Australian Government
National Health and Medical Research Council

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National COVID-19 Health and Research Advisory Committee[1]

Date of report: 21 May 2020

Accurately measuring antibody levels to better understand population and individual immunity

Focus

The focus of this report is on whether it is currently possible to accurately measure antibody levels in people who have been infected by the SARS-CoV-2 virus, and the usefulness of antibody levels to understand population or individual immunity and/or past infection.

This report is point in time and may need further review as more evidence is available.

Conclusions

NCHRAC conclusion 1: There is no "clearly superior" assay currently available for measuring SARS-CoV-2 antibody levels, with false positive reactions expected in all currently available tests (inadequate specificity for purpose).

In drawing conclusion 1, NCHRAC considered the:

- advice of the PHLN
- expert advice of NCHRAC working group members and external experts on current tests being assessed
- work of organisations such as FIND (the Foundation for Innovative New Diagnostics)[2] and the Saw Swee Hock School of Public Health[3] in Singapore in collating information on the specificity and sensitivity of antibody tests, and
- tests approved by the TGA for supply (not necessarily use) on the Australian Register of Therapeutic Goods (ARTG)[4].

NCHRAC conclusion 2: There are important challenges and limitations to the successful use of currently available SARS-CoV-2 antibody tests in Australia.

NCHRAC conclusion 3: Using antibody tests with inadequate specificity and/or sensitivity presents several risks for both individuals and the community.

Conclusions 2 and 3 follow from Conclusion 1 and expert opinion based on the available evidence.[i,ii] Experts identified that use of tests with inadequate specificity in a population

[1] NHMRC is providing secretariat and project support for the Committee, which was established to provide advice to the Commonwealth Chief Medical Officer on Australia's health response to the COVID-19 pandemic. The Committee is not established under the NHMRC Act and does not advise the NHMRC CEO.
[2] https://www.finddx.org/covid-19/pipeline/
[3] https://sph.nus.edu.sg/covid-19/research/
[4] https://www.tga.gov.au/covid-19-test-kits-included-artg-legal-supply-australia

with very low prevalence of disease can result in inaccurate data. Further, it was noted that there is evidence that some individuals (such as children or people with asymptomatic infection) may not produce detectable SARS-CoV-2 antibodies after mild infection.[iii,iv]

NCHRAC conclusion 4: Since the relationship between antibody levels and population or individual immunity is not yet understood for SARS-CoV-2, it should be the subject of further research and antibody testing should not yet be used to estimate population level immunity or inform decisions about easing local restrictions.

For Conclusion 4, the findings of the Rapid Research Information Forum[v] were considered, along with expert opinion that it is not yet known whether antibodies confer immunity to SARS-CoV-2.[vi]

Background

Antibody tests can detect one aspect of an individual's immune response to a virus. Tests are done either at the point of care or by laboratory tests such as enzyme-linked immunosorbent assays (ELISAs) using serum or plasma from blood. Depending on the protocol and assay used, information can be obtained on both the level and type (total or IgG, IgA or IgM, for example) of antibody present.

Antibody tests can provide information on whether an individual has been recently infected with SARS-CoV-2 (IgM), or has been exposed to the virus in the past (IgG or total antibody). This is because, although there is a lag between virus infection and the development of antibodies, antibodies persist after the infection has been cleared. The virus can be detected before antibodies are produced and antibodies can be detected after the virus has become undetectable.[vii] The duration and variability of antibody persistence is not yet known for SARS-CoV-2.[viii]

For many other viruses, it is known that the presence of antibodies for that virus means the person cannot be re-infected or, if infected, will have a milder clinical illness. It is not known whether this is true for SARS-CoV-2, and if so, what level or type of antibodies would be required to give protection. If enough of the community were to develop protective levels of antibodies, whether through infection or vaccination, then population level immunity would reduce the reproduction rate of the infection. Separate to immunity, detection of recent or past infections with SARS-CoV-2 is necessary to determine the population prevalence of past infection, and in turn to more accurately estimate the true rate of mortality or severe disease relative to mild or asymptomatic infections.[ix,x] This information also supports disease surveillance.

Other considerations

In the course of developing this advice, NCHRAC identified the following considerations that were out of scope for this advice, but are important and related matters that may warrant consideration:

- comparisons of SARS-CoV-2 antibody tests with other laboratory diagnostic tests

- the roles of target groups for antibody testing to determine prevalence of exposure to COVID-19 – such as upstream and downstream contact tracing around index cases, and selection of sentinel groups considered at risk of infection[xi,xii]
- if and when a national SARS-CoV-2 serosurveillance exercise should be considered and, if so:
    - processes to select the test(s) to be used
    - specifics of jurisdictional involvement and coordination, and
    - how to ensure maximum benefit through selection of numbers, demographics, geography and national data collection and analysis.

NCHRAC is aware that other groups, in particular the CDNA, PHLN, TGA and NRL have the technical expertise and appropriate jurisdictional representation to provide advice on these types of issues. PHLN has expertise in the technical aspects of currently available SARS-CoV-2 antibody tests and is aware of current testing taking place within Australia. The TGA approves tests for supply via the Australian Register of Therapeutic Goods, and some of these tests are currently being assessed for recommended use by The Peter Doherty Institute for Infection and Immunity.

Attachments

Attachment 1: Specific research questions by priority for understanding individual antibody responses and immunity following exposure to SARS-CoV-2

Attachment 2: Glossary

Attachment 3: NCHRAC antibody working group members and contributors

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Attachment 1

Specific research questions by priority for understanding individual antibody responses and immunity following exposure to SARS-CoV-2

1. What is the natural history of antibody development and its time course following infection – early (days), medium (weeks) and long term (years)?
2. Is the antibody response related to COVID-19 disease severity, patient immune status, gender or age (e.g. are there age cohort differences between children versus adults)? Do asymptomatic individuals raise an antibody response? How common is asymptomatic infection and what is its contribution to virus transmissibility in the population? Also, does seropositivity (i.e., the development of antibodies) mean the individual is no longer infectious, even if the virus PCR is (still) positive?
3. Do antibodies confer immunity to SARS-CoV-2 and, if so, which antibodies reflect immunity best? Is there also a role for cell-mediated immunity? If present, what is the duration of immunity?
4. What platforms and assays provide best sensitivity and specificity?

Attachment 2

Glossary[1]

Term or acronym	*Meaning as related to COVID-19 and its testing*
antibody	A protein made by your body to combat infection by virus. Neutralising antibodies to COVID-19 are expected but not yet proven to protect the body from re-infection as they block the virus from entering cells.
antibody test	Is a test to see if a patient has generated antibodies (see IgG and IgM) to the COVID-19 virus.
cell-mediated immunity	An immune response made by cells of the immune system, not antibodies.
contact tracing	The process of identification of persons who may have come into contact with a person infected with SARS-CoV-2 and collection of information about these contacts.
COVID-19	The name given to the disease caused by the SARS-CoV-2 virus which arose in the Wuhan Province in China in late 2019.
cycle thresholds	A relative measure of the concentration of a RNA/DNA target in a quantitative PCR test, which can be used to estimate the level of virus in a sample. Lower cycle threshold = higher amount of RNA/DNA.
ELISA	Enzyme-linked immunosorbent assay. In the context of COVID-19 this is a test conducted in a diagnostic laboratory to test for antibodies (see IgG and IgM) to coronavirus. It could be used as a barometer of the immune response to the virus.
false negative	When a test for COVID-19 is negative when in fact the patient is carrying the virus.
false positive	When a test for COVID-19 is positive when in fact the patient has not been infected by the virus.
IgG	A type of antibody that is typically generated later in the COVID-19 infection.
IgM	A type of antibody that is typically generated earlier in the COVID-19 infection.
immunity	Resistance to infection or other disease.

[1] Based on the glossary from NZ Government's 'COVID-19 Testing Landscape' report

index case	The first documented patient in a disease epidemic or cluster within a population, or the first documented patient in an epidemiological study.
PCR	Polymerase Chain Reaction; a test by which RNA (or DNA) is repeatedly copied. This is the core test for COVID-19 virus as it is very sensitive and specific and directly measures the virus itself.
point of care test	A test that can be conducted rapidly at the patient's bedside or their home or in a GP clinic and typically gives a 'yes/no' answer.
population level immunity	A form of indirect protection from infectious disease that occurs when a large percentage of a population has become immune to an infection, whether through previous infections or vaccination, thereby providing a measure of protection for individuals who are not immune. Also referred to as herd immunity.
prevalence	The proportion of a particular population found to be exposed to the SARS-CoV-2 virus at a specific time.
SARS-CoV-2	The virus that is responsible for the COVID-19 epidemic.
sensitivity	How often a test correctly generates a positive result for people who have been infected with the SARS-CoV-2 virus.
seroconversion	The time period during which antibodies develop for the SARS-CoV-2 virus and become detectable in the blood; serology goes from negative to positive.
serology	The study of body fluids such as blood, for example to measure antibodies against the virus.
serosurveillance	Monitoring by serology in a population, for example to estimate antibody levels against SARS-CoV-2 as an indicator of population immunity due to past infection.
specificity	How often a test correctly generates a negative result for people who have not been infected with the SARS-CoV-2 virus.
viral shedding	Occurs when a virus replicates inside a person's body and is released into the environment. At that point, it may be infectious to others. It is not known exactly when this occurs after someone is infected with SARS-CoV-2.

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Attachment 3

About the Committee and the Working Group

About the National COVID-19 Health and Research Advisory Committee

The National COVID-19 Health and Research Advisory Committee (NCHRAC) was established in April 2020 to provide advice to the Commonwealth Chief Medical Officer advice on Australia's health response to the COVID-19 pandemic. NCHRAC provides rapid and evidence-based advice (or expert advice in the absence of evidence) on Australia's health response to the COVID-19 pandemic with the aim of preventing new cases, optimising the treatment of current cases, and assisting in optimising overall health system readiness to deal with the pandemic as it progresses.

Further information on the terms of reference and membership of the Committee is available at: www.nhmrc.gov.au/nchrac. NHMRC is providing secretariat and project support for the Committee. The Committee is not established under the NHMRC Act and does not advise the NHMRC CEO.

Working Group Membership

NCHRAC convenes working groups of its members and external experts to deliver its reports. The following NCHRAC members were involved in the development of this advice:

Committee Members

Professor Bart Currie (Chair)

Professor Jonathan Carapetis AM

Professor Brendan Crabb AC

Professor Michael Good AO

Professor Anne Kelso AO

Professor Kamalini Lokuge OMA

Professor Raina MacIntyre

Additional experts

Professor David Anderson (Burnet Institute)

Ms Anna-Maria Arabia (Australian Academy of Science)

Dr Jana Phan (Australian Academy of Science)