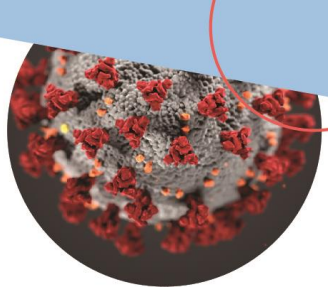
taskforce on bbvs
sexual health and covid-19



ASHM COVID-19 Taskforce interim report on the adaptive immune response to COVID-19 infection

Prepared by members of the Taskforce's Virology Cluster Group and the Taskforce Chair, April 2020

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Disclaimer: This ASHM document is designed to provide available, relevant information to clinicians and other healthcare providers to optimise the health and wellbeing of people living with HIV, hepatitis B and hepatitis C during the COVID-19 pandemic**.** The recommendations provided are the opinions of the authors and are not intended to provide a standard of care, or practice. This document does not reflect a systematic review of the evidence, but will be revised to include relevant future systematic review findings of the National COVID-19 Clinical Evidence Taskforce(1) and other relevant information.

Increasingly there are news reports of people who have recovered from COVID-19 illness and are congregating together because social distancing measures are assumed to no longer hold for them. Similarly there are early reports of healthcare workers being able to work with evidence of a proven immune response following their recent COVID-19 illness (2). In Italy, Britain and other countries, the idea of people carrying immunity certificates or passports is being raised (3).

In this interim review we examine what is currently known about

- The adaptive immune response to infection with SARS-CoV-2
- The durability of the adaptive immune response and its capacity to prevent re-infection with SARS-CoV-2
- The adaptive immune response in people who have had asymptomatic SARS-CoV-2 infection
- Whether populations living with HIV/HBV/HCV including pregnant women are less likely to develop an effective adaptive immune response to SARS-CoV-2

The Immune response to infection with SARS-CoV-2

The first report of the immune response to SARS-CoV-2 was from Melbourne, Australia and showed that both B cell and T cell responses occurred during the clinical illness of a woman hospitalised with COVID-19 illness(4). Further reports have since emerged from China providing more details on the timing and development of IgM and IgG antibody responses in patients hospitalised with SARS-CoV-2 infection(4-6) and are summarised in Table 1.

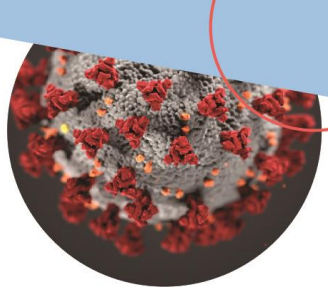
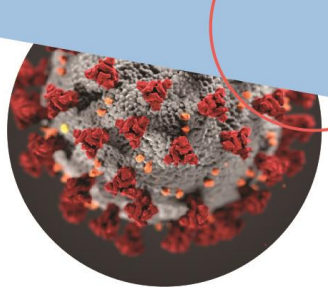


Table 1. Adaptive immune responses to SARS-CoV-2 infection

Study	Patients N=Number Confirmed = SARS-CoV-2 RNA PCR positive	Total Ab and IgM Ab	IgG Ab	B and T cell responses
Thevarajan et al, Nat Med, 2020	N= 1 Hospitalised Confirmed	IgM detected on day 7	IgG detected on day 7	Antibody secreting cells, circulating follicular helper T cells and CD38+HLA-DR+ CD8+ T cells detected on day 7
Zhao et al, Clin Infect Dis 2020	N= 173 All hospitalised All confirmed	Median time to total Ab seroconversion: 11 days Total Ab present Week 1: 36/94 samples Week 2: 121/135 samples Week 3: 90/90 samples Median time to IgM Ab seroconversion: 12 days IgM Ab present Week 1: 27/94 samples Week 2: 99/135 samples Week 3: 83/90 samples	Median time to IgG Ab seroconversion: 14 days IgG Ab present Week 1: 18/94 samples Week 2: 73/135 samples Week 3: 71/90 samples	N/A
Guo et al Clin Infect Dis, 2020	N= 140 All hospitalised N= 82 confirmed N= 58 probable	Median time to IgM Ab detection, 5 days [IQR 3-6] 35/41 (85.4%) samples tested at week 1 were positive for IgM Ab	Median time to IgG Ab detection, 14 days [IQR 10-18] 162/208 (77.9%) samples were positive for IgG Ab	N/A

A recent paper which has not yet been peer reviewed, has provided data on the neutralising antibodies produced during SARS-CoV-2 infection(7). The authors reported on 175 patients hospitalised with confirmed mild COVID-19 illness; all patients recovered. In the 175 patients, SARS-CoV-2 specific neutralising antibodies were detected at days 10-15 following illness onset. Of note, 30% of these patients generated low titres of SARS-CoV-2 specific neutralising antibodies, despite their full recovery. Also of note, older patients developed higher levels of SARS-CoV-2 specific neutralising antibodies and the titres of these patients' antibodies were significantly higher than those of younger patients(7). Further data are needed on SARS-CoV-2



specific neutralising antibodies to determine their role in future protection against COVID-19 illness and to guide vaccine development.

There are several key issues arising in these early studies on the adaptive immune response to SARS-CoV-2. Importantly, antibodies targeted the receptor binding domain of the SARS-CoV-2 spike protein and the SARS-CoV-2 specific neutralising antibodies reflect immune responses that are likely to protect against SARS-CoV-2 infection. However, the immune protective effect of antibodies which target other viral elements, such as the IgG antibodies that were reported in Zhao et al, which bind to the viral nucleoprotein(5), are not known. Other key issues include that the timing of the sampling of antibody responses varies between studies, making it hard to confidently determine the time to seroconversion following infection with SARS-CoV-2; there is likely to be variability in the reporting of symptom onset in patients; the follow-up periods are short in these studies hence the longevity and the levels of IgM and IgG antibodies are not yet well described and finally the studies remain relatively small at this stage.

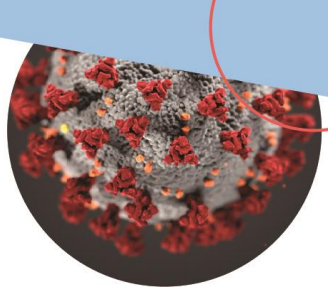
The durability of the immune response and its capacity to prevent re-infection with SARS-CoV-2

The durability of the immune response and the relative contribution of B and T cell responses to SARS-CoV-2 infection have not yet been ascertained. It is plausible that longterm immunity to SARS-CoV-2 may be conferred largely by T cells. Of 23 patients infected with the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), 60% had virus specific memory T cell responses six years following their acute infection with SARS-CoV (8). By contrast specific IgG antibody to SARS-CoV was not detected in any of these patients.

Less is known about the long-term immune protection against Middle Eastern Respiratory Syndrome coronavirus (MERS- CoV) infection. In mice, both antibody and T cell responses are important for initial clearance of the virus(9). In one small study, six of seven humans with prior probable MERs-CoV infection were shown to have neutralising antibodies detected 34 months following the original outbreak in Jordan(10). However whether these neutralising antibodies are protective against re-infection with MERs-CoV is unknown.

There are currently very few data available to determine how long lasting the immune response is following infection with SARS-CoV-2 and whether it confers protection against re-infection.

Recently a small study reported results from the rechallenge of three rhesus macaques with SARS-CoV-2 and found that re-infection did not occur following re-challenge with the virus (11). Results from this study should be interpreted carefully because it has not yet been peer reviewed, the study was relatively small and the



monkeys were re-challenged 28 days after their initial infection so one cannot deduce that longterm immunity was conferred.

In this study four rhesus macaques were infected intra-tracheally with SARS-CoV-2 and all developed signs of illness wherein the monkeys remained afebrile but had weight loss, increased respiratory rate and pneumonia occurred in at least two monkeys. SARS-CoV-2 viral loads from nasal, pharyngeal and anal swabs peaked at day 3. One monkey was sacrificed at day 7 and the virus was detected in numerous tissues including the lung where features of pneumonia were present. Prior to intra-nasal re-challenge at day 28, the authors reported that the remaining three monkeys were clinically stable with clear chest x-rays and negative nasopharyngeal and anal swabs. Two monkeys were rechallenged intra-tracheally and the authors reported that both had a rise in temperature, but no weight loss. One monkey was sacrificed at day 5 post re-challenge and no virus was detected in any tissues and no pathological changes were observed it the lung. Repeat nasaopharyngeal and anal swabs remained negative post-rechallenge in the remaining monkey over several days(11).

Broadly, the current thinking among virologists and immunologists is that the immune response is likely to be protective against re-infection with SARS-CoV-2 , but more data are required to determine this.

The adaptive immune response in people who have had asymptomatic SARS-CoV-2 infection

It is estimated that between 18%-30% of people with SARS-CoV-2 infection remain asymptomatic, i.e. do not develop symptoms despite being infected with the virus(12-15). There are currently no data on the nature of the adaptive immune response in people with asymptomatic SARS-CoV-2 infection.

Adaptive immune responses in populations living with HIV/HBV/HCV including pregnant women are less likely to develop an effective immune response to SARS-CoV-2

There are currently no data available to determine whether these populations are less likely to develop an effective adaptive immune response to SARS-CoV-2. More data are required in these patient populations.

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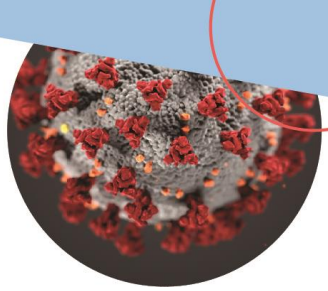

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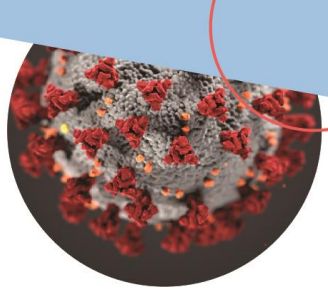

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