

## **Omicron variant partially escapes the T-cell response induced by SARS-CoV-2 vaccines**

Damon H. May,<sup>1</sup> Benjamin Rubin,<sup>1</sup> Sudeb C. Dalai,<sup>1,2</sup> Krishna Patel,<sup>1</sup> Shahin Shafiani,<sup>1</sup> Rebecca Elyanow,<sup>1</sup> Matthew T. Noakes,<sup>1</sup> Thomas M. Snyder,<sup>1</sup> and Harlan S. Robins<sup>1</sup>

<sup>1</sup>Adaptive Biotechnologies, Seattle, Washington, USA

<sup>2</sup>Stanford University School of Medicine, Stanford, California, USA

Corresponding author:

Harlan S. Robins, PhD

1551 Eastlake Ave E.

Seattle, WA 98109

Tel (206) 693-2191

[hrobins@adaptivebiotech.com](mailto:hrobins@adaptivebiotech.com)

### **Abstract**

The Omicron SARS-CoV-2 variant contains 34 mutations in the Spike gene likely impacting protective efficacy from vaccines. We evaluated the potential impact to the cellular immune response. Combining epitope mapping to SARS-CoV-2 vaccines that we have determined from past experiments along with TCR repertoire sequencing from thousands of vaccinated or naturally infected individuals, we estimate the abrogation of the cellular immune response in Omicron. Although the fraction of CD4<sup>+</sup> T-cell epitopes that are potentially affected accounts for 20%, the loss of T-cell immunity is estimated to be slightly above 30% as some of the epitopes have higher immunogenicity and generate a stronger T-cell response. For CD8<sup>+</sup> T cells, we estimate a loss of approximately 20%. These reductions in T-cell immunity are substantially larger than observed in other widely distributed variants. Combined with the expected substantial loss of neutralization from antibodies, the overall protection provided by SARS-CoV-2 vaccines could be impacted adversely. From analysis of prior variants, the efficacy of vaccines against symptomatic infection has been largely maintained and is strongly correlated with the T-cell response but not as strongly with the neutralizing antibody response. We expect the remaining 70% to 80% of on-target T cells induced by SARS-CoV-2 vaccination to be sufficient to limit morbidity and mortality from infection with Omicron and other variants of concern.

## Introduction

As the SARS-CoV-2 virus continues to evolve into new strains, the amino acid sequence coding for the surface glycoprotein (“Spike protein”) is diverging from the originally identified strain upon which all currently available COVID-19 vaccines were designed. Given the global scale of the pandemic, a vast amount of data has been collected on the immune response induced by SARS-CoV-2 vaccines, the effect of this response on each strain and the efficacy of the vaccines in each context.<sup>1-7,28</sup> Both components of the adaptive immune system, T cells and antibody-producing B cells, have been well-characterized in the setting of SARS-CoV-2 infection or vaccination<sup>8-15</sup>.

The SARS-CoV-2 virus appears to violate the dogma that vaccine efficacy is primarily determined by neutralization from antibodies. Despite the observation that circulating variants escape most of the neutralization induced by the vaccines, the efficacy of the available SARS-CoV-2 vaccines has remained high.<sup>2,3,6</sup> The SARS-CoV-2 vaccines induce a more robust T-cell response than expected,<sup>16,17</sup> which has played a role in preventing severe (or even symptomatic) disease in vaccine recipients.<sup>18</sup> The T-cell response has been only mildly affected by the mutations in the variants.<sup>19,20</sup> Surprisingly, the T-cell response appears to partially offset the abrogation of neutralization from antibodies and helps control infection as well (Figure 1), with recent research demonstrating direct influence of cytotoxic T-cell responses to some antigens leading to milder disease.<sup>14,12,21</sup>

Early data regarding Omicron, a new SARS-CoV-2 variant which emerged in November 2021, suggest rapid worldwide spread.<sup>22</sup> The Omicron variant encodes 34 mutations in the *spike* gene as compared to the original SARS-CoV-2 strain used to formulate the current set of available vaccines. For comparison, the current and previous widely circulated variants contained 12 or fewer mutations in the *spike* gene. The neutralizing antibody response generated by the currently available SARS-CoV-2 vaccines was reduced against the previous Alpha, Beta, and Delta variants and several of the key efficacy-reducing mutations are conserved in Omicron. Considering the continued acquisition of mutations, it is expected the antibody response will be further diminished against Omicron.<sup>23</sup> In contrast, prior work has shown that the vast majority of the cellular immune response induced by current vaccines remains on target against widely circulating variants including Alpha, Beta, and Delta.<sup>24</sup> The substantially larger set of mutations in the spike protein in the Omicron variant increases the potential to avoid the cellular immune response induced by SARS-CoV-2 vaccines. Here, we assess the fraction of both the HLA class I and class II-restricted cellular immune response impacted by the mutations in the Omicron variant.

## Results

As part of the ImmuneCODE project, we have mapped the cellular immune response to SARS-CoV-2. This mapping includes resolution of 199 class I epitopes across sSpike protein, with resolution to exact n-mers or short overlapping stretches, as well as resolution of the full set of class II epitopes to the level of approximately 50 amino acid windows. Additionally, we have accumulated data from immunosequencing of the T-cell receptor repertoires from over 5,000 individuals following SARS-CoV-2 infection or vaccination. Combining these two sources of data

allows us to determine the relative fraction of T cells induced by each antigen as well as the HLA association of each T-cell clone.

Utilizing these data and a few simple assumptions, we are able to assess the impact of the mutations on cellular immune response. The primary assumption is that the mutations were not selected to avoid the cellular immune response; confidence in this assumption is supported by the diversity of HLA molecules that present the epitopes. To test this assumption, we reviewed our available data to identify if there were any significant enrichment of class I or II HLAs for prior variants and for Omicron looking across all antigen mutations; we did not observe any statistically significant enrichments from the Delta and Omicron variants within spike; however, a class II HLA association (DQA1\*05:05+DQB1\*03:01) connected to a nucleocapsid phosphoprotein antigen mutation (R203M in Delta and R203K/G204R in Omicron) was identified from both repertoire-focused and antigen-focused analyses. The second assumption relates to the probability that a mutation in an epitope or flanking sequence either prevents the epitope from being presented or affects binding, rendering vaccine- or infection-induced TCRs off-target. As a conservative assumption, we estimate any coding mutation spanning a presented epitope would impact all binding of TCRs to that epitope.

Given these assumptions, we determined that the mutations in the Omicron variant impact as much as 21% of the class I-restricted cellular immune response and 33% of the class II-restricted cellular immune response induced by SARS-CoV-2 vaccines (Figure 2, averaged projection in Figure 1B). Some mutations may not impact antigen presentation or recognition by certain TCRs, but this assessment score is an upper bound on the impact that can be inferred from available experimental data. For T-cell responses targeted to non-spike regions that are induced by natural infection, the impact on the Omicron variant is miniscule ( $\leq 5\%$ ), because the mutations are concentrated in spike and rare in the rest of the genome.

## Discussion

We have estimated the impact of Omicron mutations on the binding of the vaccine-induced cellular immune response, both for CD4<sup>+</sup> and CD8<sup>+</sup> T cells. Although there is a measurable reduction in on-target T-cell memory, over two-thirds of the cellular immune response is expected to remain preserved. For individuals with prior SARS-CoV-2 infection with other variants, we expect a similar reduction in the spike-specific cellular immune memory. However, the mutations in Omicron are highly concentrated in the spike protein.<sup>25</sup> As the number of mutations impacting T-cell epitopes in other genes of SARS-CoV-2 is comparable to prior variants with over 95% conservation, we expect almost no abrogation of the cellular immune response outside of the spike region. In particular, the CD8<sup>+</sup> T-cell response to natural SARS-CoV-2 infection is distributed across the full viral genome and is expected to remain well-directed against Omicron regardless of which variant was responsible for the natural infection.

It remains unresolved whether the T-cell response to SARS-CoV-2 can prevent initial, symptomatic, mild, and/or severe infection. The present dogma is that T cells can prevent severe and possibly mild COVID-19 illness but likely do not prevent initial infection.<sup>26-27</sup>

However, these considerations may be less relevant in the context of vaccine-associated prevention of SARS-CoV-2 transmission and symptomatic control. For example, it is conceivable that a mucosal T-cell response could eliminate virus-infected cells along the respiratory tract sufficiently enough that an individual may experience mild or asymptomatic illness with reduced or absent risk of transmission to others and lower likelihood of testing positive for SARS-CoV-2 infection. In other words, given a robust T-cell response, the dogma that antibodies can prevent infection while T cells play a role in resolving infection may not be a meaningful distinction.

The differences in the protective efficacy of SARS-CoV-2 vaccines predicted from evaluation of humoral vs. cellular immune responses underscore the importance of T-cell testing as a reliable measure of vaccine-induced immune protection, particularly in the setting of new and emerging viral variants that can evade immune surveillance. The recent development of a high-throughput, scalable assay to measure the cellular immune response to SARS-CoV-2 empowers such an approach to measuring immune protection against variant infection, with important implications for identifying individuals and groups who may be at high risk of severe illness<sup>36-39</sup>.

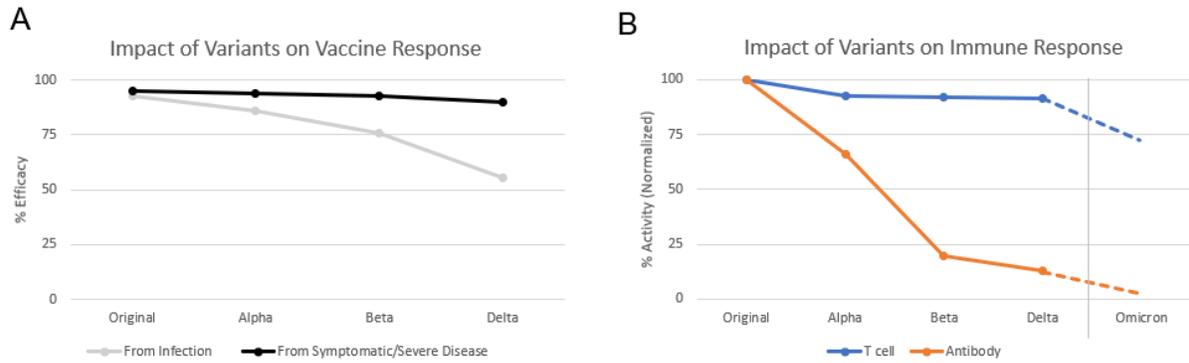


Figure 1A displays the apparent impact of variants of SARS-CoV-2 on the efficacy of vaccines, splitting out reported efficacy from infection from reported efficacy for severe or symptomatic disease. 1B displays the apparent impact of variants on two aspects of the immune response towards the spike protein, from T cells and from neutralizing antibody titers (normalized to the peak of response expected against the initial strain of SARS-CoV-2). Projections are made for Omicron based on early evidence and the analysis performed here. Both panels aggregate data from multiple publications and vaccines/antibody tests to give a representative view of trajectories.

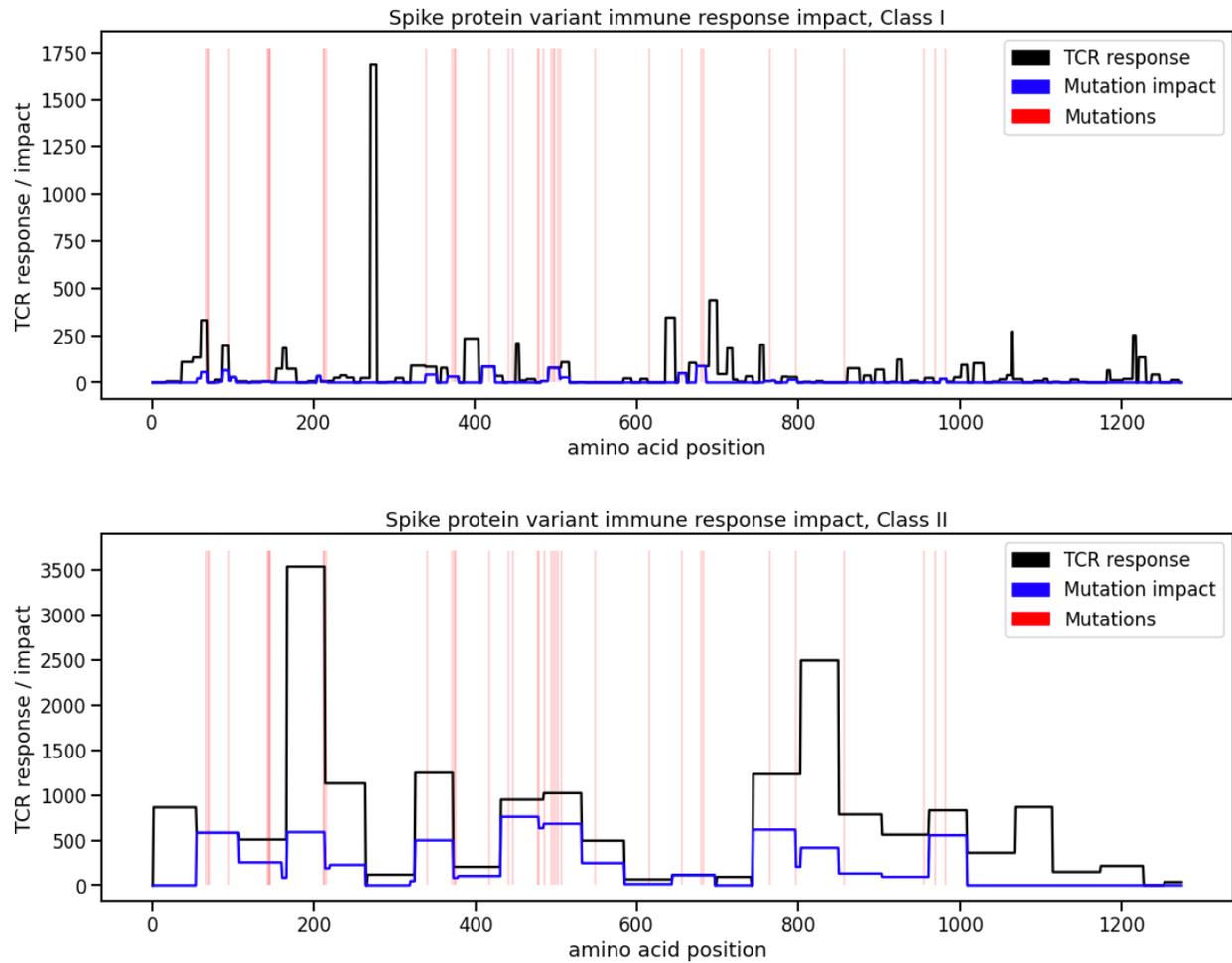


Figure 2 displays the mapping of the T-cell epitopes, the Omicron mutations and the relative size of the T-cell response to each epitope range in the population. We have generated an impact score that combines these variables to estimate the amount of the cellular immune response that is off-target within each epitope window when challenged with Omicron.

## **Methods**

### ***Meta-analysis of vaccine efficacy***

Vaccine efficacy estimates from literature were gathered for BNT162b2 = Pfizer,<sup>1,2,3,28</sup> mRNA-1273 = Moderna,<sup>3,4,28</sup> and Ad26.COVS = Janssen vaccines,<sup>5,6</sup> including the registrational studies run by these vaccine makers and real-world large scale efficacy studies organized by others. Separate measures of protection against symptomatic or severe infection, or protection from any infection, were taken based off endpoints reported across studies. Recognizing vaccine efficacy changes with time, outputs focused on first 3 months after full vaccine administration were prioritized in aggregating data for comparison to variants.

### ***Meta-analysis of antibody activity against variants***

Neutralizing antibody and other antibody readouts were gathered from multiple published studies, including studies that included DFT (IC50) measures to allow some comparison across vaccines, primarily from Yu et al (2021)<sup>29</sup> and supported by Sadoff et al (2021)<sup>6</sup>, Jackson et al (2020)<sup>30</sup>, Folegatti et al (2020)<sup>31</sup>, and Walsh et al (2020)<sup>32</sup>. The fold change of neutralizing antibody response to these variants compared to the original strain was gathered for each vaccine from other publications: BNT162b2 (Pfizer) from Anichini et al (2021)<sup>8</sup>, Edara et al (2021)<sup>9</sup>, with support from Tada et al (2021)<sup>11</sup> and Garcia-Beltran et al (2020)<sup>33</sup>; for mRNA-1273 (Moderna) from Wu et al (2021)<sup>10</sup>, Edara et al (2021)<sup>9</sup>, with support from Wang et al (2021)<sup>34</sup> and Garcia-Beltran et al (2020)<sup>33</sup>; for Ad26.COVS (Janssen), Tada et al (2021)<sup>11</sup> and Alter et al (2021)<sup>12</sup>, with support from Naranbhai et al (2021)<sup>35</sup>. While there was some missing data for given vaccines and variants, the meta-analysis revealed consistent trends in drop-offs for variants when averaging the fold-change results.

### ***Mutation identification for Omicron***

172 published sequences for individuals infected with Omicron in GISAID (available on Nov 30, 2021; <https://www.gisaid.org/hcov19-variants/>) were aligned and mutations seen in over 75% of the individuals retained as the reference sequence for Omicron. This preliminary definition has remained consistent with the now >1,000 sequences available for analysis.

### ***Analysis of T cell activity against variants including Omicron***

To estimate the proportion of the cellular immune response impacted by the Omicron mutations, we overlapped the Omicron spike mutation list with each antigen using a convalescent COVID donor-based MIRA/antigen mapping dataset in ImmuneCODE and its associated T cell count as a measure of immunogenicity. For individually addressed antigens in CD8<sup>+</sup> T cells, a peptide with any mutation was considered to remove 100% of the response for that antigen. For multiply addressed antigens in CD4<sup>+</sup> or CD8<sup>+</sup> T cells, we calculated the proportion of the peptides within each set of antigens presented together that contain one or more Omicron mutations and used that fraction to calculate an impact score. Across all antigen

positions, we then estimated the total cellular immune impact over that region as the number of T cells responding multiplied by the proportion of the cellular immune response impacted, shown as the blue lines in Figure 2. The final estimates of CD4<sup>+</sup> and CD8<sup>+</sup> T cell reduced efficacy reflect the impacted count of T cells over the original count of T cells for all spike antigens.

## References:

1. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, Perez JL, Pérez Marc G, Moreira ED, Zerbini C, Bailey R, Swanson KA, Roychoudhury S, Koury K, Li P, Kalina WV, Cooper D, Frenck RW Jr, Hammitt LL, Türeci Ö, Nell H, Schaefer A, Ünal S, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med.* 2020 Dec 31;383(27):2603-2615. doi: 10.1056/NEJMoa2034577. Epub 2020 Dec 10. PMID: 33301246; PMCID: PMC7745181.
2. Lopez Bernal J, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, Stowe J, Tessier E, Groves N, Dabrera G, Myers R, Campbell CNJ, Amirthalingam G, Edmunds M, Zambon M, Brown KE, Hopkins S, Chand M, Ramsay M. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. *N Engl J Med.* 2021 Aug 12;385(7):585-594. doi: 10.1056/NEJMoa2108891. Epub 2021 Jul 21. PMID: 34289274; PMCID: PMC8314739.
3. Tang P, Hasan MR, Chemaitelly H, Yassine HM, Benslimane FM, Al Khatib HA, AlMukdad S, Coyle P, Ayoub HH, Al Kanaani Z, Al Kuwari E, Jeremijenko A, Kaleeckal AH, Latif AN, Shaik RM, Abdul Rahim HF, Nasrallah GK, Al Kuwari MG, Al Romaihi HE, Butt AA, Al-Thani MH, Al Khal A, Bertollini R, Abu-Raddad LJ. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the SARS-CoV-2 Delta variant in Qatar. *Nat Med.* 2021 Nov 2. doi: 10.1038/s41591-021-01583-4. Epub ahead of print. PMID: 34728831.
4. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, Diemert D, Spector SA, Rouphael N, Creech CB, McGettigan J, Khetan S, Segall N, Solis J, Brosz A, Fierro C, Schwartz H, Neuzil K, Corey L, Gilbert P, Janes H, Follmann D, Marovich M, Mascola J, Polakowski L, Ledgerwood J, Graham BS, Bennett H, Pajon R, Knightly C, Leav B, Deng W, Zhou H, Han S, Ivarsson M, Miller J, Zaks T; COVE Study Group. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med.* 2021 Feb 4;384(5):403-416. doi: 10.1056/NEJMoa2035389. Epub 2020 Dec 30. PMID: 33378609; PMCID: PMC7787219.
5. Corchado-Garcia J, Zemmour D, Hughes T, Bandi H, Cristea-Platon T, Lenehan P, Pawlowski C, Bade S, O'Horo JC, Gores GJ, Williams AW, Badley AD, Halamka J, Virk A, Swift MD, Wagner T, Soundararajan V. Analysis of the Effectiveness of the Ad26.COVS Adenoviral Vector Vaccine for Preventing COVID-19. *JAMA Netw Open.* 2021 Nov 1;4(11):e2132540. doi: 10.1001/jamanetworkopen.2021.32540. PMID: 34726743; PMCID: PMC8564583.
6. Sadoff J, Le Gars M, Shukarev G, Heerwegh D, Truyers C, de Groot AM, Stoop J, Tete S, Van Damme W, Leroux-Roels I, Berghmans PJ, Kimmel M, Van Damme P, de Hoon J, Smith W, Stephenson KE, De Rosa SC, Cohen KW, McElrath MJ, Cormier E, Scheper G, Barouch DH, Hendriks J, Struyf F, Douoguih M, Van Hoof J, Schuitemaker H. Interim Results of a Phase 1-2a Trial of Ad26.COVS Covid-19 Vaccine. *N Engl J Med.* 2021 May 13;384(19):1824-1835. doi: 10.1056/NEJMoa2034201. Epub 2021 Jan 13. PMID: 33440088; PMCID: PMC7821985.
7. Falsey AR, Sobieszczyk ME, Hirsch I, Sproule S, Robb ML, Corey L, Neuzil KM, Hahn W, Hunt J, Mulligan MJ, McEvoy C, DeJesus E, Hassman M, Little SJ, Pahud BA, Durbin A, Pickrell P, Daar ES, Bush L, Solis J, Carr QO, Oyedele T, Buchbinder S, Cowden J, Vargas SL, Benavides AG, Call R, Keefer MC, Kirkpatrick BD, Pullman J, Tong T, Isaacs MB, Benkeser D, Janes HE, Nason MC, Green

- JA, Kelly EJ, Maaske J, Mueller N, Shoemaker K, Takas T, Marshall RP, Pangalos MN, Villafana T, Gonzalez-Lopez A; AstraZeneca AZD1222 Clinical Study Group. Phase 3 Safety and Efficacy of AZD1222 (ChAdOx1 nCoV-19) Covid-19 Vaccine. *N Engl J Med*. 2021 Sep 29;NEJMoa2105290. doi: 10.1056/NEJMoa2105290. Epub ahead of print. PMID: 34587382; PMCID: PMC8522798.
8. Anichini G, Terrosi C, Gori Savellini G, Gandolfo C, Franchi F, Cusi MG. Neutralizing Antibody Response of Vaccinees to SARS-CoV-2 Variants. *Vaccines (Basel)*. 2021 May 18;9(5):517. doi: 10.3390/vaccines9050517. PMID: 34069852; PMCID: PMC8157345.
  9. Edara VV, Lai L, Sahoo MK, Floyd K, Sibai M, Solis D, Flowers MW, Hussaini L, Ciric CR, Bechnack S, Stephens K, Mokhtari EB, Mudvari P, Creanga A, Pegu A, Derrien-Colemyn A, Henry AR, Gagne M, Graham BS, Wrammert J, Douek DC, Boritz E, Pinsky BA, Suthar MS. Infection and vaccine-induced neutralizing antibody responses to the SARS-CoV-2 B.1.617.1 variant. *bioRxiv [Preprint]*. 2021 May 10:2021.05.09.443299. doi: 10.1101/2021.05.09.443299. Update in: *N Engl J Med*. 2021 Jul 7;; PMID: 34013272; PMCID: PMC8132229.
  10. Wu K, Werner AP, Moliva JI, Koch M, Choi A, Stewart-Jones GBE, Bennett H, Boyoglu-Barnum S, Shi W, Graham BS, Carfi A, Corbett KS, Seder RA, Edwards DK. mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants. *bioRxiv [Preprint]*. 2021 Jan 25:2021.01.25.427948. doi: 10.1101/2021.01.25.427948. PMID: 33501442; PMCID: PMC7836112.
  11. Tada T, Zhou H, Samanovic MI, Dcosta BM, Cornelius A, Mulligan MJ, Landau NR. Comparison of Neutralizing Antibody Titers Elicited by mRNA and Adenoviral Vector Vaccine against SARS-CoV-2 Variants. *bioRxiv [Preprint]*. 2021 Aug 6:2021.07.19.452771. doi: 10.1101/2021.07.19.452771. PMID: 34312623; PMCID: PMC8312895.
  12. Alter G, Yu J, Liu J, Chandrashekar A, Borducchi EN, Tostanoski LH, McMahan K, Jacob-Dolan C, Martinez DR, Chang A, Anioke T, Lifton M, Nkolola J, Stephenson KE, Atyeo C, Shin S, Fields P, Kaplan I, Robins H, Amanat F, Krammer F, Baric RS, Le Gars M, Sadoff J, de Groot AM, Heerwegh D, Struyf F, Douoguih M, van Hoof J, Schuitemaker H, Barouch DH. Immunogenicity of Ad26.COV2.S vaccine against SARS-CoV-2 variants in humans. *Nature*. 2021 Aug;596(7871):268-272. doi: 10.1038/s41586-021-03681-2. Epub 2021 Jun 9. PMID: 34107529; PMCID: PMC8357629.
  13. Wall EC, Wu M, Harvey R, Kelly G, Warchal S, Sawyer C, Daniels R, Adams L, Hobson P, Hatipoglu E, Ngai Y, Hussain S, Ambrose K, Hindmarsh S, Beale R, Riddell A, Gamblin S, Howell M, Kassiotis G, Libri V, Williams B, Swanton C, Gandhi S, Bauer DL. AZD1222-induced neutralising antibody activity against SARS-CoV-2 Delta VOC. *Lancet*. 2021 Jul 17;398(10296):207-209. doi: 10.1016/S0140-6736(21)01462-8. Epub 2021 Jun 28. PMID: 34197809; PMCID: PMC8238446.
  14. Guerrero G, Picozza M, D'Orso S, Placido R, Pirronello M, Verdiani A, Termine A, Fabrizio C, Giannesi F, Sambucci M, Balice MP, Caltagirone C, Salvia A, Rossini A, Battistini L, Borsellino G. BNT162b2 vaccination induces durable SARS-CoV-2 specific T cells with a stem cell memory phenotype. *Sci Immunol*. 2021 Nov 2:eabl5344. doi: 10.1126/sciimmunol.abl5344. Epub ahead of print. PMID: 34726470.
  15. Parry H, Bruton R, Stephens C, Brown K, Amirthalingam G, Otter A, Hallis B, Zuo J, Moss P. Differential immunogenicity of BNT162b2 or ChAdOx1 vaccines after extended-interval homologous dual vaccination in older people. *Immun Ageing*. 2021 Aug 20;18(1):34. doi: 10.1186/s12979-021-00246-9. PMID: 34416887; PMCID: PMC8377354.
  16. Barouch DH, Stephenson KE, Sadoff J, Yu J, Chang A, Gebre M, McMahan K, Liu J, Chandrashekar A, Patel S, Le Gars M, de Groot AM, Heerwegh D, Struyf F, Douoguih M, van Hoof J, Schuitemaker H. Durable Humoral and Cellular Immune Responses 8 Months after Ad26.COV2.S Vaccination. *N Engl J Med*. 2021 Sep 2;385(10):951-953. doi: 10.1056/NEJMc2108829. Epub 2021 Jul 14. PMID: 34260834; PMCID: PMC8314733.

17. Skelly DT, Harding AC, Gilbert-Jaramillo J, Knight ML, Longet S, Brown A, Adele S, Adland E, Brown H; Medawar Laboratory Team, Tipton T, Stafford L, Mentzer AJ, Johnson SA, Amini A; OPTIC (Oxford Protective T cell Immunology for COVID-19) Clinical Group, Tan TK, Schimanski L, Huang KA, Rijal P; PITCH (Protective Immunity T cells in Health Care Worker) Study Group; C-MORE/PHOSP-C Group, Frater J, Goulder P, Conlon CP, Jeffery K, Dold C, Pollard AJ, Sigal A, de Oliveira T, Townsend AR, Klenerman P, Dunachie SJ, Barnes E, Carroll MW, James WS. Two doses of SARS-CoV-2 vaccination induce robust immune responses to emerging SARS-CoV-2 variants of concern. *Nat Commun.* 2021 Aug 17;12(1):5061. doi: 10.1038/s41467-021-25167-5. PMID: 34404775; PMCID: PMC8371089.
18. Geers D, Shamier MC, Bogers S, den Hartog G, Gommers L, Nieuwkoop NN, Schmitz KS, Rijsbergen LC, van Osch JAT, Dijkhuizen E, Smits G, Comvalius A, van Mourik D, Caniels TG, van Gils MJ, Sanders RW, Oude Munnink BB, Molenkamp R, de Jager HJ, Haagmans BL, de Swart RL, Koopmans MPG, van Binnendijk RS, de Vries RD, GeurtsvanKessel CH. SARS-CoV-2 variants of concern partially escape humoral but not T-cell responses in COVID-19 convalescent donors and vaccinees. *Sci Immunol.* 2021 May 25;6(59):eabj1750. doi: 10.1126/sciimmunol.abj1750. PMID: 34035118.
19. Tarke A, Sidney J, Methot N, Yu ED, Zhang Y, Dan JM, Goodwin B, Rubiro P, Sutherland A, Wang E, Frazier A, Ramirez SI, Rawlings SA, Smith DM, da Silva Antunes R, Peters B, Scheuermann RH, Weiskopf D, Crotty S, Grifoni A, Sette A. Impact of SARS-CoV-2 variants on the total CD4<sup>+</sup> and CD8<sup>+</sup> T cell reactivity in infected or vaccinated individuals. *Cell Rep Med.* 2021 Jul 20;2(7):100355. doi: 10.1016/j.xcrm.2021.100355. Epub 2021 Jul 2. PMID: 34230917; PMCID: PMC8249675.
20. Noh JY, Jeong HW, Kim JH, Shin EC. T cell-oriented strategies for controlling the COVID-19 pandemic. *Nat Rev Immunol.* 2021 Nov;21(11):687-688. doi: 10.1038/s41577-021-00625-9. PMID: 34497383; PMCID: PMC8424399.
21. Peng Y, Felce SL, Dong D, Penkava F, Mentzer AJ, Yao X, Liu G, Yin Z, Chen JL, Lu Y, Wellington D, Wing PAC, Dominey-Foy DCC, Jin C, Wang W, Hamid MA, Fernandes RA, Wang B, Fries A, Zhuang X, Ashley N, Rostron T, Waugh C, Sopp P, Hublitz P, Beveridge R, Tan TK, Dold C, Kwok AJ, Rich-Griffin C, Dejnirattisa W, Liu C, Kurupati P, Nassiri I, Watson RA, Tong O, Taylor CA, Kumar Sharma P, Sun B, Curion F, Revale S, Garner LC, Jansen K, Ferreira RC, Attar M, Fry JW, Russell RA; COMBAT Consortium, Stauss HJ, James W, Townsend A, Ho LP, Klenerman P, Mongkolsapaya J, Sreaton GR, Dendrou C, Sansom SN, Bashford-Rogers R, Chain B, Smith GL, McKeating JA, Fairfax BP, Bowness P, McMichael AJ, Ogg G, Knight JC, Dong T. An immunodominant NP<sub>105-113</sub>-B\*07:02 cytotoxic T cell response controls viral replication and is associated with less severe COVID-19 disease. *Nat Immunol.* 2021 Dec 1. doi: 10.1038/s41590-021-01084-z. Epub ahead of print. PMID: 34853448.
22. Graham F. Daily briefing: Omicron was already spreading in Europe. *Nature.* 2021 Dec 1. doi: 10.1038/d41586-021-03610-3. Epub ahead of print. PMID: 34857944.
23. Sandile Cele, Laurelle Jackson, Khadija Khan, David S Khoury, Thandeka Moyo-Gwete, Houriiyah Tegally, Cathrine Scheepers, Daniel Amoako, Farina Karim, Mallory Bernstein, Gila Lustig, Derseree Archary, Muneerah Smith, Yashica Ganga, Zesuliwe Jule, Kajal Reedoy, James Emmanuel San, Shi-Hsia Hwa, Jennifer Giandhari, Jonathan Blackburn, Bernadett I Gosnell, Salim Abdool Karim, Willem Hanekom, NGS-SA, COMMIT-KZN Team, Anne von Gottberg, Jinal Bhiman, Richard Lessells, Mahomed-Yunus S Moosa, Miles Philip Davenport, Tulio de Oliveira, Penny Philip Moore, Alex Sigal. SARS-CoV-2 Omicron has extensive but incomplete escape of Pfizer BNT162b2 elicited neutralization and requires ACE2 for infection. *medRxiv* 2021.12.08.21267417; doi: <https://doi.org/10.1101/2021.12.08.21267417>.

24. Jordan SC, Shin BH, Gadsden TM, Chu M, Petrosyan A, Le CN, Zabner R, Oft J, Pedraza I, Cheng S, Vo A, Ammerman N, Plummer J, Ge S, Froch M, Berg A, Toyoda M, Zhang R. T cell immune responses to SARS-CoV-2 and variants of concern (Alpha and Delta) in infected and vaccinated individuals. *Cell Mol Immunol*. 2021 Nov;18(11):2554-2556. doi: 10.1038/s41423-021-00767-9. Epub 2021 Sep 16. PMID: 34531555; PMCID: PMC8443898.
25. Chen J, Wang R, Gilby NB, Wei GW. Omicron (B.1.1.529): Infectivity, vaccine breakthrough, and antibody resistance. *ArXiv [Preprint]*. 2021 Dec 1:arXiv:2112.01318v1. PMID: 34873578; PMCID: PMC8647651.
26. Tan AT, Linster M, Tan CW, Le Bert N, Chia WN, Kunasegaran K, Zhuang Y, Tham CYL, Chia A, Smith GJD, Young B, Kalimuddin S, Low JGH, Lye D, Wang LF, Bertoletti A. Early induction of functional SARS-CoV-2-specific T cells associates with rapid viral clearance and mild disease in COVID-19 patients. *Cell Rep*. 2021 Feb 9;34(6):108728. doi: 10.1016/j.celrep.2021.108728. Epub 2021 Jan 21. PMID: 33516277; PMCID: PMC7826084.
27. Ledford H. How 'killer' T cells could boost COVID immunity in face of new variants. *Nature*. 2021 Feb;590(7846):374-375. doi: 10.1038/d41586-021-00367-7. PMID: 33580217.
28. Cohn BA, Cirillo PM, Murphy CC, Krigbaum NY, Wallace AW. SARS-CoV-2 vaccine protection and deaths among US veterans during 2021 [published online ahead of print, 2021 Nov 4]. *Science*. 2021;eabm0620. doi:10.1126/science.abm0620
29. Yu S, Chen K, Fang L, et al. Comparison and Analysis of Neutralizing Antibody Levels in Serum after Inoculating with SARS-CoV-2, MERS-CoV, or SARS-CoV Vaccines in Humans. *Vaccines (Basel)*. 2021;9(6):588. Published 2021 Jun 2. doi:10.3390/vaccines9060588
30. Jackson LA, Anderson EJ, Roupheal NG, et al. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. *N Engl J Med*. 2020;383(20):1920-1931. doi:10.1056/NEJMoa2022483
31. Folegatti PM, Ewer KJ, Aley PK, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial [published correction appears in *Lancet*. 2020 Aug 15;396(10249):466] [published correction appears in *Lancet*. 2020 Dec 12;396(10266):1884]. *Lancet*. 2020;396(10249):467-478. doi:10.1016/S0140-6736(20)31604-4
32. Walsh EE, Frenck RW Jr, Falsey AR, et al. Safety and Immunogenicity of Two RNA-Based Covid-19 Vaccine Candidates. *N Engl J Med*. 2020;383(25):2439-2450. doi:10.1056/NEJMoa2027906
33. Garcia-Beltran WF, Lam EC, Astudillo MG, et al. COVID-19-neutralizing antibodies predict disease severity and survival. *Cell*. 2021;184(2):476-488.e11. doi:10.1016/j.cell.2020.12.015
34. Wang P, Nair MS, Liu L, et al. Antibody Resistance of SARS-CoV-2 Variants B.1.351 and B.1.1.7. Preprint. *bioRxiv*. 2021;2021.01.25.428137. Published 2021 Feb 12. doi:10.1101/2021.01.25.428137
35. Naranbhai V, Garcia-Beltran WF, Chang CC, et al. Comparative immunogenicity and effectiveness of mRNA-1273, BNT162b2 and Ad26.COVS COVID-19 vaccines. Preprint. *medRxiv*. 2021;2021.07.18.21260732. Published 2021 Oct 13. doi:10.1101/2021.07.18.21260732
36. Elyanow R, Snyder TM, Dalai SC, et al. T-cell receptor sequencing identifies prior SARS-CoV-2 infection and correlates with neutralizing antibody titers and disease severity. Preprint. *medRxiv*. 2021;2021.03.19.21251426. Published 2021 Mar 22. doi:10.1101/2021.03.19.21251426
37. Sudeb C, Dalai, Jennifer N. Dines, Thomas M. Snyder, Rachel M. Gittelman, Tera Eerkes, Pashmi Vaney, Sally Howard, Kipp Akers, Lynell Skewis, Anthony Monteforte, Pam Witte, Cristina Wolf, Hans Nesse, Megan Herndon, Jia Qadeer, Sarah Duffy, Emily Svejnoha, Caroline Taromino, Ian M. Kaplan, John Alsobrook, Thomas Manley, Lance Baldo. Clinical Validation of a Novel T-cell Receptor Sequencing Assay for Identification of Recent or Prior SARS-CoV-2 Infection *medRxiv* 2021.01.06.21249345; doi: <https://doi.org/10.1101/2021.01.06.21249345>

38. Snyder TM, Gittelman RM, Klinger M, et al. Magnitude and Dynamics of the T-Cell Response to SARS-CoV-2 Infection at Both Individual and Population Levels. Preprint. *medRxiv*. 2020;2020.07.31.20165647. Published 2020 Sep 17. doi:10.1101/2020.07.31.20165647
39. Rachel M. Gittelman, Enrico Lavezzo, Thomas M. Snyder, H. Jabran Zahid, Rebecca Elyanow, Sudeb Dalai, Ilan Kirsch, Lance Baldo, Laura Manuto, Elisa Franchin, Claudia Del Vecchio, Fabio Simeoni, Jessica Bordini, Nicola I. Lorè, Dejan Lazarevic, Daniela M. Cirillo, Paolo Ghia, Stefano Toppo, Jonathan M. Carlson, Harlan S. Robins, Giovanni Tonon, Andrea Crisanti. Diagnosis and Tracking of Past SARS-CoV-2 Infection in a Large Study of Vo', Italy Through T-Cell Receptor Sequencing. *medRxiv* 2020.11.09.20228023; doi: <https://doi.org/10.1101/2020.11.09.20228023>

### **Data Availability**

As part of the ImmuneCODE data resource (Nolan 2020), the COVID-19 MIRA data and COVID-19 study immunosequencing data are freely available for analysis and download from the Adaptive Biotechnologies immuneACCESS site under the immuneACCESS Terms of Use at <https://clients.adaptivebiotech.com/pub/covid-2020>. This resource is being updated with the additional vaccine repertoire and other data included in this analysis.

### **Acknowledgments**

The ImmuneCODE data resource that underlies this analysis paper is the result of collaboration among many individuals and organizations working together to advance global understanding of SARS-CoV-2 and COVID-19. We are grateful for the support and participation of all our partners. We are especially grateful for the generosity of the participants who donated blood for this and other studies.

We would like to thank Rachel Gittelman and Mark Klinger for helpful discussions and review of some of these findings. We would like to thank Kristin MacIntosh for editorial support.