

Synthesis Summary

Immunity to COVID-19 and SARS-CoV-2 Infection

April 16, 2021

COVID-19 Literature Report Team:

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Much of the information in this synthesis report is drawn from summaries included in the daily [COVID-19 Literature Situation Report](#). This is not intended to be a systematic or comprehensive summary, rather it is a **frequently updated compilation and synthesis of evidence related to immunity to SARS-CoV-2 infection and protection against COVID-19 disease following recovery from an initial SARS-CoV-2 infection.**

Evidence of SARS-CoV-2-specific antibody and other immune responses following natural infection

Antibody responses following natural infection

Natural infection with SARS-CoV-2 results in a robust antibody response in up to 95% of immunocompetent persons ([Arkhipova-Jenkins](#), [Van Elslande](#)), peaking approximately 3-4 weeks after infection. Most data on the immune response comes from the detection of antibodies against the spike protein that surrounds the virus. Anti-spike IgM titers rapidly wane by approximately 12 weeks whereas IgG titers persist ([Cheng](#), [Sherina](#)). There are also antibody responses against other portions of the SARS-CoV-2 virus. Antibodies directed against nucleocapsid are generally detected earlier ([Semmler](#)), but wane more rapidly than antibodies directed against the spike protein. Seroreversion (having a negative antibody serology test following a period of being seropositive) is relatively common; however the relevance of this waning of detectable antibodies to immunity against reinfection is unclear and there is evidence that immune activity against SARS-CoV-2 persists among individuals who serorevert to a negative antibody test.

Several clinical and demographic variables are associated with different antibody responses. Younger children and older adults have been observed to produce higher levels of antibodies ([Yang](#)). More severe infections are generally associated with higher anti-Spike antibody titers across all isotypes, including neutralization titers ([Chia](#), [Bartsch](#)); however, antibodies are commonly detected in those with asymptomatic infections and in individuals with no suspected exposure to SARS-CoV-2 ([Tsitsilonis](#)).

Cellular immune responses following natural infection

Compared to the plasma antibody response, CD4+ and CD8+ T cells are more readily detectable after asymptomatic or mild infection (or even exposure) and are generally more durable ([Zuo](#), [Wang](#), [Shin](#)).

Evidence of protection from re-infection following natural infection (including reports of re-infection)

There is strong evidence that infection with **SARS-CoV-2 confers some level of immunity against reinfection** but cases of re-infection have been reported, including cases with severe outcomes during the second infection.

- The CDC defines suspected SARS-CoV-2 reinfection as an infection that occurs >90 days after initial documented infection with SARS-CoV-2.
- The level of protection against re-infection is not fully known, but estimates of protection are as high as 80% to 95% ([Sheehan](#), [Hansen](#), [Leidi](#), [Letizia](#)), although these estimates are based on observational studies that may over- or underestimate the actual level of protection.
- Immunity appears to be strongest for protection against the same strain of the virus as the initial infection, although there appears to be at least partial immunity to other viral variants (refer to the section below on the impact of variants on natural immune protection).
- Cases of reinfection with SARS-CoV-2 have been reported ([Lee](#)), including in individuals with a symptomatic initial infection ([Cavanaugh](#)). There is particular concern regarding reinfection with the P.1, P.2, and B.1.351 variants following an initial infection with an earlier strain of the virus ([Fintelman-Rodrigues](#), [Nonaka](#)).

Impact of variants on natural immune protection

The emergence of several SARS-CoV-2 “variants of concern” with mutations in the spike protein has complicated the landscape for immunity through natural infection and vaccination as well as treatment using monoclonal antibodies. The literature is complex and fast moving but conceptually there are mutations that lead to enhanced viral fitness (including replication), such as the B.1.1.7 variant first identified in the UK, and mutations that lead to immune escape, such as the B.1.351 first identified in South Africa. Studies are ongoing, but it is reasonable to expect larger effects of the mutations on the efficacy of monoclonal antibodies and smaller effects on immunity from natural infection and vaccination.

- Tests of the ability of antibodies from individuals who have been infected with earlier strains of SARS-CoV-2 indicate lower levels of viral neutralization against the B.1.351, P.1, and CAL.20C variants ([Jangra](#), [McCallum](#), [Dejnirattisai](#), [Becker](#), [Wang](#), [Vogel](#), [Widera](#), [Li](#), [Edara](#), [Zhou](#), [Planas](#), [Collier](#), [Redd](#), [Diamond](#), [Betton](#)), but similar neutralization against the B.1.1.7 variant ([Becker](#)). The impact of lower neutralization titers on actual protection from re-infection is not yet understood.
- Antibodies produced in response to infection with the B.1.351 variant appear to be cross-reactive against other strains of the virus, including P.1 ([Moyo-Gwete](#), [Betton](#)).

Other factors associated with protection against COVID-19

Several groups have reported that receipt of non-COVID vaccines is associated with both reduced risk of SARS-CoV-2 diagnosis and severe COVID disease. Vaccines that have been observationally associated with lower incidence of COVID-19 include the pneumococcal and influenza vaccines ([Lewnard](#), [Wilcox](#)).

Cross-reactive immunity, presumably generated by infection with seasonal coronaviruses, is common in samples taken prior to the pandemic, but the presence of this immunity does not appear to affect clinical outcomes after infection with SARS-CoV-2 ([Anderson](#)). Similarly, virologically confirmed infection with seasonal coronavirus is not associated with protection against subsequent infection with SARS-CoV-2 ([Ringlander](#)).

Summaries of relevant articles

Reverse chronological order within topical categories

Evidence of SARS-CoV-2-specific antibody and other immune responses following natural infection

Antibody responses following natural infection

Tsitsilonis et al. (Mar 2, 2021). SARS-CoV-2 Infection Is Asymptomatic in Nearly Half of Adults with Robust Anti-Spike Protein Receptor-Binding Domain Antibody Response. Vaccines.

<https://doi.org/10.3390/vaccines9030207>

- In a study of 4996 participants (aged 18–82 years, 34.5% men) from Greece with plasma antibodies against SARS-CoV-2 nucleocapsid protein between June and November 2020, 49% of seropositive cases (39/79) reported no history of SARS-CoV-2 infection-related clinical symptoms. The majority of SARS-CoV-2 asymptomatic infections were “unsuspected” cases (26/39) who had no known contact with a confirmed or suspected COVID-19 case. Anti-SARS-CoV-2 antibody levels against the spike-protein receptor binding domain were similar between symptomatic and asymptomatic individuals, with no differences by age or gender.

Cheng et al. (Mar 31, 2021). Longitudinal Dynamics of Antibody Responses in Recovered COVID-19 Patients. Signal Transduction and Targeted Therapy. <https://doi.org/10.1038/s41392-021-00559-7>

- SARS-CoV-2-specific IgG antibody titers gradually increased with neutralizing antibody titers while IgM titers more quickly waned in a study of the antibody response dynamics in 24 COVID-19 recovered patients followed up to 42 weeks. While IgG titers were higher among severe than among mild cases, titers did not decline significantly over time in either group. 17% of patients were IgM-negative by 8-11 weeks, and the proportion continued to increase during the following weeks. Neutralizing antibody titers initially showed significant drops up to week 13, but remained stable through 42 weeks.

Chia et al. (Mar 23, 2021). Dynamics of SARS-CoV-2 Neutralising Antibody Responses and Duration of Immunity: A Longitudinal Study. The Lancet Microbe. [https://doi.org/10.1016/S2666-5247\(21\)00025-2](https://doi.org/10.1016/S2666-5247(21)00025-2)

- Five distinct patterns of SARS-CoV-2 neutralizing antibody dynamics were found in a longitudinal study of 164 SARS-CoV-2-infected patients in Singapore with follow-up of up to 180 days post-symptom onset. The different dynamics were defined by the trajectory by which antibody levels waned or evolved. Persistent dynamics, observed in the largest group of patients (32%), was characterized by minimal neutralizing antibody decay and associated with disease severity and inflammatory biomarkers. Delayed response dynamics, characterized by an unexpected increase of neutralizing titers at 90 or 180 days post-symptom onset, was observed in the smallest group (2%). Despite differing neutralizing antibody dynamics, T-cell responses were similar across groups.

Yang et al. (Mar 22, 2021). Association of Age With SARS-CoV-2 Antibody Response. JAMA Network Open. <https://doi.org/10.1001/jamanetworkopen.2021.4302>

- SARS-CoV-2 antibody responses are distinct in different age groups, according to a cross-sectional study of a New York City hospital using 31,426 SARS-CoV-2 antibody test results from pediatric and adult patients. IgG levels were negatively correlated with age in the pediatric population ($r = -0.45$, $P < .001$), but moderately positively correlated with age in adults ($r = 0.24$, $P < .001$). Patients aged 19 to 30 years exhibited the lowest IgG levels, whereas adolescents and children had higher antibody levels.

Arkhipova-Jenkins et al. (Mar 16, 2021). *Antibody Response After SARS-CoV-2 Infection and Implications for Immunity*. *Annals of Internal Medicine*. <https://doi.org/10.7326/M20-7547>

- A review of 66 observational studies found that most adults with SARS-CoV-2 infection develop IgM and IgG antibody responses. Among studies measuring IgM antibody responses (n=21 studies), 80% of adults developed responses, peaking at 20 days. Among studies measuring IgG antibody responses (n=24 studies), 95% of adults developed responses, peaking at 25 days and remaining detectable up to 120 days. Studies evaluating neutralizing responses (n=8 studies) were more varied in methodology, but suggest that 99% develop neutralizing antibodies.

Van Elslande et al. (Mar 8, 2021). *Estimated Half-Life of SARS-CoV-2 Anti-Spike Antibodies More than Double the Half-Life of Anti-Nucleocapsid Antibodies in Healthcare Workers*. *Clinical Infectious Diseases*. <https://doi.org/10.1093/cid/ciab219>

- Among healthcare-workers (HCWs) (n=118) who had a previous SARS-CoV-2 infection, 92% were still positive for anti-spike (S) antibodies compared to only 18% for IgG anti-nucleocapsid (N) antibodies after 7-10 months. At 1-3 months, 98% of HCWs were positive for anti-S antibodies compared to 85.6% anti-N antibodies. The mean half-life for anti-S antibodies was 19 days compared to 76.4 days for anti-N antibodies. The majority of participants had experienced mild COVID-19 disease; 6 participants had been briefly hospitalized. These findings could have implications for the estimated duration of the antibody response after vaccination.

Manisty et al. (Mar 2, 2021). *Time Series Analysis and Mechanistic Modelling of Heterogeneity and Sero-Reversion in Antibody Responses to Mild SARS-CoV-2 Infection*. *EBioMedicine*. <https://doi.org/10.1016/j.ebiom.2021.103259>

- A prospective serology cohort study among UK healthcare workers found that by 21 weeks, 22% (31 of 143) of those previously positive for anti-SARS-CoV-2 spike (S1) antibodies reverted to being S1 negative, while only 4% (6 of 150) of those previously positive for anti-SARS-CoV-2 nucleocapsid (NP) antibodies reverted to being NP negative, which the authors suggest may indicate that anti-S mediated humoral immunity in some individuals may not persist long after the initial post-infection period. Additionally, while both anti-S1 and anti-NP measurements correlated well, only anti-S1 measurements correlated with neutralizing antibody titers. Mathematical modelling showed that anti-S1 antibodies cleared faster compared to anti-NP antibodies (median half-life 2.5 weeks vs 4 weeks), transitioned earlier to decreased antibody production (median 8 vs 13 weeks), and had lower relative production rates after the transition (median 35% vs 50%).

Semmler et al. (Feb 18, 2021). *Assessment of S1, S2 and NCP-Specific IgM, IgA, and IgG Antibody Kinetics in Acute SARS-CoV-2 Infection by a Microarray and Twelve Other Immunoassays*. *Journal of Clinical Microbiology*. <https://doi.org/10.1128/JCM.02890-20>

- A study examining antibody kinetics of multiple immunoglobulins in patients hospitalized with acute SARS-CoV-2 infection showed that nucleocapsid protein (NCP)-specific IgA and IgG antibodies are detected earlier, while higher spike (S)1-specific IgA antibody levels occur in severely ill patients. The analysis was conducted using a microarray, eleven different commercial immunoassays (ELISA and CLIA), and one rapid test by seven manufacturers. NCP-specific IgA and IgG antibodies continuously displayed higher detection rates than S1- and S2-specific ones, though S1-specific IgG antibodies reached higher peak values. Detection rates by commercial immunoassays generally resembled those of the microarray (corresponding to the target antigen) but sensitivities and specificities varied among all tests.

Cosma et al. (Feb 2, 2021). Longitudinal Analysis of Antibody Response Following SARS-CoV-2 Infection in Pregnancy: From the First Trimester to Delivery. Journal of Reproductive Immunology.

<https://doi.org/10.1016/j.jri.2021.103285>

- In a cohort of 17 SARS-CoV-2 PCR-positive pregnant women followed from the end of the first trimester to delivery, IgG non-neutralizing antibodies (nNAbs) were detected in 71% (12 of 17), while neutralizing antibodies (NAbs) were detected in 53% of individuals (9 of the 12 who seroconverted with IgG nNAbs). Levels of NAbs remained stable throughout pregnancy. In contrast, nNAbs declined over the pregnancy, with a statistically significant decrease observed by week 16.

Sherina et al. (Feb 2021). Persistence of SARS-CoV-2 Specific B- and T-Cell Responses in Convalescent COVID-19 Patients 6-8 Months after the Infection. Med. <https://doi.org/10.1016/j.medj.2021.02.001>

- Anti-SARS-CoV-2 antibodies were detected in 85% of 119 samples collected from 88 COVID-19 convalescent donors within 4 weeks post symptom onset. IgM/IgA levels declined after 1 month, while IgG levels remained relatively stable and were detected in 80% of samples up to 6-8 months irrespective of disease severity. SARS-CoV-2-specific memory B- and T-cell responses developed over time and were detected in all patients up to 6-8 months.

Bartsch et al. (Feb 2021). Discrete SARS-CoV-2 Antibody Titers Track with Functional Humoral Stability. Nature Communications. <https://www.nature.com/articles/s41467-021-21336-8>

- There may be a distinct threshold of immune activity, defined by the level of antibodies, in response to SARS-CoV-2 infection that is required to elicit a vigorous humoral and cellular response necessary to prevent subsequent re-infection. These conclusions were based on a community-based surveillance study of 120 SARS-CoV-2 convalescent patients, which found that sustained functional humoral responses were mostly observed in individuals who had antibody titers to the SARS-CoV-2 receptor binding domain (RBD) that were above a certain threshold. The authors note that unlike mild/asymptomatic natural infection, vaccine boosting is likely to result in the induction of broad robust protective immunity.

Cellular immune responses following natural infection

Jin et al. (Mar 10, 2021). Age Cohorts Stratified According to Age-Distributions of COVID-19 Morbidity Statistics Identify Uniquely Age-Dependent CD3 + CD8 + T-Cell Lymphocytopenia in COVID-19 Patients without Comorbidities on Admission. *Aging*. <https://doi.org/10.18632/aging.202691>

- SARS-CoV-2 infection was associated with age-dependent reductions in CD8+ T cell count in a retrospective study of 447 individuals stratified by five age-group cohorts spanning ages 2 to 79. CD4+ T cell, B cell, and natural killer cell counts did not differ between age strata. Plasma C-reactive protein concentrations increased with age.

Shin et al. (Mar 8, 2021). SARS-CoV-2-Specific T Cell Memory Is Sustained in COVID-19 Convalescents for 8 Months with Successful Development of Stem Cell-like Memory T Cells. Pre-print downloaded Mar 9 from <https://doi.org/10.1101/2021.03.04.21252658>

- [Pre-print, not peer-reviewed] Whole blood analysis from 94 individuals who had been infected with SARS-CoV-2 in South Korea found that SARS-CoV-2-specific memory T cell responses were maintained at up to 8 months post-symptom onset. Among 30 individuals with longitudinal samples beyond the first month, no significant differences in memory T cell responses were observed between paired samples from different time points. The proportion of stem cell-like memory T cells peaked at 4 months post-symptom onset. Given the self-renewal capacity and multipotency of stem cell-like memory T cells, the authors suggest they may confer long-lasting memory T cell production against SARS-CoV-2.

Zuo et al. (Mar 5, 2021). Robust SARS-CoV-2-Specific T Cell Immunity Is Maintained at 6 Months Following Primary Infection. *Nature Immunology*. <https://doi.org/10.1038/s41590-021-00902-8>

- Functional SARS-CoV-2-specific T cell responses were retained 6 months after initial SARS-CoV-2 infection among 100 convalescent donors between March and April 2020. Interferon (IFN)- γ ELISPOT analysis was used to determine the magnitude of the T cell response. Cell responses were present among all donors and characterized by predominant CD4+ T cell responses with strong interleukin (IL)-2 cytokine expression. Median T cell responses were 50% higher in donors who had an initial symptomatic infection, and T cell responses to spike and nucleoprotein/membrane proteins correlated with peak antibody levels. In addition, higher levels of nucleoprotein-specific T cells were associated with preservation of nucleoprotein-specific antibody level.

Wang et al. (Dec 19, 2021). Exposure to SARS-CoV-2 Generates T-Cell Memory in the Absence of a Detectable Viral Infection. *Nature Communications*. <https://doi.org/10.1038/s41467-021-22036-z>

- Exposure to SARS-CoV-2 may still lead to the development of SARS-CoV-2-specific memory T cells in the absence of detectable SARS-CoV-2 virus or antibodies against SARS-CoV-2 antigens (spike and nucleocapsid). In blood samples collected from 69 individuals between 48 and 86 days after close contact with an individual with a confirmed SARS-CoV-2 infection, 58% and 14% of individuals developed SARS-CoV-2-specific CD4+ and CD8+ T cells, respectively. In contrast, only 3.7% of blood samples from 63 healthy donors collected before September 2019 contained detectable levels of CD4+ and CD8+ T cells.

Evidence of protection from re-infection following natural infection (including reports of re-infection)

Letizia et al. (Apr 15, 2021). SARS-CoV-2 Seropositivity and Subsequent Infection Risk in Healthy Young Adults: A Prospective Cohort Study. *The Lancet Respiratory Medicine*. [https://doi.org/10.1016/S2213-2600\(21\)00158-2](https://doi.org/10.1016/S2213-2600(21)00158-2)

- US Marine recruits who were seropositive for SARS-CoV-2 antibodies at baseline were 82% less likely than seronegative individuals to have a PCR-confirmed SARS-CoV-2 infection during a 6-week long cohort study. The study population consisted of predominantly male US Marine recruits aged 18-20 years (n=3,076). At baseline, all participants were PCR-negative. During the study period, 19 of 189 seropositive participants (10%) had at least one positive PCR test compared to 1,079 of 2,247 seronegative participants (48%) (1.1 vs 6.2 cases per person-year). Among seropositive participants, infection was less likely among those with higher baseline IgG titers. Higher baseline neutralizing titers were more frequently detected in seropositive participants who remained uninfected than those who were infected (83% vs 32%).

Leidi et al. (Mar 20, 2021). Risk of Reinfection after Seroconversion to SARS-CoV-2 A Population-Based Propensity-Score Matched Cohort Study. Pre-print downloaded Mar 23 from <https://doi.org/10.1101/2021.03.19.21253889>

- [Pre-print, not peer-reviewed] Swiss adults who were seropositive for SARS-CoV-2 IgG antibodies were less likely to have a SARS-CoV-2 PCR positive test than propensity-score-matched seronegative adults in the 8 months following antibody measurements. Of the 498 seropositive individuals, only 5 (1%) retested positive (likely indicative of reinfection) after a mean follow-up of 36 weeks. In contrast, 154 of 996 (16%) matched seronegative individuals tested positive during a similar mean follow-up of 35 weeks. These findings suggest that seropositivity is associated with a 94% reduction in hazard of retesting positive. The authors note that while testing rates were similar between seropositive and seronegative individuals, risk of detection may be underestimated among seropositive individuals if individuals with reinfection are less likely to be symptomatic.

Hansen et al. (Mar 17, 2021). Assessment of Protection against Reinfection with SARS-CoV-2 among 4 Million PCR-Tested Individuals in Denmark in 2020: A Population-Level Observational Study. *The Lancet*. [https://doi.org/10.1016/S0140-6736\(21\)00575-4](https://doi.org/10.1016/S0140-6736(21)00575-4)

- Individuals with a positive SARS-CoV-2 PCR test during the first surge in Denmark (prior to June 2020) were less likely to get a positive test during the second surge (September to December 2020) compared to individuals with a negative SARS-CoV-2 PCR test during the first surge. In this nationwide cohort study (n=525,339), 72 of 11,068 (0.65%) individuals who were initially positive retested positive again compared to 16,819 of 514,271 (3.27%) who were initially negative but retested positive, suggesting an estimated protection against a repeat infection of 80%. Among those aged 65 years and older, observed protection against a repeat infection was 47%. [EDITORIAL NOTE: Differences between those who do and do not retest for SARS-CoV-2 after an initial positive or negative test result could affect the observed test positivity. Conclusions based on these findings about the effectiveness of prior infection against re-infection should be made with caution.]

Sheehan et al. (Mar 15, 2021). *Reinfection Rates among Patients Who Previously Tested Positive for COVID-19: A Retrospective Cohort Study*. *Clinical Infectious Diseases*.

<https://doi.org/10.1093/cid/ciab234>

- Previous SARS-CoV-2 infection was associated with a lower likelihood of subsequent reinfection compared to those without a previous history of infection. These results are based on a cohort study of over 150,000 patients from a multi-hospital system in Ohio and Florida. Among 8,845 initially PCR-positive patients, 1,278 were retested after ≥ 90 days and 62 (0.4%) had reinfection (CDC definition of reinfection is a positive test ≥ 90 days after initial positive test). Of 141,480 initially PCR-negative patients, 39,487 were retested after ≥ 90 days and 3,191 (2.3%) had positive results. [EDITORIAL NOTE: This analysis relies on medical records of SARS-CoV-2 PCR testing and does not represent a random sample of people with and without prior SARS-CoV-2 infection. Differences between those who do and do not retest for SARS-CoV-2 after an initial positive or negative test result could greatly affect the observed test positivity. Conclusions based on these findings about the effectiveness of prior infection against re-infection should be made with great caution.]

Cavanaugh et al. (Feb 26, 2021). *Suspected Recurrent SARS-CoV-2 Infections Among Residents of a Skilled Nursing Facility During a Second COVID-19 Outbreak — Kentucky, July–November 2020*. *MMWR. Morbidity and Mortality Weekly Report*. <https://doi.org/10.15585/mmwr.mm7008a3>

- SARS-CoV-2 reinfection is suspected among residents of a skilled nursing facility in Kentucky, where 5 residents received positive RT-PCR test results in two separate COVID-19 outbreaks separated by 3 months with at least four negative test results for each resident in between the outbreaks. While only 2 of 5 patients had symptomatic infection during the first outbreak, all 5 had symptomatic infection during the second outbreak. The two patients who had symptomatic infection during the first outbreak experienced worse symptoms. Samples were not stored, and therefore it was not possible to confirm reinfection with genomic sequencing.

Harvey et al. (Feb 24, 2021). *Association of SARS-CoV-2 Seropositive Antibody Test With Risk of Future Infection*. *JAMA Internal Medicine*. <https://doi.org/10.1001/jamainternmed.2021.0366>

- In a cohort study of over 3.2 million US patients with a SARS-CoV-2 antibody test result (88% negative), the ratio of seropositive to seronegative patients with a positive SARS-CoV-2 nucleic acid amplification test (NAAT) decreased from 3% within 30 days of the antibody test to 0.1% after at least 90 days following the antibody test. Among seropositive patients, 18% converted to seronegative over the follow-up period. The authors suggest that a higher likelihood of NAAT positivity among seropositive patients is consistent with prolonged viral RNA shedding, but that seroconversion may reduce future risk of SARS-CoV-2 infection.

Lee et al. (Feb 18, 2021). *Clinical and Laboratory Findings in Patients with Potential SARS-CoV-2 Reinfection, May–July 2020*. *Clinical Infectious Diseases*. <https://pubmed.ncbi.nlm.nih.gov/33598716/>

- A clinical and laboratory investigation of potential SARS-CoV-2 reinfection reported to CDC by clinicians in the US did not confirm any cases of reinfection within 90 days of the initial infection, supporting current CDC guidance about retesting for people recovered from COVID-19. Among 73 potential reinfection patients with available records, 70% of patients either had recurrent COVID-19 symptoms explained by alternative diagnoses or remained asymptomatic after recovery but were incidentally found to have recurrent or persistent RT-PCR positivity through surveillance and contact

investigations. The 19 patients who developed recurrent symptoms but did not receive an alternative non-COVID diagnosis were mostly healthcare workers. However, laboratory investigation of nine samples from this group could not confirm reinfection.

Impact of variants on natural immune protection

Betton et al. (Apr 14, 2021). Sera Neutralizing Activities against SARS-CoV-2 and Multiple Variants Six Month after Hospitalization for COVID-19. Clinical Infectious Diseases.

<https://doi.org/10.1093/cid/ciab308>

- Neutralizing activity in sera of SARS-CoV-2 infected individuals (n=104) against the variants D614G, B.1.1.7, and P.1 up to 6 months after infection was similar compared to the prototypic strain isolated originally in Wuhan, but was reduced 3-fold against the B.1.351 variant. Similar to other studies, anti-spike and anti-nucleocapsid IgG levels waned over time (2.8% reverted to seronegative status by 6 months), and higher neutralizing activity was observed among individuals with a more severe disease course.

Jangra et al. (Apr 7, 2021). SARS-CoV-2 Spike E484K Mutation Reduces Antibody Neutralisation. The Lancet Microbe. [https://doi.org/10.1016/S2666-5247\(21\)00068-9](https://doi.org/10.1016/S2666-5247(21)00068-9)

- An *in vitro* study of serum from persons with either prior SARS-CoV-2 infection or two doses of the Pfizer-BioNTech vaccine (N=34) found that antibody neutralization in all samples was reduced against SARS-CoV-2 virus with a single spike E484K mutation compared to the USA-WA1/2020 strain (the strain first detected in the US). The largest reductions in antibody neutralization were observed in samples with low and moderate IgG antibody levels. Samples with high IgG levels from individuals with two doses of the vaccine were still able to fully neutralize virus. The authors suggest this data may indicate that delaying the second vaccine dose may leave persons vulnerable to infection with a variant containing the E484K mutation; however, the study did not include sera from persons with only one dose as a comparison.

Moyo-Gwete et al. (Apr 7, 2021). Cross-Reactive Neutralizing Antibody Responses Elicited by SARS-CoV-2 501Y.V2 (B.1.351). New England Journal of Medicine. <https://doi.org/10.1056/NEJMc2104192>

- Antibody responses to the B.1.351 SARS-CoV-2 variant (aka, 501Y.V2) in a cohort of patients hospitalized with COVID-19 in South Africa (n=89) were found to be robust and showed high levels of cross-reactivity against the virus strain from the first wave. Furthermore, sera from patients infected with B.1.351 also neutralized the P.1 variant (aka, 501Y.V3) first described in Brazil, suggesting that the antibody response in patients infected with the B.1.351 variant has high levels of cross-reactivity across variants. The authors suggest that these results indicate that vaccines built on the spike protein of B.1.351 may be promising candidates for eliciting cross-reactive neutralizing antibody responses to SARS-CoV-2. [EDITORIAL NOTE: A pre-print version of this article was summarized in this report on March 10, 2021].

Fintelman-Rodrigues et al. (Apr 1, 2021). Genetic Evidence and Host Immune Response in Persons Reinfecting with SARS-CoV-2, Brazil. Emerging Infectious Disease Journal.

https://wwwnc.cdc.gov/eid/article/27/5/20-4912_article

- 4 cases of possible SARS-CoV-2 reinfection characterized by a more severe second episode were identified in a case series in Brazil. In March 2020, all patients recovered from a mild course of COVID-19 and retested with negative PCR results during early April. In the last week of May, all 4 cases reported SARS-CoV-2 symptoms and had higher viral loads and worse clinical symptoms than they did in March. Sequenced genomes from the second episode compared to those obtained in the first episode and prior circulating variants suggest that reinfection was caused by different strains.

McCallum et al. (Apr 1, 2021). SARS-CoV-2 Immune Evasion by Variant B.1.427/B.1.429. Pre-print downloaded Apr 2 from <https://doi.org/10.1101/2021.03.31.437925>

- [Pre-print, not peer-reviewed] The SARS-CoV-2 variant CAL.20C (also known as B.1.427/B.1.429, with key mutations S13I, W152C and L452R), which was first described in California, has plasma neutralizing activity that is 3- to 4-fold lower in individuals fully vaccinated with the Moderna or Pfizer-BioNTech vaccines compared to the wild-type SARS-CoV-2 strain. Reduction in neutralizing activity among fully vaccinated individuals with prior SARS-CoV-2 infection was also similar. Neutralizing activity among individuals with prior SARS-CoV-2 infection was reduced 5-fold, but neutralizing activity was reduced to nearly undetectable levels among those with prior infection from the B.1.1.7 variant. The Regeneron monoclonal antibody (mAb) cocktail (casirivimab/imdevimab) maintained neutralizing activity against CAL.20C compared to the wild-type strain, but 14 out of 35 mAbs tested showed reduced neutralization potency. Specifically, all mAbs targeting the N-terminal domain had abolished neutralizing activity, likely as a result of the S13I and W152C mutations.

Xiao et al. (Mar 29, 2021). SARS-CoV-2 Variant B.1.1.7 Caused HLA-A2+ CD8+ T Cell Epitope Mutations for Impaired Cellular Immune Response. Pre-print downloaded Mar 30 from <https://doi.org/10.1101/2021.03.28.437363>

- [Pre-print, not peer-reviewed] The SARS-CoV-2 B.1.1.7 variant is associated with reduced CD8+ T cell activation due to at least two specific mutations in ORF1. The authors used algorithms to predict HLA-A2 binding epitopes in both the B.1.1.7 strain and the ancestral Wuhan strain and determined whether these epitopes could activate CD8+ T cells using an artificial antigen presentation system. Two mutations located in non-structural proteins of the B.1.1.7 variant (A1708D mutation in ORF1ab1707-1716 and I2230T mutation in ORF1ab2230-2238) were linked in the decreased activation of CD8+ T cells. The authors then constructed SARS-CoV-2 CD8+ tetramers based upon these predicted epitopes and used them to probe the CD8+ T cell memory from convalescent patients. They found that most CD8+ T cells from convalescent patients had an effector memory phenotype and furthermore there was substantially reduced recognition of the B.1.1.7 mutant epitopes.

Dejnirattisai et al. (Mar 19, 2021). Antibody Evasion by the Brazilian P.1 Strain of SARS-CoV-2. Pre-print downloaded Mar 16 from <https://doi.org/10.1101/2021.03.12.435194>

- [Pre-print, not peer-reviewed] The SARS-CoV-2 P.1 variant, which has caused large outbreaks in Brazil, is less resistant to neutralization from both convalescent serum and vaccine-induced serum than the B.1.351 variant originally identified in South Africa, despite containing similar receptor binding domain (RBD) mutations (E484K, K417N/T and N501Y). Similar to the B.1.351 variant, mutations associated with the P1 variant completely abrogated the binding of multiple neutralizing

antibodies directed against the RBD, including a variety of antibodies currently in development for therapeutic use. In contrast, the reduction in neutralization activity of convalescent plasma from recovered volunteers against the P.1 variant was only modest (~3-fold reduction versus the ancestral Victoria strain) when compared to the reduction in neutralization observed with B.1.351 variant (~13-fold reduction versus the Victoria strain). Sera from recipients of either the Pfizer-BioNTech or Oxford-Aztrazeneca vaccine had similar modest reductions in neutralization activity (~3-fold) when compared to the reductions in neutralization observed with the B.1.351 variant (~8-9 fold).

Becker et al. (Mar 10, 2021). *Immune Response to SARS-CoV-2 Variants of Concern in Vaccinated Individuals*. Pre-print downloaded Mar 11 from <https://doi.org/10.1101/2021.03.08.21252958>

- [Pre-print, not peer-reviewed] Sera from both individuals with prior SARS-CoV-2 infection (n=35) and individuals fully vaccinated with the Pfizer-BioNTech vaccine (n=23) showed nearly identical antibody binding responses against the B.1.1.7 Cluster 5 and CAL.20C variants compared to wild-type SARS-CoV-2. In contrast, both binding and neutralizing antibody responses among vaccinated individuals were diminished against the B.1.351 variant compared to wild-type SARS-CoV-2, although the 2nd vaccine dose appeared to confer increased neutralization capacities. In a separate analysis, the authors found that individuals with prior SARS-CoV-2 infection had higher IgA antibody titers in saliva, while vaccinated individuals had high IgG titers.

Wang et al. (Mar 9, 2021). *Spike Mutations in SARS-CoV-2 Variants Confer Resistance to Antibody Neutralization*. Pre-print downloaded Mar 10 from <https://doi.org/10.1101/2021.03.09.434497>

- [Pre-print, not peer-reviewed] A panel of 28 SARS-CoV-2 pseudoviruses bearing single or combined spike protein mutations found in the 501Y.V1, 501Y.V2, and 501Y.V3 variants tested against a panel of monoclonal antibodies (mAbs) and convalescent patient plasma collected early in the pandemic showed that the 501Y.V2 variant was the most resistant against mAbs and convalescent plasma, followed by 501Y.V3, and then 501Y.V1. This corresponded with mutations in the N-terminal domain and receptor binding domain (RBD) of the spike protein. Analysis of the RBD carrying triple K417N/E484K/N501Y mutations found in the 501Y.V2 variant bound with mAb P2C-1F11 revealed a potential molecular basis for antibody escape.

Moyo-Gwete et al. (Mar 6, 2021). *SARS-CoV-2 501Y.V2 (B.1.351) Elicits Cross-Reactive Neutralizing Antibodies*. Pre-print downloaded Mar 10 from <https://doi.org/10.1101/2021.03.06.434193>

- [Pre-print, not peer-reviewed] Antibody responses to the 501Y.V2 SARS-CoV-2 variant in a cohort of patients hospitalized with COVID-19 in South Africa (n = 89) were found to be robust and showed high levels of cross-reactivity against the virus strain from the first wave. Furthermore, sera from patients infected with 501Y.V2 also neutralized the 501Y.V3 (P.1) variant first described in Brazil, suggesting that the antibody response in patients infected with 501Y.V2 has broad specificity.

Vogel et al. (Mar 4, 2021). *SARS-CoV-2 Variant with Higher Affinity to ACE2 Shows Reduced Sera Neutralization Susceptibility*. Pre-print downloaded Mar 5 from <https://doi.org/10.1101/2021.03.04.433887>

- [Pre-print, not peer-reviewed] An *in vitro* study of newly-emerging SARS-CoV-2 mutations in the receptor binding domain (RBD) of the viral spike protein found in the P.1 variant (first described in

Brazil) demonstrated increased angiotensin-converting enzyme 2 (ACE2) affinity for the mutant RBD and reduced neutralization ability of immune sera induced from prior strains. RBD mutations at K417N, E484K and N501Y resulted in increased affinity of SARS-CoV-2 for ACE2 by a factor of 2. Both mouse immune-induced sera and human sera from convalescent patients showed reduced capacity to block binding of ACE2 in mutant RBD, providing evidence that the P.1 variant may be more infectious and less susceptible to neutralization by antibodies induced with previous strains.

Widera et al. (Feb 26, 2021). *Bamlanivimab Does Not Neutralize Two SARS-CoV-2 Variants Carrying E484K in Vitro*. Pre-print downloaded Feb 26 from <https://doi.org/10.1101/2021.02.24.21252372>

- [Pre-print, not peer-reviewed] An *in vitro* study of the neutralizing ability of the monoclonal antibody treatment bamlanivimab against five emerging SARS-CoV-2 variants of concern determined no neutralization effect could be detected against either the B.1.351 (first described in South Africa) or P.2 (first described in Brazil) variants, both of which harbor the E484K substitution. The antibody was able to efficiently neutralize the B.1.17 variant (first described in the UK), as well as isolates FFM1 and FFM7 from early 2020. These findings indicate screening for E484K substitutions may be needed before initiating monoclonal antibody treatment with bamlanivimab.
- Neutralizing effect of vaccine-elicited sera (following vaccination with the Pfizer-BioNTech COVID-19 Vaccine [BNT162b2]) and convalescent sera were also tested in the 5 variant strains. Vaccine-elicited sera showed neutralizing activity against FFM1 and FFM7, and slightly decreased activity against B1.1.7, B.1.351 and P.2. Convalescent sera showed lower neutralizing activity against B1.1.7, B.1.135 and P.2 compared to FFM1 and FFM7. [EDITORIAL NOTE: The manuscript refers to both B.1.351 and B.1.135. It is assumed that B.1.135 was a typographical error and B.1.351 was used throughout in this summary.]

Li, Q et al. (Feb 23, 2021). *SARS-CoV-2 501Y.V2 variants lack higher infectivity but do have immune escape*. *Cell*. <https://doi.org/10.1016/j.cell.2021.02.042>

- The infectivity of the 501Y.V2 variants (which include the B.1.351 variant that was first identified in South Africa) was not significantly different than the reference strain (D614G) across multiple cell types. The neutralizing activity of multiple RBD-targeting monoclonal antibodies decreased significantly, and polyclonal antibodies (from RBD-immunized mouse sera and from SARS-CoV-2 convalescent sera) also had decreased neutralizing activity against 501Y.V2 variants.

Edara et al. (Feb 22, 2021). *Reduced Binding and Neutralization of Infection- and Vaccine-Induced Antibodies to the B.1.351 (South African) SARS-CoV-2 Variant*. Pre-print downloaded Feb 23 from <https://doi.org/10.1101/2021.02.20.432046>

- [Pre-print, not peer-reviewed] Antibodies collected from people who had been infected with SARS-CoV-2 or who had received the Moderna vaccine showed lower levels of binding to the SARS-CoV-2 B.1.351 variant (first described in South Africa) compared to the D614G variant that has been dominant globally. This effect was observed for antibodies from individuals with acute infection within 5-19 days post-symptom onset (n=19), recovering individuals through 8 months post-symptom onset (n=30), and individuals within 14 days of the 2nd dose of the Moderna vaccine (n=19). There was a 4.3-fold average reduction in IgG antibody titers to the B.1.351-derived receptor binding domain of the spike protein and 3.5-fold average reduction in neutralizing titers. Reduction in neutralizing titers was lowest among convalescent individuals at the 3-8 month timepoint (2.1-

fold reduction), followed by vaccinated individuals (3.8-fold reduction). However, most sera from acutely infected (74%) and convalescent individuals (77% at 1-3 months and 85% at 1-3 months) and all sera from vaccinated individuals neutralized the SARS-CoV-2 B.1.351 variant *in vitro*.

Nonaka et al. (Feb 19, 2021). Genomic Evidence of SARS-CoV-2 Reinfection Involving E484K Spike Mutation, Brazil. *Emerging Infectious Diseases*. https://wwwnc.cdc.gov/eid/article/27/5/21-0191_article

- SARS-CoV-2 reinfection with a variant harboring the E484K mutation (occurring in the P.2 variant) was confirmed by genome sequencing in a case study in Brazil. The primary infection occurred in May 2020 by a widely circulating variant B.1.1.33 without the E484K mutation, while the reinfection occurred 147 days later in October 2020. Findings from this case study corroborate experimental studies suggesting that variants containing the E484K mutation have the potential to escape neutralizing antibodies.

Zhou et al. (Feb 17, 2021). Evidence of Escape of SARS-CoV-2 Variant B.1.351 from Natural and Vaccine Induced Sera. *Cell*. <https://doi.org/10.1016/j.cell.2021.02.037>

- Neutralizing antibody titers were lower in assays against the SARS-CoV-2 B.1.351 variant compared to an early isolate from Wuhan across several sample sources. The geometric mean neutralizing titers were lower by 13.3-fold in convalescent plasma from patients infected during the first wave in the UK (n=34), by 3.1-fold in sera from patients infected with the B.1.1.7 variant (n=13), by 7.6-fold in sera from Pfizer vaccine recipients 14-28 days after the 2nd dose (n=25), and by 9-fold in sera from Oxford-AstraZeneca vaccine recipients 4-17 days after the 2nd dose (n=25).
- In a panel of 377 monoclonal antibodies (mAbs) raised from convalescent sera of first-wave patients in the UK, 14 out of the 20 of the most potent mAbs had a greater than 10-fold reduction in neutralization titers. In the mAb-based treatments from Regeneron and AstraZeneca, one of the Regeneron mAb pairs (casirivimab) had up to a 773-fold reduction in neutralization titers, while both of the AstraZeneca mAbs had little to no reduction.
- Structure-function analysis suggests that the mechanism by which the B.1.351 variant escapes neutralization and provides tighter binding to the angiotensin-converting enzyme-2 (ACE2) receptor to more efficiently enter human cells is primarily driven by the E484K mutation.

Planas et al. (Feb 12, 2021). Sensitivity of Infectious SARS-CoV-2 B.1.1.7 and B.1.351 Variants to Neutralizing Antibodies. Pre-print downloaded Feb 16 from <https://doi.org/10.1101/2021.02.12.430472>

- [Pre-print, not peer reviewed] The SARS-CoV-2 B.1.1.7 variant (first described in the UK) was experimentally shown to have similar sensitivity to the neutralizing activity of convalescent sera (n=83) collected up to 9 months post symptom onset compared to the wild-type virus. In contrast, neutralizing titers had a mean 6-fold reduction against the B.1.351 variant (first described in South Africa) and a loss of neutralizing activity in 40% of convalescent sera at 9 months post symptom onset.
- Among sera from 19 vaccinees collected at various timepoints during the vaccination regimen, neutralizing titers were lower against the B.1.1.7 variant and to a greater extent against the B.1.351 variant compared to the wild-type virus. After the second dose, at a 1/30 serum dilution, 80% of sera neutralized the wild-type and the B.1.1.7 variant but only 60% neutralized the B.1.351 variant.
- No neutralizing activity against the wild-type virus and the variants was detected in the nasal swabs from the vaccinees 2-3 weeks post vaccination, except among 3 vaccinees who had a history of

SARS-CoV-2 infection. Neutralizing activity was similar for the wild-type virus and B.1.1.7 variant, but was absent for the B.1.351 variant.

Collier et al. (Feb 2021). SARS-CoV-2 B.1.1.7 Sensitivity to mRNA Vaccine-Elicited, Convalescent and Monoclonal Antibodies. Pre-print downloaded Feb 24 from

<https://doi.org/10.1101/2021.01.19.21249840>

- [Pre-print, not peer-reviewed] An assessment of immune responses following a single dose of the Pfizer-BioNTech vaccine (BNT162b2) vaccine using pseudoviruses expressing the wild-type Spike protein or the B.1.1.7 spike protein showed that the vaccine-elicited antibodies modestly reduced activity against the B.1.1.7 variant. This reduction was also observed in sera from some convalescent patients and with monoclonal antibodies (mAbs) targeting the N-terminal domain (9 out of 10) and the Receptor Binding Motif (RBM) (5 out of 31), but not in neutralizing mAbs binding outside the RBM. Introduction of the E484K mutation in B.1.1.7 led to a greater loss of neutralizing activity by sera from vaccinees and mAbs (19 out of 31).

Redd et al. (Feb 2021). CD8+ T Cell Responses in COVID-19 Convalescent Individuals Target Conserved Epitopes from Multiple Prominent SARS-CoV-2 Circulating Variants. Pre-print downloaded Feb 17 from

<https://doi.org/10.1101/2021.02.11.21251585>

- [Pre-print, not peer-reviewed] A study assessing whether CD8+ T-cells from COVID-19 convalescent individuals (n=30) can recognize SARS-CoV-2 variant epitopes showed that only one of the three most prominent variants (the B.1.351 variant, first described in South Africa) had a mutation that overlapped with a low-prevalence CD8+ epitope. Out of 45 mutations assessed, this mutation was found on the third residue of the epitope. The authors argue that these findings suggest that virtually all anti-SARS-CoV-2 CD8+ T-cell responses should recognize these newly described variants.

Diamond et al. (Feb 2021). SARS-CoV-2 Variants Show Resistance to Neutralization by Many Monoclonal and Serum-Derived Polyclonal Antibodies. Research Square. <https://doi.org/10.21203/rs.3.rs-228079/v1>

- [Pre-print, not peer-reviewed] Most convalescent sera from people who had recovered from COVID-19 and virtually all Pfizer-BioNTech mRNA vaccine-induced immune sera were shown to have diminished neutralizing activity against engineered SARS-CoV-2 strains including a chimeric strain combining a strain identified in Washington state with a B.1.351 spike gene (Wash SA-B.1.351 strain), or recombinant viruses containing mutations at position 484 and 501. Several highly neutralizing monoclonal antibodies (mAbs) lost inhibitory activity against Wash SA-B.1.351 or recombinant variants with an E484K spike mutation. The authors note that targeting of highly conserved regions, enhancement of mAb potency, or adjustments to the spike sequences of vaccines may be needed to prevent loss of protection *in vivo*.

Other factors associated with protection against COVID-19

Ringlander et al. (Mar 29, 2021). Verified infections with endemic common cold coronaviruses do not entail significant protection against SARS-CoV-2. *Journal of Infectious Disease*.

<https://doi.org/10.1093/infdis/jiab089>

- A previous confirmed seasonal coronavirus infection does not appear to provide protection against subsequent infection with SARS-CoV-2, according to analysis of a large database of respiratory specimens in Sweden. The analysis is based on a database of >75,000 respiratory specimens collected from 2013-2020 and linked to 10,000 samples collected during the pandemic (February-

November 2020). There was substantial overlap in the patient population between the two cohorts, allowing the authors to determine whether a previous PCR confirmed coronavirus infection was associated with a reduced likelihood of a subsequent SARS-CoV-2 infection. They found no relationship between a prior coronavirus infection and subsequent SARS-CoV-2 infection when compared to previous infection with the immunologically unrelated rhinovirus, including when restricting their analysis to either alpha or beta-coronaviruses. Additionally, they found no relationship with either viral load or hospitalization (although only 20 participants were hospitalized with COVID-19).

Lewnard et al. (Mar 9, 2021). Prevention of COVID-19 among older adults receiving pneumococcal conjugate vaccine suggests interactions between *Streptococcus pneumoniae* and SARS-CoV-2 in the respiratory tract. *The Journal of Infectious Diseases*. <https://doi.org/10.1093/infdis/jiab128>

- Receipt of the 13-valent pneumococcal conjugate vaccine (PCV13) was associated with lower incidence of any COVID-19 diagnosis, COVID-19 hospitalization, and fatal COVID-19 hospitalization after accounting for potential sources of confounding, according to a cohort study of 531,033 US adults aged ≥ 65 years.

Anderson et al. (Feb 9, 2021). Seasonal Human Coronavirus Antibodies Are Boosted upon SARS-CoV-2 Infection but Not Associated with Protection. *Cell*. <https://doi.org/10.1016/j.cell.2021.02.010>

- Cross reactive antibodies generated by pre-pandemic human coronavirus (hCoV) infections are common but are not associated with protection against infection or poor clinical outcomes after infection with SARS-CoV-2. Using samples from a pre-pandemic biobank, 4% of pre-pandemic sera contained antibodies that bound the full-length spike from SARS-CoV-2 and 16% of samples contained antibodies capable of binding SARS-CoV-2 nucleocapsid. Pre-pandemic serum containing these antibodies was wholly incapable of neutralizing SARS-CoV-2 in either pseudovirus or live virus assays. The baseline presence or absence of non-neutralizing cross-reactive antibodies was not associated with protection against SARS-CoV-2 infection or clinical outcomes after infection in a cohort of 251 participants who went on to develop SARS-CoV-2. Levels of some of these hCoV antibodies were boosted upon infection with SARS-CoV-2.

Wilcox et al. (Mar 4, 2021). Association between Influenza Vaccination and Hospitalisation or All-Cause Mortality in People with COVID-19: A Retrospective Cohort Study. *BMJ Open Respiratory Research*. <https://doi.org/10.1136/bmjresp-2020-000857>

- A retrospective cohort study using routinely collected health records from patients with COVID-19 ($n= 6,921$) in South West England between January and July 2020 found that receiving the influenza vaccination sometime between January 1, 2019 and COVID-19 diagnosis was associated with a 15% reduced odds of all-cause mortality or hospitalization (aOR=0.85), and a 24% reduced odds of all-cause mortality alone. Differences between vaccinated and unvaccinated individuals was accounted for using a propensity score.