic there are some critical questions to ask about testing now, and in the future[1]. The WHO has advocated strongly for testing to be scaled up[2]. However, with potential shortages of reagents (regional, national and international) and physical constraints on testing capacity in laboratories, the question remains: what is our Plan B? Can our PCR-based tests continue at the current burn rate? How prepared is New Zealand to conduct alternative testing procedures? What is the state of development of antibody and viral antigen tests? Is there value in testing whether an individual has developed protective antibodies after exposure? Can a reliable supply of reagents be sourced from overseas? What capacity already exists to generate testing reagents within New Zealand?

The speed of this pandemic has tested the globe's ability to rapidly develop diagnostic tests. FIND, the Foundation for Innovative New Diagnostics has taken on the task of collating tests that have been commercialized and those that are in development around the world (https://www.finddx.org/covid-19/pipeline/). Likewise, the Saw Swee Hock School of Public Health in Singapore (https://sph.nus.edu.sg/covid-19/) has a dynamic list of tests published in their weekly update. Australia recently provided a list of suppliers: https://www.tga.gov.au/covid-19-diagnostic-tests-included-artg-legal-supply-australia

These collective lists extend to many 100s of diagnostic possibilities and timely identification of those most suited to New Zealand is a challenging task.

In an ideal scenario there would be a rapid 'point of care' and/or laboratory-based test for the virus responsible for COVID-19 (termed SARS-CoV-2) and there would be sensitive tests available to:

(i)   see if an individual has the virus (i.e. an infectious phase) and

(ii)   to detect if a person has already been exposed to SARS-CoV-2 (and therefore can't be infected again).

Unfortunately, there is no single test that can determine both if a person is currently infected or has been infected in the past.

No jurisdiction seems as yet to have developed the capability and deploy this dual-test strategy at scale – it remains a work in progress. This two-pronged approach is ultimately

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[1] https://www.nature.com/articles/d41587-020-00010-2
[2] https://www.who.int/emergencies/diseases/novel-coronavirus-2019

where the testing regime for COVID-19 will need to end up for best pandemic control. The speed of the pandemic coupled with the development timelines for diagnostic tests has, to date, prevented this ideal testing scenario from being implemented anywhere across the globe.

Below is a summary table of the three primary types of tests currently available or that are in development phase:

Type of test	What does it detect?	When can it work?	How long does it take?	Format	Approval status
PCR Tests	Virus	2-5 days before symptoms, in asymptomatic people	~12-48 hrs	Laboratory test	WHO approved
Antigen Tests	Virus	2-5 days post symptoms (no published data about asymptomatic individuals).	2-4hrs (lab), 10-20mins (POC)	Laboratory test or Point of Care test	Research only – in development
Antibody Tests	Individuals' response to virus	~5-20 days post symptoms	In-laboratory ELISA, 2-3hrs, or 10-20mins (POC)	Laboratory test or Point of Care test	Diagnostic approved in some cases

To see if an individual has the virus the most common way is to use a PCR assay - this approach is highly sensitive and precise as well as being reasonably rapid (12-48hrs).

It may be technically feasible to use antigen tests (that directly identify virus surface proteins) to see if someone's samples (saliva, blood etc.) might contain COVID-19 virions. However, there is limited evidence that this approach is currently viable. There remains a risk that by the time some technologies are developed, distributed and validated (i.e. determination of false positive and false negative rates) that they run the risk of 'missing the boat' given the pandemic timelines.

Accordingly, the only current viable test to use for New Zealand's 'track-and-trace' response are PCR-based tests. There are moves to make this PCR test more rapid (45 mins to 2 hours). It is the view the authors that, again, the timelines to validate these rapid tests (which often employ different reagents to standard COVID-19 PCR tests and specialised readers) means they may not be ready until well after they were needed in the pandemic response timeline.

A test to determine if an individual has been previously exposed to COVID-19 and developed antibodies is also a valuable part of the testing toolkit but is a technology that is of more use once the 'track and trace' phase is over. Antibody testing will become increasingly useful in the New Zealand pandemic response, with lab-based testing becoming a crucial part of testing hospitalised patients. There is a high chance that accurate antibody data generated in laboratories will enable us to better predict disease progression (and thus demand on hospitals).

If a patient has developed antibodies to the virus then there is evidence that they can neutralise the virus (and cannot be infected again). This kind of data is highly useful within the pandemic responses as these patients can likely circulate with more freedom in society without fear of increasing the transmission of the virus.

The published table below summarises the three primary approaches for COVID-19 testing (source: http://www.seegene.com/covid19_detection). In this document these tests are classified as Antigen Tests (green), Antibody Tests (blue) and PCR tests (red).

COVID-19 diagnosis	Antigen-based immunoassy	Antibody-based immunoassay	Real-time PCR
Analyte	Antigen	Antibody	Gene
Detection time	From a few days after onset of symptoms	From 7-28 days after onset of symptoms	All of stages
Sensitivity	50-70% (expected)*	More than 95%	More than 95%
Specificity	50-70%*	Not clear*	More than 95%
Detection of asymptomatic infection	Depending on the amount of viral antigen	At the later stage of infection	From the early stage of infection
Status of use	Only some regions	Only some regions	All of countries (recommended by WHO & CDC)

* Based on conventional rapid diagnostic tests, Affected by seasonal coronaviruses.
Reference: Oral presentation from online forum of KOFST(The Korean Federation of Science and Technology Societies)

PCR tests for SARS-CoV-2 – what are the risks?
In the context of New Zealand's pandemic response, PCR-based testing is the best currently available technology for the task. While there are some cases that are 'missed' early in infection (due to low viral loads), the test still operates with a high sensitivity and precision. It is highly likely that multiplex PCR (which tests for multiple viral target sequences simultaneously) will remain the backbone of the testing procedure as advocated by the WHO. It is worth noting that South Korea's 'pandemic curve flattening' phase was achieved nearly exclusively with extensive PCR testing.

There remains an undetermined risk the global demand for testing ramps up there may be shortages of reagents, namely the RNA extraction kits used to isolate the virus's genetic material. There are some media and anecdotal reports of this occurring[3]. Unless global supplies of these RNA kits continue to flow there may need to be alternative strategies for the extraction of viral genetic material. If New Zealand is going to continue to 'ring-fence' the virus using a 'test-track-trace' response then it must maintain the ability to test many thousands of samples per day (for the current week an average of ~1400 samples per day were processed[4]). There is some risk that if tests 'run out' that tough questions will be asked regarding the decision to adopt this strategy in the first instance – accordingly New Zealand must work hard to maintain its testing capacity at scale. One option is to consider running a subset of lower priority samples using other laboratories that might use 'non-validated' RNA

[3] https://www.the-scientist.com/news-opinion/rna-extraction-kits-for-covid-19-tests-are-in-short-supply-in-us-67250
[4] NZ Director General of Health media conference 29th March.

extraction methods. Another option (currently in use in Western Australia) is to combine multiple patient swabs in a single test (called pooling) in order to preserve reagents – an option that is messy but may have utility on low-probability samples. This process is only of use early in the epidemic when the majority of tests will be negative. There are some reports of this emerging in the COVID-19 literature[5].

It is essential that New Zealand makes the most of the regents and supply chains that are currently in use in the country. National coordination of reagents and testing would prevent situations where some sites lack both regents and testing capability when resources exist in other areas.

It is important to note that in most scenarios, the costs of scaling up COVID-19 testing is low in comparison to the hospitalisation costs[6] – overall implementation of large-scale testing is likely to preserve life and be more cost effective. This was the strategy adopted in South Korea.

Alternatives to the PCR test to detect virus – what else is out there?
An alternative (non-PCR) viral testing method is termed an 'Antigen Test'. In this form of testing a laboratory generated antibody (called a monoclonal) that detects a diagnostic part of the virus can be overlaid on a sample of sputum, blood, serum or faeces to see if there are any viral particles present. There are manufacturers that are selling reagents that could form the basis of such tests (see later in section labelled set#3). However, there is very limited information on how sensitive they are and what the false positive and false negative rates are. False positives using these types of tests with other viruses (e.g. 'common cold' viruses) remain an ongoing concern. Accordingly, such tests might be considered presumptive rather than confirmatory.

Antigen testing for virus might be considered as a back-up to PCR tests but their efficacy remains unknown[7] and (unlike PCR tests) remains completely contingent on a supply of reagents from a 3rd party suppliers (that hold the monoclonal antibody as proprietary reagents). It is unlikely that antigen tests will be as sensitive as PCR based approaches which already seem to lack some sensitivity at early stages of infection and can deliver false negatives due primarily to poorly collected samples, poor storage and/or degradation of RNA.

What about antibodies that are generated within patients in response to infection – are these useful indicators?
Rather than trying to detect COVID-19 virus directly, an alternative approach is to ask the question is there any evidence that an individual has already encountered the virus? This approach involves detecting antibodies generated by our immune systems against the virus; IgM and IgG are the two main types of antibodies that are tested for. Antibody responses to COVID-19 are not well characterised as yet and while is not completely clear about which type of antibody develops first[8], it looks likely there is an IgM followed by IgG. Most, but not all, antibody testing kits against COVID-19 are designed to detect both antibodies at the same time. Individuals develop their immune response to viruses at different rates. In the case of

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[5] https://www.medrxiv.org/content/10.1101/2020.03.26.20039438v1
[6] https://www.medrxiv.org/content/10.1101/2020.03.22.20041137v1
[7] https://reaction.life/will-the-uks-new-covid-19-tests-work/
[8] Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet.* Kelvin Kai-Wang To, MD et al. Published: March 23, 2020DOI:https://doi.org/10.1016/S1473-3099(20)30196-1

COVID-19 there are reports of it taking anywhere between 4-20 days after the onset of symptoms to detect antibodies (see figure inset[9]). Moreover, it is worth noting that every person's immune system will respond differently to the infection, meaning that it is to be expected that there is a variable antibody response across the population.
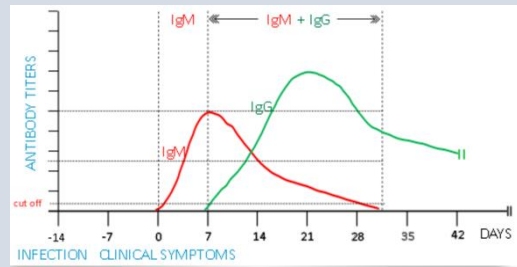
On 22nd March the WHO stated: "*Serological (i.e. antibody) assays will play an important role in research and surveillance but are not currently recommended for case detection*". This is primarily due to the delay between infection and the development of antibody responses. This delay makes these tests poorly suited for rapid evaluation of infection status. In addition, antibody tests require a steady stream of proprietary reagents coupled with the fact that there are limits to its scalability on the international stage. However, in this regard the small population size of New Zealand and the delayed transmission history (relative to other countries) provides an important opportunity to diversify our testing portfolio.

There is a large body of evidence that some COVID-19 infected individuals remain largely asymptomatic[10]. Advocates for adoption of antibody-based testing will (rightly) point out that the subclinical infection means that PCR-based tests may 'miss' individuals either because they are never tested or because their viral loads are too low. This is perhaps best explained though comparisons with influenza infections: a (meta) analysis of available literature measured the fraction of asymptomatic infections detected by PCR assays as approximately 16%, while the fraction of asymptomatic infections detected by antibody response was measured as approximately 75%[11]. Put simply, in cases where the patient has formed antibodies and cleared the virus that a legacy remains of past exposure to the virus that PCR tests can't detect.

Does the presence of viral antibodies mean that a person has been exposed to COVID-19?
Yes, barring the likelihood of a false positive result; if a patient has developed antibodies to COVID-19, that it is reasonable to suspect that they have been exposed. There is a growing body of literature that shows patients that have generated antibody responses are able to neutralise the virus and cannot be reinfected. Not all patients will generate effective antibody responses in the same way or in the same timeframes.

Have antibody tests been used in the past to detect similar Coronoviruses?
Antibody tests were used in past coronavirus outbreaks (e.g. SARS-CoV and MERS) but these are noted to have taken a long time to develop. Indeed, the development of such resources are far from trivial and are noted as being resource intensive[12].

Is measuring antibody response a useful indicator in the contact tracing phase?
It can be, but its utility will be more evident in later pandemic phases. Once key feature of the COVID-19 pandemic is the relatively high number of people that have no/low/mild symptoms. For individuals that test positive by PCR there is some value in testing close contacts to see if

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[9] https://pharmact-health.com/en/sars-cov-2-rapid-test/
[10] BMJ 2020; 368 doi: https://doi.org/10.1136/bmj.m1165 (Published 23 March 2020)
[11] Leung, N. H., Xu, C., Ip, D. K. & Cowling, B. J. Review Article: The Fraction of Influenza Virus Infections That Are Asymptomatic: A Systematic Review and Meta-analysis. *Epidemiology* **26**, 862-872, doi:10.1097/EDE.0000000000000340 (2015).
[12] http://www.centerforhealthsecurity.org/resources/COVID-19/200228-Serology-testing-COVID.pdf

they have unknowingly been exposed to the virus and already cleared the infection. This approach has been trialled in Singapore.

Are these antibody tests useful at this point in time?
Right at this point in time (26-29th March) in New Zealand's pandemic trajectory the best use for these tests is for identifying healthcare and essential services workers that have acquired immunity. This gives a cohort of people who could safely perform frontline activities. Right now, these tests remain of limited value in New Zealand's current track and trace phase because of the time it takes for our bodies to mount an antibody response to COVID-19. This 'time-lag' makes these kinds of tests a poor proxy for active infection relative to our current suite of PCR tests.

I read on the news that take-home antibody tests are about to hit the market – is this correct?
On the 25th/26th March there was a flurry of news pieces about the potential for a COVID-19 home testing kit that can detect antibody. The UK has reportedly ordered 3.5 million tests[13]. The notion that there is an easy DIY kit to test for virus infection is something that clearly resonates with the public.

There is a residual risk when using these antibody tests surrounding the frequency of false positive and false negative results. For example, if someone takes the test and this falsely indicates prior exposure then an individual might unwittingly expose themselves to the virus thinking that they have neutralising antibodies. Likewise, someone may remain in isolation when they have in fact generated immunity. New Zealand will have the benefit in the coming weeks of seeing how these increasingly available tests are used by healthcare professionals and the public in the UK and other jurisdictions.

How do antibody tests actually work?
The key point with regard to antibody detection is finding a section of the virus that (i) our antibodies form an immunological response to and, (ii) that is different enough from other coronaviruses. In recent weeks, parts of the virus have been made synthetically and a number of commercial providers now sell parts of the virus spike proteins and ELISA and strip (lateral or 'dip-stick') kits. There are also reports that New Zealand already has imported the tools needed to make viral proteins[14].
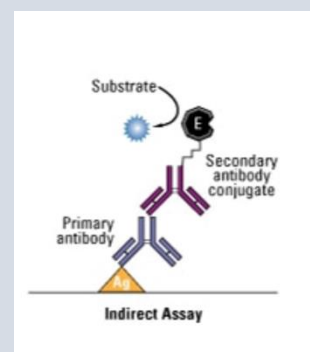
The basic concept of an antibody test is that a surface is coated with viral protein and patient serum is passed over the surface. If the patient has been exposed to the virus it would have developed antibodies which will stick to the surface, all other antibodies will wash away. The presence of the antibody test can now be easily determined via a colour change (see figure above).

What are the limitations of these antibody tests – are they validated?
The fundamental issue with antibody tests such as these is that everybody's antibodies are different and that antibodies are inherently 'sticky' molecules and can bind to things that are not targets. Accordingly, the likely false positive and false negative rates can be high. Some

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[13] https://reaction.life/will-the-uks-new-covid-19-tests-work/
[14] https://rd.callaghaninnovation.govt.nz/biotechnologies/protein-science/

preliminary results reported a sensitivity and specificity of 70% for a COVID-19 antibody test. Some manufacturers report values of 100% but often have been tested on low numbers of patient samples. The rush to market has resulted in little to no validation, with some manufacturers seemingly offering tests before they are market ready or have even rudimentary validation. Some validations will, through necessity, occur 'on the fly'.

What are the positives of antibody testing over PCR?
Speed, and the ability to avoid the need to isolate and enrich RNA provide some obvious benefits. The primary benefit is, however, that once the virus clears, PCR tests will be negative and there will be no other way to determine if the patient had been infected previously. This is a real risk in the COVID-19 pandemic due to the number of asymptomatic people.

In an ideal scenario both PCR and Antibody tests would be employed in a way that plays to their strengths and purposes. It is vital that antibody tests (in contrast to antigen tests) should never be regarded as a replacement for PCR tests – they are complementary and serve a different purpose

What are the possible scenarios for New Zealand to adopt POC and laboratory-based antibody tests for COVID-19?

Scenario#1 - Stick with PCR: New Zealand maintains, in accordance with current WHO guidelines, that PCR tests are the best way to track and trace the COVD-19 pandemic. It could argue that antibody-based testing is not readily available on a scale that will enable nationwide coverage and that while it is 'nice to have' within the 'track and trace' phase, PCR detects virus earlier. Some jurisdictions have taken this approach. *Benefit:* the focus of diagnostic labs remains on a single diagnostic test. *Risk:* We're not able to identify healthcare and essential services people who have acquired immunity and unnecessarily place others without immunity at risk on the frontline. We would miss the opportunity to enable immune people to return to work and re-start the economy. Finally, it is likely that such a stance would be criticised by the public but also by many infectious disease physicians who consider this an essential part of confirming diagnosis, especially in hospitalised patients.

Scenario#2 – 'Kick the tyres' of a few antibody tests: New Zealand could reasonably choose to explore the value of antibody tests to build expertise and validate tests across its laboratory resource. To some degree this is already occurring, albeit with no obvious coordination. Ordering reagents from promising suppliers (listed below) might enable diagnostic laboratories to test the efficacy, speed and precision of antibody testing. This approach could be applied to both Antibody tests and Antigen tests. This approach would ensure we have the ability to use the eventual best candidate in a timely manner. *Benefit:* This approach would enhance existing capacity and expertise that will better prepare New Zealand labs to scale-up testing if the need and opportunity arise. Adoption of these tests will reassure the public that our science labs are 'watching and learning' from what approaches are being trialled overseas. *Risk*: There remains a risk that the modalities that we might choose to adopt for testing are quickly overtaken by other commercial tests thus time may be wasted. This needs to weighed against the risk of missing out or being too slow to act.

Senario#3 – Jump in the deep end and order. New Zealand could seek to implement antibody testing at scale to diversify its testing toolkit. Accordingly, New Zealand could rapidly select 2-3 preferred suppliers of tests and reagents and seek to secure supply chain so that it can reliably receive and distribute the tests around the country. *Benefit:* Widespread serological

testing could enrich some of the contact tracing and provide some capacity to test for acquired immunity and thus identify those who cannot become infected or transmit the virus. **Risks:** There are a number of inherent risks to implementing this scenario at scale – they include:

  (i)   Cost in terms of reagent and time to develop. There is risk that we choose the 'wrong' option in a fast-moving diagnostic testing landscape. This should be mitigated by choosing multiple tests.

  (ii)   Availability in terms of reagents – tests available at scale? Testing on small scales is relatively easy, producing them for many thousands of tests more challenging for a company to deliver the tests in a timely fashion.

  (iii) Since New Zealand cannot (currently) manufacture these reagents we would be reliant on an out-of-country supply chain operating. This can be mitigated by funding existing New Zealand expertise and capability to manufacture testing reagents.

What are the possible scenarios for New Zealand to adopt <u>Antigen tests</u> for COVID-19.

Scenario#1. New Zealand takes the position that Antigen tests are not yet on the market, adopt a wait-and-see approach and test these at small scale when/if they come to market. *Benefit*: time and money is not spent on unproven technologies. *Risk*: that antigen tests are used effectively elsewhere but New Zealand is behind other purchasers in the queue for already scarce material.

Scenario#2 That New Zealand immediately places orders with manufactures of POC antigen tests. Procurement decisions will likely need to be rushed with multiple choices pursued to create a hedge strategy. *Benefit:* That New Zealand will be in a strong position if the tests perform well. *Risk:* That time and resources are wasted on kits that fail to live up to expectations. There is a real risk that false negatives (the result of poorly performing kits) will be taken as a COVID-19 negative result and the patients will circulate in the population and spread virus.

<u>Recommendations and review of testing reagents;</u>

There are a variety of molecular tests available on the market – many healthcare providers are scrambling to secure market share. Clearly there is need for haste in decision making but there are consequences if the test fails to function reliably or if supplies run out. While the list below will make some recommendations, prior to decisions being made, suppliers need to be contacted to better understand if their supply/manufacturing chains are able to keep up with demand and discuss the state of their validation for the tests.

 Our research (to date) reveals the two sites that best list and discuss the available diagnostic options that are at or near market:

  (i)   https://sph.nus.edu.sg/covid-19/ - there is a weekly report with the most recent being: https://sph.nus.edu.sg/wp-content/uploads/2020/03/COVID-19-Science-Report-Diagnostics-23-Mar.pdf

  (ii)   https://www.finddx.org and the listing at: https://www.finddx.org/covid-19/pipeline/

These two sites have extensive lists of available PCR, antibody and even CT scan tests. Naturally, many of the tests listed in these resources are 'in development' many give no information about specificity and/or sensitivity and are on a spectrum from 'no validation' to validation that is not fit for purpose. We have reproduced these lists in the appendix of this document but note that the website above are 'live' documents.

It is inherently difficult to select one specific technology/kit over another. Part of this difficulty is due to the speed at which this pandemic has presented. Another challenge is the break-neck speed of the COVID-19 diagnostic marketplace. Even over the three days it took to write this report there have been developments – accordingly it is likely the reader will find these recommendations out of date.

From the above published lists and exploring online diagnostic websites (on the 26-29th March) the tests that we deem are worth considering at this point in time are noted below. While there are many tests that could do the job, these stood out as non-PCR based solutions that we think offer the best chance of success.

Set#1: POC antibody tests - these tests are rapid lateral antibody tests that are able to detect if a patient has generated an IgM or IgG response. There are a raft of these tests coming, or about to come, onto the market place. It is difficult to choose between the options as the companies' efficacy claims need to be taken with caution. Many of them are silent with regard to off target effects and the limitations of their products. The four POC tests selected below appeared more advanced in terms of validation and documentation. Other (lateral flow) kits that were considered but found to be lacking in data, validations or information were from RayBiotech, Fastep, Mologic and Tigsun. Some of these distributors may in fact be using exactly the same (commercial) antigen impregnated into strip assays. In an attempt to secure market share information is sparse on the exact biochemical setup of these tests.

Biomedomics point-of-care antibody test.
https://www.biomedomics.com/products/infectious-disease/covid-19-rt/

This Biomedomics Rapid IgM/IgG test is commercially available now, uses a skin prick test, and is rapid (10-15 mins) and is used at 'point-of-care'. Importantly it has reported sensitivity and specificity values (88.6% and 90.6% respectively) and has a solid protocol that underpins the test. It uses both IgG and IgM tests, has an internal positive control. The test has used on over 500 cases been submitted for FDA approval. It is worth noting that the manufacturer notes: '*Positive results may be due to past or present infection with non-SARS-CoV-2 coronavirus strains, such as coronavirus HKU1, NL63, OC43, or 229E*'. Like all tests of this nature there are caveats around relying solely on this test as a predictor of past/present COVID-19 status.

CTK: OnSite COVID-19 IgG/IgM Rapid Test
See: https://ctkbiotech.com/covid-19/

OnSite COVID-19 IgG/IgM Rapid Test

Cat # R0180C

- The *OnSite* COVID-19 IgG/IgM Rapid Test is designed for initial screening by detecting anti-SARS-CoV-2 IgG and IgM antibodies in either human serum, plasma or whole blood within just 10 minutes.
- This test is easy-to-use, requires only minimally skilled personnel with basic equipment needs.
- The *OnSite* COVID-19 IgG/IgM Rapid Test has 96.9% sensitivity and 99.4% specificity making it one of the most effective screening tests for COVID-19.

The CTK OnSite COVID-19 IgG/IgM Rapid Test is nearly identical to the Biomedomics test (above) this is a lateral test that detects IgG and IgM. This test boasts higher sensitivity and specificity but was only tested on 126 samples so these number lack power to be reliable. CTK is a Californian company with over 10 years' experience in the sector.

Sugentech's IgG/IgM antibody testing kit
http://sugentech.com/products/products-view.php?ct=7&target=32

Similar to the above two POC kit Sugentech's kit was used extensively in South Korea. It is arguably the test that has stood up to in-field use. Surprisingly, there is little online information on kit performance. In South Korea this lateral test was used alongside PCR-based testing. Further information should be sought on this test if it was to be considered for use in New Zealand, in many respects New Zealand could benefit from mirroring South Korea's testing response.

PharmACT: SARS CoV-2 Rapid Test POC
See: https://pharmact-health.com/en/sars-cov-2-rapid-test/

The PharmACT point of care test utilises the same technology as the other tests described in Set#1. The company reports 0 false positives in 126 tests with uninfected subjects, and 70% sensitivity compared with PCR in infected patients with IgM at 4-10 days following onset of symptoms. At Days 11-24 post symptom onset agreement with PCR testing sits at 92.3% for IgM and 98.6% IgG. PharmACT has an established record in POC tests for diabetes, liver disease and heart disease.
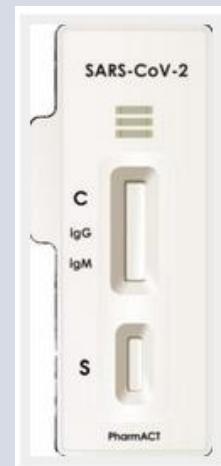
Set#2: Laboratory-based Antibody tests via ELISA - these are antibody tests for IgG and IgM but instead of a lateral (dipstick) based test these are lab based using ELISA and are conducted in laboratories using specialised equipment. Conducting these tests in the lab (rather than POC) may offers better standardisation and can be more sensitive/specific. However, the market (and public) seems more intent on POC lateral tests. There is a key difference between POC qualitative tests and the kind of quantitative Set#2 tests that lab-based providers can generate. Using ELISA in the lab clinicians could work up correlates of protection, while the yes/no answer of a lateral flow test cannot.

MAGLUMI 2019-nCoV (official name SARS-CoV-2) IgM/IgG Kits
http://www.snibe.com/zh_en/en_newsView.aspx?id=576

These immune assays have reportedly been used in both China and Italy. It is able to detect both IgM and IgE. This test is purported to hold a CE mark (Feb 2020) but there remains little online information on its sensitivity and precision – presumably as it is sold for 'Research use only'

mybiosource COVID-19 elisa kit: SARS-CoV-2 IgG/IgM
https://www.mybiosource.com/covid-19-human-elisa-kits/sars-cov-2-igg-igm-2019-ncov-coronavirus/3809905

The array of COVID-related antibodies, ELISA's antigens and associated protocols found at the mybiosource website (https://www.mybiosource.com) is extensive. There are a variety of formats and scales which, taken together, make this distributer worth considering for laboratory-based ELISA assays. The 96-well format may be the platform that can enable scalable testing that is automated. With 2-8°C storage (easy shipping) and clear information on the antigens used. Like many of the antibody testing kits this product is marked at 'Research use only' meaning that it is not technically sold for clinical samples – accordingly they can report none of the sensitivity/specificity tests and their suitability for clinical tests needs to be considered. This 14-year-old San Diego (USA) based company has a long and established track record in immunoassays.

EUROIMMUN Anti-SARS-CoV-2 ELISAs IgA and IgG
See: https://www.coronavirus-diagnostics.com/produkte.html

One of the first European ELISA tests to receive a CE mark for diagnostic use in Europe, the 96 well plate format is readily scalable (supply chain dependent) and fit for purpose in New Zealand diagnostic laboratories. However, there is no validation data available online for the kits. Euroimmun is a German company with more than 30 years' experience in medical laboratory diagnostics and majority owned by major US company PerkinElmer.

Set#3: Antigen testing - The third possible set of tests is to directly detect the virus. In many respects this category remains largely unproven. All of the tests evaluated, at the current point in time, appear as poor substitutes for PCR-based approaches in terms of scalability and selectivity. It remains our collective view that by the time this are actually on the market, that the window for their (effective) use within the pandemic may have closed – but this ultimately depends on the temporal and spatial trajectory of the pandemic across New Zealand.

Sona-GE health care direct virus detection:
https://sonanano.com/sona-partners-with-ge-healthcare-life-sciences-to-complete-coronavirus-rapid-screening-test/

This test has the advantage over lateral flow antibody tests in that it directly detects the virus rather than the body's antibody responses to it. Of all the projects we evaluated on (or close to) market this 'solution' seemed to have (i) a reputable development program (ii) posted updates (iii) had a track record in similar product development. This product may be weeks away from market, so its performance remains unknown. Of note is the fact that 'Bioeasy's' test which used a similar technology has an attractive website but little information on the product. This Bioeasy product has been heavily criticised in the media when tests in Spain only yielded 30% sensitivity[15]. This is a poignant example of the risks inherent to adopting unproven technologies.

Concluding remarks and Recommendations:

New Zealand's pandemic trajectory has afforded it some valuable time relative to other countries. This benefits many parts of New Zealand's pandemic preparedness, including which diagnostic tests to implement and when.

However, in a pandemic situation moving as fast as this, New Zealand can't afford to see which path plays out. Instead we must hedge our decisions so that we are prepared for whichever future eventuates. Events may overtake prudent planning, and it is a real possibility that we may enter supply chains too late to get the right products that within the timelines that they are needed.

Virus testing:
After a rapid 'point-in-time' review of the literature and diagnostic products both on, and coming to market, it is our view that New Zealand needs to continue its primary testing focus on PCR-based testing. At this stage of community infection, the number one priority needs to be PCR testing and source tracking. Accordingly, every effort needs to be made to secure supply chains of RNA extraction reagents, prioritising the labs that have automation (liquid handling) capabilities as they are more readily scalable. Central coordination of these processes will be essential.

There is no clear 'Plan B' for an alternative to PCR testing. Direct antigen testing for virus performed poorly in Spain[15] and alternatives seem slow to market.

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[15] (www.businessinsider.com.au/coronavirus-spain-says-rapid-tests-sent-from-china-missing-cases-2020-3?r=US&IR=T)

Testing for patient IgG and IgM responses is not a replacement for direct viral testing because it is typically days, if not weeks, behind the PCR result (i.e the infectious period).

New Zealand must do everything possible to maintain (and optimise) this testing capability. Supply chains of reagents must remain a top priority. Losing our PCR testing capability would have catastrophic consequences. The volume of tests required now, and in the future, needs to be constantly monitored.

Antibody Testing (POC and ELISA):
After reviewing the market tests New Zealand should urgently consider evaluation, purchasing and testing POC lateral tests – we make four recommendations that could be investigated further (see set#1 above). Of these tests only one of these (Sugentech) seems to have been used in the field. However, Biomedomics, CTK and PharmACT tests appear fit for purpose and report sensitivity and specificity values. The availability of testing kits and supply chains into New Zealand may be a deciding factor in which test(s) to both trial and invest in. These POC tests are complementary to, and do not replace PCR testing – they serve a different purpose. This message needs to be carefully delivered as relying on a negative lateral antibody test result could give COVID-19 patients a false sense that they do not harbour the virus. There is only limited information on how these POC kits might cross react with other pathogens and thus might yield false positives.

Separately from POC antibody tests our diagnostic testing laboratories should urgently explore 96-well ELISA testing for IgG and IgM. as these labs are 'geared up' to scale this testing. An ELISA test run in a lab would be a valuable back up to the POC tests.

Report Recommendations:

Recommendation#1: As much resource as possible should be targeted at monitoring and executing testing capabilities. This all-of-government response should include; (i) a COVID-19 PCR taskforce and; (ii) a COVID-19 'antibody/antigen' taskforce. These groups should urgently coordinate purchasing, validation, funding requests, timelines, priorities, adoption and scope local (New Zealand-based) capabilities and expertise.

Recommendation#2: New Zealand should continue to prioritise its PCR testing capabilities. Securing supply lines, scalability and speed of testing should be the country's primary diagnostic focus at this point in time. Other countries are ahead of New Zealand on the infection curve and we are behind them in the queue for already scarce material.

Recommendation#3: New Zealand should actively engage with the rapidly developing 'Point-of-care' (POC) lateral flow diagnostic space for virus antigen and antibody. Purchasing decisions may need to be separated from adoption decisions to preserve optionality. There are risks in adopting the 'wrong' test, or a poor test - valuable resources may be expended if poor decisions are made and there are also risks of delaying decisions and missing out. The role and utility of new POC tests must be carefully explained to avoid unrealistic expectations and perverse outcomes (e.g. patients who think they are immune, but are not, as the result of a false test for antibodies).

Recommendation#4: New Zealand should rapidly pursue testing capability to detect antibodies in a laboratory setting. Tests for antibodies in New Zealand's diagnostic laboratories (a test called 'ELISA') should also be considered for large scale serological testing

in the coming weeks. It is likely these tests will be deployed with only partial validation. These tests can be purchased from overseas suppliers, but New Zealand laboratories are already working on generating viral proteins and antibodies needed for these tests. Coordination, funding and support for these New Zealand-based initiatives should be mobilised to prevent fragmentation and duplication.