COVID-19 serology: use and interpretation in New Zealand

Gary N McAuliffe, Timothy K Blackmore

ABSTRACT

Serology is now a well-established diagnostic tool for the diagnosis of COVID-19 infections in New Zealand. Using local and international experience, we provide an overview of serological response to infection and vaccination as well as the use and interpretation of antibody tests in our setting. We also discuss the potential future role of post-vaccination serology testing as a correlate of immunity. We conclude that, given the pitfalls of testing, clinical microbiologist advice is necessary for interpretation of high-consequence cases.

Nucleic acid amplification tests (NAAT), such as reverse transcriptase PCR or transcription- mediated amplification, are the most widely used tests in New Zealand for the diagnosis of acute COVID-19 infections. But serology, which detects an immune response to past SARS-CoV-2 infections or vaccination, is also now well established as a diagnostic tool.

Several types of tests are used in New Zealand diagnostic laboratories, including plate-based enzyme-linked immunoassays (ELISAs), which are labour intensive but suit low-throughput testing scenarios, and chemiluminescent assays, which are performed on higher-throughput machines with a faster sample to answer time.

New Zealand has a very low prevalence of COVID-19,[1] and therefore, in contrast to serology tests performed in diagnostic laboratories, point-of-care or lateral flow tests have suboptimal sensitivity and specificity in our setting; since April 2020, importation of these devices has been restricted.[2]

Serological response to infection

Following SARS-CoV-2 infection, antibodies are produced against various viral proteins including the receptor-binding domain (RBD) of the spike (S) protein and to nucleocapsid (N) (Figure 1). This antibody response involves IgA, IgM and IgG, which are detectable concurrently, and in some individuals as early as 0–5 days after symptom onset. As IgM appears around the same time as IgG and may persist for months, it is not reliable as a marker of acute versus past infection.[3,4]

Antibody tests used in New Zealand's diagnostic laboratories generally perform well for the detection of past infection, demonstrating sensitivities >90% by 14 days after onset of symptoms and specificities >99%.[5] Antibodies wane over time and appear to decline more rapidly to different antigens, with only 54% of individuals still positive for anti-N compared with 96% to anti-S in a New Zealand cohort at or more than 125 days after infection.[3] The strength and duration of the immune response is quite variable between individuals and also differs according to severity of disease.

Depending on the antigen to which the antibodies bind, they may be either neutralising or non-neutralising. In the case of SARS-CoV-2, antibodies to the RBD/spike are most likely to be neutralising and protective against subsequent symptomatic infection.

In New Zealand, COVID-19 serology is not centrally funded but may be funded for selected patients by district health boards. Approval for testing is usually determined by the clinical microbiologist overseeing the testing laboratory. Use is primarily as part of public health investigations, where it can confirm past infections in NAAT-negative individuals or when using paired acute and convalescent sera to differentiate acute from past infection in NAAT-positive/antibody-negative individuals. There are some countries

that require pre-departure serology testing as part of their entry requirements; this testing is undertaken as a fee for service by certain New Zealand laboratories.

Given the very low prevalence of past COVID-19 infection in the general population outside managed isolation facilities (MIF), the positive predictive value of a positive antibody test varies widely between these populations. For example, a positive pre-departure IgM has a positive predictive value approaching zero, whereas a positive total antibody from MIF is highly likely to be a true positive. Consequently, confirmation of a positive antibody result by testing on a second assay is warranted in some situations but unnecessary in others.

The pitfalls of interpretation of serology in the New Zealand context mean that discussion with a clinical microbiologist is required prior to testing for other indications, such as diagnosis of complications of COVID-19 (eg, myocarditis), and also for any positive or negative results that may have individual or public health consequence.

Serological response to vaccination

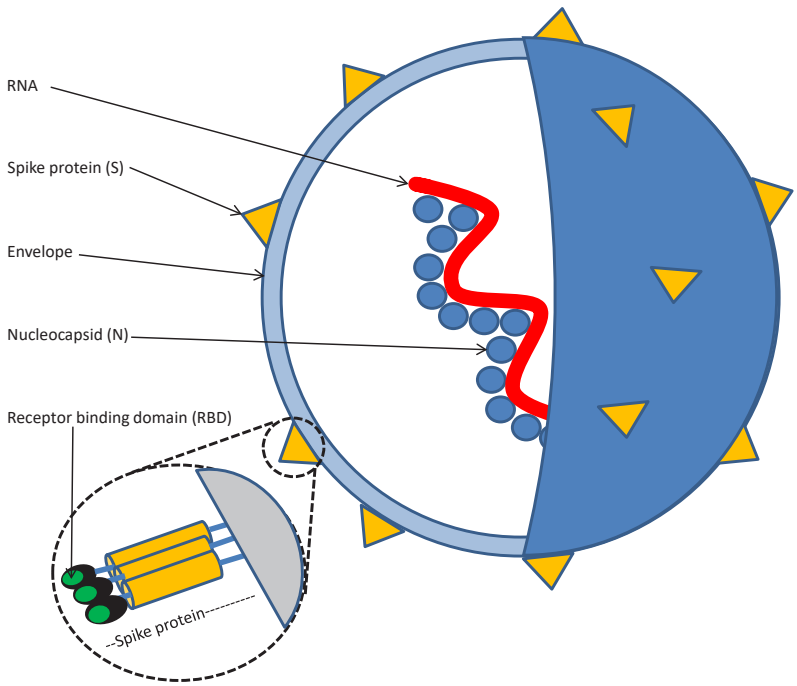
Vaccines produce an immune response against specific viral proteins, and an immunological response to vaccination can only be detected if laboratories test for these specific antibodies. For example, an individual receiving the Pfizer-BioNTech vaccine produces neutralising antibodies directed against the RBD of the S protein and will test positive for anti-S but negative for anti-N unless the individual has also had natural infection (Table 1). Some inactivated virus vaccines in use outside New Zealand (eg, Sinopharm) are expected to give a response that may include anti-N.

Preliminary studies post Pfizer-BioNTech vaccination have shown a crude correlation between positive results for anti-RBD or anti-S and neutralising antibody production. However, at this stage, the level of antibody required for immunity is not known; quantitative values between different manufacturers are highly variable;[6] and the longevity of antibody response (and protection) is unclear.

Role of serology in assessing immunity

With these factors in mind, serology is not currently recommended to assess for immunity to COVID-19 in a vaccinated person, or to assess the need for vaccination in an unvaccinated person[4] (for those with

Figure 1: Schematic representation of SARS-CoV-2 structure.



prior COVID-19 infection, vaccination is recommended). This may change in the future as correlates of immunity become clearer; studies looking at this are underway. New quantitative assays to detect anti-S antibodies have become available and may be useful for measuring contemporaneous immunity, but formal studies of correlates of protection are awaited.[6] Dependent on these findings, future applications of serology may include testing antibody levels in certain groups after vaccination, after a COVID-19 exposure event in others, or for allowing risk-stratified quarantine decisions to be made by confirming vaccination or immunity status in travellers.

Other immune responses to vaccination or infection

T-cell immunity is likely to play an important role, but at present there are no commercially available or easily standardisable assays. It appears that seroconversion is associated with the development of cellular immunity, but the relative contributions of humoral and cellular immunity are unclear at present.[7]

Summary

COVID-19 serology is currently available in diagnostic laboratories in New Zealand as a test that requires microbiologist approval. Testing may provide useful information in public health investigations or select cases of post-infectious complications and is necessary for overseas travel to some destinations. However, test reliability varies substantially according to the testing scenario. Depending on the available tests, vaccine response and natural infection can be differentiated, but the role of post-vaccination serology testing as a correlate of immunity has not yet been determined. We conclude that, given the pitfalls of testing, clinical microbiologist advice is necessary for interpretation of high-consequence cases.

Table 1: Antibody response to infection or Pfizer-BioNTech vaccine.

	Anti-S	**Anti-N**
Natural infection	+	+
Pfizer-BioNtech vaccine response	+	-
Prior natural infection and post-Pfizer-BioNtech vaccine	+	+ (-)*

Legend: *anti-N may wane faster than anti-S, and with time some infected individuals may test negative.

Competing interests:
Nil.
Acknowledgements:
Thanks to all the clinicians, scientists and researchers in New Zealand who have contributed to knowledge and discussion on this topic.
Author information:
Gary N McAuliffe: Clinical Microbiologist and Virologist, LabPlus, Auckland hospital, Auckland.
Timothy K Blackmore: Infectious Diseases Physician and Microbiologist, Wellington SCL and Capital & Coast District Health Board, Wellington.
Corresponding author:
Dr Gary McAuliffe, Clinical Microbiologist and Virologist, Department of Virology and Immunology, LabPlus, Auckland hospital, Park Road, Grafton, Auckland, 021 02157069
gmcauliffe@adhb.govt.nz
URL:
www.nzma.org.nz/journal-articles/covid-19-serology-use-and-interpretation-in-new-zealand-open-access

REFERENCES

1. New Zealand Ministry of Health [Internet]. COVID-19 current cases; 2021 [cited 2021 20 Mar]. Available from: https://www.health.govt.nz/our-work/diseases-and-conditions/covid-19-novel-coronavirus/covid-19-data-and-statistics/covid-19-current-cases
2. Medsafe [Internet]. COVID-19 point of care test kits restriction on importation, manufacture, supply and use; 2020 [cited 2021 20 Mar]. Available from: https://www.medsafe.govt.nz/Medicines/policy-statements/COVID-19PointOfCareTestKits.asp
3. Whitcombe, A L, McGregor, R, Craigie, A, et al. (2021). Comprehensive analysis of SARS-CoV-2 antibody dynamics in New Zealand. Clinical & translational immunology, 10(3), e1261.
4. Centers for Disease Control and Prevention [Internet]. Interim guidelines for COVID-19 Antibody testing; 2021 [cited 2021 20 Mar]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/lab/resources/antibody-tests-guidelines.html
5. Fox-Lewis S, Whitcombe A, McGregor R, et al. A comparison of SARS-CoV-2 antibody assays evaluated in Auckland, New Zealand. N Z Med J. 2020;133:127-131.
6. Perkmann T, Perkmann-Nagele N, Koller T, et al. Anti-Spike protein assays to determine post-vaccination antibody levels: a head-to-head comparison of five quantitative assays. medRxiv 2021.03.05.21252977
7. Flanagan KL, Best E, Crawford NW, et al. Progress and Pitfalls in the Quest for Effective SARS-CoV-2 (COVID-19) Vaccines. Front Immunol. 2020 Oct 2;11:579250.