Immunity Post-COVID-19 Infection: Literature Review as of April 5, 2021

Stephanie Schulte and Kenya Moyers, on behalf of Safe Campus & Scientific Advisory Committee

Methods

A rapid search of LitCovid supplemented with full Pubmed, plus a scan of popular media via a web search was conducted using terms such as COVID-19 and SARS combined with reinfection, immunity, antibodies, and immune response. Findings of studies targeting the topic were selected and summarized.

Duration and Strength of Immunity

Knowledge about the duration and strength of the immune response in patients who have recovered from COVID-19 is evolving quickly. More severe illness has been shown to elicit a strong immune response.[1,2] However, even mild illness has produced lasting immune responses, although with significantly lower mean titers of neutralizing antibodies when compared to those with mild to severe pneumonia.[1] In contrast, Wu et al. found 30% of recovered mild COVID-19 patients from China had low levels of neutralizing antibodies at the time of discharge (median 16 days in hospital; 22 days of illness duration), with 10/175 having them below the limits of detection.[3] Others have looked at more specific antibodies over a longer follow-up time and found that antibodies to the receptor binding domain and the S2 region of the spike protein of SARS CoV-2 were still high at 2-3 months post-infection, but those against the nucleocapsid varied and rapidly declined in many.[2] Their work also demonstrated stronger responses in more severe illness. Another analysis of 15 patients who had recovered from mild cases of COVID-19 found maintenance of anti-RBD IgG levels above negative threshold. 71% and 36% of patients maintained anti-RBD IgM and IgA, respectively, at a median of 86 days post-symptom onset.[4]

A study conducted in Northern Ireland was designed to measure SARS-CoV-2 antibody levels in plasma samples through use of three different immunoassays to analyze immune dynamics over time.[5] Samples were included if the participants had previously tested PCR positive or had experienced loss of taste and smell as symptoms. Results from the study indicated that IgG antibodies could still be detected in individuals across all three immunoassays up to 20 weeks (day 140) post infection. Antibody levels peaked at different weeks for the assays, but collectively, by weeks 21-24, the median score for all tests dropped below the positivity cut-off. A few RT-PCR sample remained above the cutoff at later timepoints. The detection of antibodies post 140 days after RT-PCR positive results indicates the persistence of IgG antibodies to both spike protein and nucleocapsid protein. Where others report SARS-CoV-2 antibody decline at 90 days, Robertson et al. noted a statistically significant decline over time, but levels remain detectable at 140 days.[5]

While most vaccine development utilizes neutralizing antibody responses as a key measure, T and B cells are also of interest for long term immunity. Sekine et al. found that T cell activation was a hallmark of COVID-19 infection and memory T cell responses were robust in recovered patients even when circulating antibodies were not detected.[6] Rodda et al. also found enhanced both memory B and T cell activity.[4] Additionally, two studies have shown development of immune responses in rhesus macaques

when they were challenged at 28-35 days post initial infection.[7,8] A recent study by Jiang et al. found evidence that IgG, NAb, and T cell responses persist in the majority of patients for at least 3–4 months after infection.[9] Sasisekharana et al. found that IgG antibody titers among asymptomatic and symptomatic patients persist for more than 4 months post symptom onset. In addition, IgG antibody levels to SARS-CoV-2 antigens correlated with clinical parameters, such as length and severity of infection.[10] A study conducted by Havervall et al. found similar results in a longitudinal cohort study of health workers [11.] And, a study conducted by L'Huillier et al. found that IgG antibodies remain in a patient up to 6 months post infection.[12]

Reports of Reinfection and Re-positives

Three recent reports of reinfection have gained attention. All appear to be considered true reinfections since the strains they were infected with were found to be genetically different and all had negative tests in between infections. One report, a 33 year old Hong Kong man, experienced his second positive 4.5 months after his first. His second infection was asymptomatic. His viral load was high despite being asymptomatic. There was a difference of 24 nucleotides between the 2 strains of SARS Cov-2 in this case.[13] Another very recent report is that of a 25 year old man from Reno, NV. According to news reports, his second bout of COVID-19 was worse than the first, which would not generally be expected.[14] Tomasini et al. present 6 potential reinfection cases in a recent paper, two of which they feel very confident are reinfections due to 84 and 87 days passing in between the infections.[15] Patients in this report did have negative tests in between their infections. An additional report is the first confirmed case of SARS-CoV-2 reinfection in South America caused by two different viral genetic variants. A 46-year-old man tested positive mid-May. Twenty-one days post-symptom onset the man tested negative. However, late July the man reported close contact with a relative diagnosed with COVID-19 and presented once with more severe symptoms suggesting COVID-19. A RT-PCR test was positive for this infection. Genetic sequencing of samples from both infections showed two unique variants.[16]

Countries such as China and South Korea had protocols whereby all positive patients (regardless of symptom levels) were hospitalized and not discharged until negative tests were recorded. These patients were also followed and re-tested after discharge. Post discharge monitoring uncovered several re-positive results. Contact tracing protocols in these reports indicate that these patients most likely did not have a new contact with a positive case, thus, these authors believe these patients had reactivated virus. The time to repositive in these reports (from initial positive diagnosis, through negative discharge, and then repositive) is generally under 40 days.[17-19]

Historical Immunity and Reinfection with MERS, SARS CoV, and Seasonal Coronaviruses

Reinfection with seasonal coronaviruses is common. A recent study of viral data from Manhattan between October 2016 and April 2018 found 86 out of 214 tested positive for one of the common seasonal coronaviruses once, while 12 were positive for the same virus multiple times (3 positive 3 times, 6 positive 2 times).[20] The range of time for recurrence was 4 to 48 weeks. Many of the reinfections (75%) were in children between 1 and 9 years old.

Immune responses to seasonable coronaviruses as well as MERS and SARS CoV have also been studied. A recent publication found 43/200 participants had a seasonal coronavirus during the study. In this population, binding antibodies were increased more than neutralizing antibodies, which they suggest increases risk for infection.[21] A recent review by Kellam et al. describes immune responses in patients who had MERS or SARS CoV.[22] With MERS, severe infection or those with prolonged viral shedding had robust functional antibody response for greater than 1 year with one study finding continued immune response nearly 3 years post infection, though the response did decline over time. Mild or asymptomatic MERS infections have more limited antibody responses or rapid decline in that response. SARS CoV was a largely symptomatic coronavirus, and lasting antibody response up to 30 months post-infection was found. However, there is a subset where that response declines significantly.

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