Australian Government

Chief Scientist

19 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 evidence for whether reinfection with SARS-CoV-2 is possible and whether there is any emerging risk that not all patients develop immunity once they clear the virus.

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,

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

GPO Box 2013
Canberra ACT 2601
Australia

Telephone: +61 2 6102 9210
Facsimile: +61 2 6213 6558

Email: chief.scientist@chiefscientist.gov.au
Web: www.chiefscientist.gov.au

19 April 2020

There have been media reports of reinfection with SARS-CoV-2. What is the evidence?

- Anecdotal reports of patients who have recovered from COVID-19 becoming reinfected may be due to testing problems. While we cannot say for certain that reinfection is not possible, the evidence for reinfection is so far not compelling.
- Overall, based on the changes detected in the blood cells and antibodies seen in most recovered patients, it could be reasonably extrapolated that individuals would be protected from reinfection with the same strain, at least in the short to medium term. However, no direct evidence for immunity in patients exists at present.
- Population-level studies would be needed to determine with greater certainty whether reinfection can occur in people who have developed antibodies to SARS-CoV-2.
- A decline in immunity or mutations in the virus could result in a future scenario in which reinfection is possible.

This rapid research brief responds to the request for advice on the evidence for whether reinfection with SARS-CoV-2 is possible and whether there is any emerging risk that not all patients develop immunity once they clear the virus.

Studies to date indicate that individuals show an antibody response while infected with SARS-CoV-2. On the basis of tissue culture experiments and antibody responses to other viruses, it is reasonable to extrapolate that these antibodies could be protective against reinfection. However, no direct evidence for immunity in patients exists at present for SARS-CoV-2 or for SARS-CoV. Well controlled clinical trials or population level studies will be needed to test if people with antibodies in their blood are immune to re-infection, and to reveal how long that protection lasts. There have been anecdotal reports of patients who have recovered from COVID-19 becoming reinfected.[1] However, these are not currently documented in the scientific literature.

Where ‘reinfection’ has been reported, it may be due to transient false negatives – where an individual previously diagnosed with SARS-CoV-2 was still carrying the virus but falsely tested negative in a subsequent test, only to later test positive again because they had in fact been infected for the entire time. Ongoing studies will provide more clarity and monitoring for reinfection would be advisable.

Background: testing for SARS-CoV-2

To understand why there are apparent cases of reinfection, it is important to first outline how we test and detect infectious agents. There are two categories of test that detect either:

1. The infectious agent.
2. An immune response to the agent.

When a new disease emerges, tests for the infectious agent are the first to market. In the case of SARS-CoV-2, viral RNA is most commonly measured through a reverse-transcriptase polymerase chain reaction (RT-PCR) test, or PCR test. Detecting viral RNA indicates that the individual has a current infection, which may be transmissible to others.

Tests in the second category take longer to develop but are important because detecting an immune response can be helpful for many purposes, including estimating prevalence of an infection, mapping an epidemic over time and testing vaccines.[2,3] Researchers are developing increasingly sophisticated diagnostic methods across both categories that can provide more detailed insights into infections and have greater sensitivity and specificity.[4,5]

The immune response to SARS-CoV-2

The evidence to date indicates that individuals show an immune response by producing antibodies in their blood, when infected with SARS-CoV-2, but no direct test of immunity to reinfection has yet been made. Data come from laboratory studies, which do not provide direct evidence of immunity to reinfection, but at this early stage in the pandemic, such studies are the best proxy evidence. Okba *et al.* studied a small number of individuals whose SARS-CoV-2 infection had been confirmed by PCR test and found that most of them developed antibodies two weeks after disease onset; Wölfel *et al.* reported similar findings in the same small cohort.[2,6] Thevarajan *et al*. reported a single case where both antibodies and immune cells known as T cells were detected before symptoms fully disappeared and persisted for at least seven days after full recovery from symptoms.[7] Wu *et al.* (not yet peer reviewed) recently tested 175 recovered patients, 94% of whom had developed a detectable antibody response that was shown to be neutralizing in a sensitive tissue culture test; that is, capable of binding to the virus and blocking its entry into host cells cultured in the laboratory.[8]

Several emerging studies have explored the effectiveness of convalescent plasma therapy in severe COVID-19 patients.[9,10] In small patient numbers they have observed that plasma from convalescent individuals who have recovered from SARS-CoV-2 infection may induce rapid clinical and radiological improvements in hospitalised patients with severe disease. These studies are not randomized controlled trials, however, they offer areas of further investigation that could help to clarify the nature of the immune response to SARS-

CoV-2. Similar uncontrolled, non-randomised preliminary studies with convalescent plasma treatment were performed in the SARS and MERS outbreaks and their collective meta-analysis indicates that, while showing a promising trend to decrease the duration of hospitalisation, no reliable conclusion can yet be drawn about the efficacy of convalescent plasma.[11] Useful information can also be drawn from related coronaviruses that also cause severe respiratory diseases. Studies of SARS-CoV show that antibodies peak at around four months and last for two to three years,[12] but it was never possible to test if these antibodies protected people from reinfection.

Overall, based on the changes detected in the blood cells and antibodies seen in most recovered patients, it could be reasonably extrapolated that individuals would be protected from reinfection with the same strain, at least in the short to medium term.

Researchers are still developing a more detailed understanding of how the immune system responds to SARS-CoV-2, including the immune response in people who have asymptomatic infection. Extended testing for evidence of antibodies or cell mediated immune responses would help define the strength and duration of immunity.

Evidence for reinfection

As of 19 April 2020, there are a number of anecdotal reports of patients being reinfected with SARS-CoV-2, which are being investigated.

Possible explanations for why a patient who tested positive, recovered from COVID-19 and has since had one or more negative PCR tests, yet subsequently tests positive again, include:

1. Negative tests were incorrect or the tests had low sensitivity, and the patient was actually infected for the entire period.
2. The person has recovered and the subsequent positive test is detecting genetic remnants of dead virus.
3. The novel coronavirus may be capable of staying dormant in tissues that are not routinely sampled, before reactivating.
4. The person has actually been reinfected.

While we cannot say for certain that reinfection is not possible, the evidence for reinfection is so far not compelling. The balance of scientific opinion at this stage is that it is more likely that the subsequent positive test detected the remnants of dead virus or that the previous negative tests were, in fact, a false negative.

We know that PCR tests can give a positive result due to the presence of virus remnants, rather than whole virus particles. The immune system can neutralise viruses by destroying their envelope or by aggregating

virus particles; but this does not eliminate the RNA, which degrades slowly over time. In many viral infections, this genetic material can potentially be detected for weeks after the onset of symptoms.[13,14]

In relation to false negatives, studies have shown that they are possible for SARS-CoV-2. Xiao *et al.* reported that in a study of 70 patients with confirmed SARS-CoV-2 infection, 15 (21%) experienced a positive PCR test after two consecutive negative PCR test results.[15] Lo *et al.* studied 10 COVID-19 patients and found that occasional negative results from PCR tests do occur.[16] There are several potential explanations for false negatives, including insufficient viral material in the sample, a laboratory error during sampling, the biological characteristics of SARS-CoV-2, or the virus may be present in sites other than the nose and throat from where the sample was collected.[17,18]

To clarify whether re-infection is real, three questions should be asked:

- **Does the patient have symptoms?** If a PCR test is positive following previous negative results, but the patient has no symptoms, it is unlikely to be clinically or epidemiologically important.
- **Is the patient shedding live virus?** Being able to culture the virus from the sample will reveal whether live virus is still present in the patient or whether the positive result is due to viral RNA detection of the dead virus.
- **Does the patient have neutralising antibody to SARS-CoV-2?** Knowing whether the patient has neutralizing antibody is critical information because reinfection is unlikely in the presence of neutralising antibody. This was clearly established in animal models of SARS.[19,20]

Monitoring for reinfection is valuable because even if it were possible in only a minority of patients, it could potentially lead to further outbreaks.

Longer-term reinfection

There have been documented instances of a declining presence of antibodies with previous types of coronaviruses, such as SARS-CoV. Wu *et al.* showed that antibodies decline after more than three years following the original onset of symptoms, meaning individuals may no longer be protected.[12] It is obviously too soon to know whether this could also be the case with SARS-CoV-2.

Reinfection could also result from a change to the virus itself – for example, if there is a mutation that changes the antigens that our immune system recognises. This kind of mutation would make the immune response ineffective against the mutated virus. We know the SARS-CoV-2 virus is mutating. Forster *et al.* have already identified three central variants, which are distributed in different geographic patterns.[21] Two key questions are whether the virus will mutate enough to reinfect people previously exposed to SARS-CoV-2, and what impact the mutation has on the virulence of the virus. It is impossible to know the timeframe of

the immune response we can expect with SARS-CoV-2; experience with other coronaviruses suggest that it is most likely to be a matter of years.[12,22]

An important note on available COVID-19 research

Much of the current COVID-19 research is available through preprint servers; many of these articles have not yet been peer-reviewed (an imperative pillar of the scientific method) and the relatively short time length 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.

References

1 Tsirtsakis, A. (2020). Are reports of coronavirus 'reinfection' a cause for concern? Available from: https://www1.racgp.org.au/newsgp/clinical/are-reports-of-coronavirus-reinfection-a-cause-for

2 Okba, NMA. *et al.* (2020). Severe Acute Respiratory Syndrome Coronavirus 2–Specific Antibody Responses in Coronavirus Disease 2019 Patients. *Emerging Infectious Diseases,* **26**, Nr 7—July 2020.

3 Petherick, A. (2020). Developing antibody tests for SARS-CoV-2. *The Lancet*, 395. pp.1101-1102.

4 Sensitivity means a test gives a positive test correctly, i.e. a 'true' positive; specificity means it gives a negative result correctly, i.e. a 'true' negative

5 Cheng, MP, e*t al.* (2020). Diagnostic Testing for Severe Acute Respiratory Syndrome–Related Coronavirus-2: A Narrative Review. *Annals of Internal Medicine.* DOI: 10.7326/M20-1301

6 Wölfel, R, *et al.* (2020). Virological assessment of hospitalized patients with COVID-2019. *Nature*. doi: https://doi.org/10.1038/s41586-020-2196-x

7 Thevarajan, I. *et al.* (2020). Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. *Nature Medicine* **26**, pp.453–455

8 Wu, F. *et al.* (2020). Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications [Preprint]. *medRxiv.* doi: https://doi.org/10.1101/2020.03.30.20047365.

9 Shen, C. *et al.* (2020). Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *Journal of the American Medical Association*, doi:10.1001/jama.2020.4783.

10 Duan, K. *et al.* (2020). The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study [Preprint]. *medRxiv.* doi: https://doi.org/10.1101/2020.03.16.20036145.

[11] Mair-Jenkins, J. *et al.* (2015). The Effectiveness of Convalescent Plasma and Hyperimmune Immunoglobulin for the Treatment of Severe Acute Respiratory Infections of Viral Etiology: A Systematic Review and Exploratory Meta-analysis. *The Journal of Infectious Diseases,* **211**, pp. 80–90.

[12] Wu, LP. (2007). Duration of Antibody Responses after Severe Acute Respiratory Syndrome. Emerging Infectious Diseases, 13, pp.1562-1564.

[13] Advani, S. *et al.* (2012). Detecting Respiratory Viruses in Asymptomatic Children; *Pediatric Infectious Diseases Journal,* **31,** pp.1221-1226

[14] Jartti, T. *et al.* (2004) Persistence of Rhinovirus and Enterovirus RNA After Acute Respiratory Illness in Children. *Journal of Medical Virology,* **72**, pp.695–699.

[15] Xiao, AT. *et al.* (2020). False-negative of RT-PCR and prolonged nucleic acid conversion in COVID-19: Rather than recurrence [Preprint]. *Journal of Medical Virology.* doi: https://doi.org/10.1002/jmv.25855

[16] Lo, IL. *et al.* (2020). Evaluation of SARS-CoV-2 RNA shedding in clinical specimens and clinical characteristics of 10 patients with COVID-19 in Macau. *International Journal of Biological Sciences,* **16**, pp.1698-1707

[17] Li, Y. *et al.* (2020). Stability issues of RT-PCR testing of SARS-CoV-2 for hospitalized patients clinically diagnosed with COVID-19. *Journal of Medical Virology*, doi: https://doi.org/10.1002/jmv.25786.

[18] Zhou, L, *et al.* (2020). Cause analysis and treatment strategies of "recurrence" with novel coronavirus pneumonia (covid-19) patients after discharge from hospital. doi: 10.3760/cma.j.cn112147-20200229-00219.

[19] Subbarao, K. *et al.* (2004). Prior Infection and Passive Transfer of Neutralizing Antibody Prevent Replication of Severe Acute Respiratory Syndrome Coronavirus in the Respiratory Tract of Mice. *Journal of Virology*, **78**, pp.3572-3577.

[20] Traggiai, E. *et al.* (2004). An efficient method to make human monoclonal antibodies from memory B cells: potent neutralization of SARS coronavirus. *Nature Medicine*, **10**, pp.871-875.

[21] Forster, P. (2020). Phylogenetic network analysis of SARS-CoV-2 genomes. *PNAS*. doi: https://doi.org/10.1073/pnas.2004999117.

[22] Zhao, Z. (2004). Moderate mutation rate in the SARS coronavirus genome and its implications. *BMC Evolutionary Biology*, **4.** doi: 10.1186/1471-2148-4-21.

APPENDIX

Contributing authors and peer reviewers of this rapid research report

Contributing authors:

Professor Andrew Cuthbertson AO FTSE FAHMS, R&D Director and Chief Scientific Officer, CSL Ltd

Professor Trevor Drew, Director, Australian Centre for Disease Preparedness, CSIRO

Professor Dale Godfrey FAHMS, Professor, Department of Microbiology and Immunology, The Doherty Institute

Professor Kanta Subbarao, Director, WHO Collaborating Centre for Reference and Research on Influenza and Professor, The Peter Doherty Institute for Infection and Immunity

Peer reviewers:

Professor Chris Goodnow FAA FRS, Director, Garvan Institute of Medical Research

Professor David Gordon, Flinders University

Dr Branka Grubor-Bauk, The University of Adelaide

Professor John Shine AC PresAA, Australian Academy of Science

Professor Carola Vinuesa FAA, Australian National University

Professor Steve Wesselingh FAHMS, South Australian Health and Medical Research Institute

The production of this rapid research report was supported by staff of the Australian Academy of Health and Medical Sciences: Ms Catherine Luckin and Ms Katrin Forslund; and the Australian Academy of Science: Mr Daniel Bouzo, Mr Chris Anderson and Ms Anna-Maria Arabia. Edited by Ms Robyn Diamond and Dr Elizabeth Finkel AM.

RAPID RESEARCH INFORMATION FORUM

Re-infection with SARS-CoV-2

The Rapid Research Information Forum (RRIF), convened by Australia's Chief Scientist, Dr Alan Finkel AO, is a forum for rapid information sharing and collaboration within the Australian research and innovation sector. It provides a mechanism to rapidly bring together relevant multidisciplinary expertise to address pressing questions about Australia's response to COVID-19, as they emerge. RRIF enables timely responses to be provided to governments based on the best available evidence. RRIF also informs the Chief Scientist's interactions and collaboration with other national chief scientific advisers. RRIF demonstrates the critical value of research and innovation in driving societal as well as economic progress now and into the future.

Forum member organisations

- Australia's Chief Scientist (Chair)
- Australian Academy of Science
- Australian Academy of Health and Medical Sciences
- Australian Academy of Technology and Engineering
- Academy of the Social Sciences in Australia
- Australian Academy of the Humanities
- Royal Society Te Apārangi (New Zealand)
- ACOLA
- State and Territory Chief Scientists
- Chief Science Advisor to the Government of New Zealand
- Scientific expert members of the National Science and Technology Council
- CSIRO
- Universities Australia
- Science & Technology Australia