Summary of Major Literature Related to COVID-19 (October 21, 2021)

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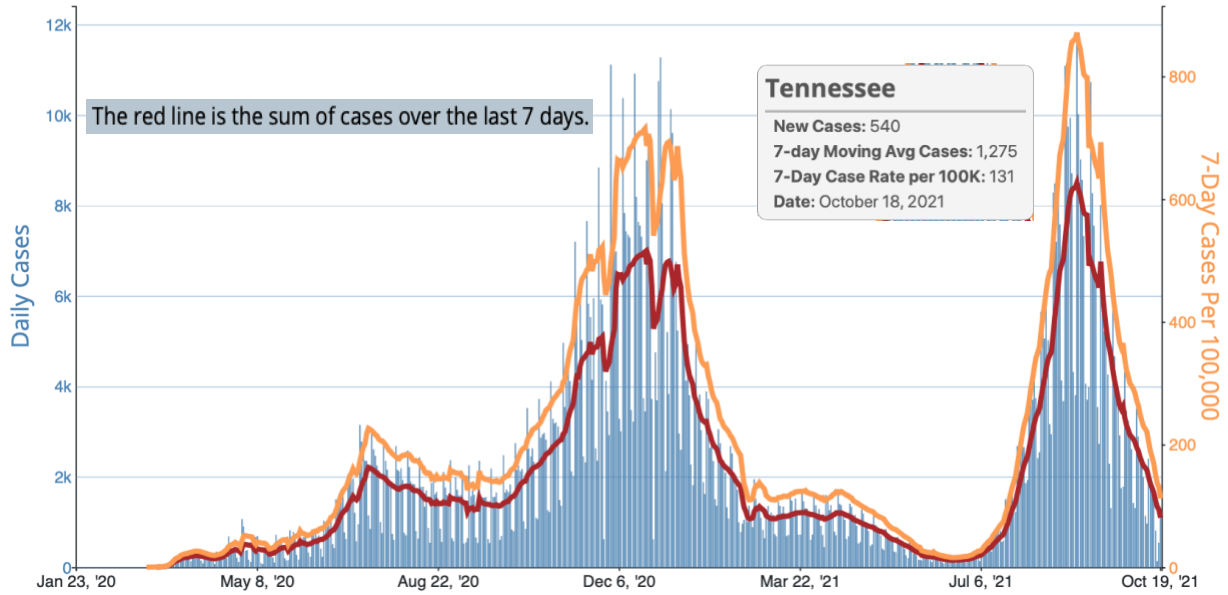
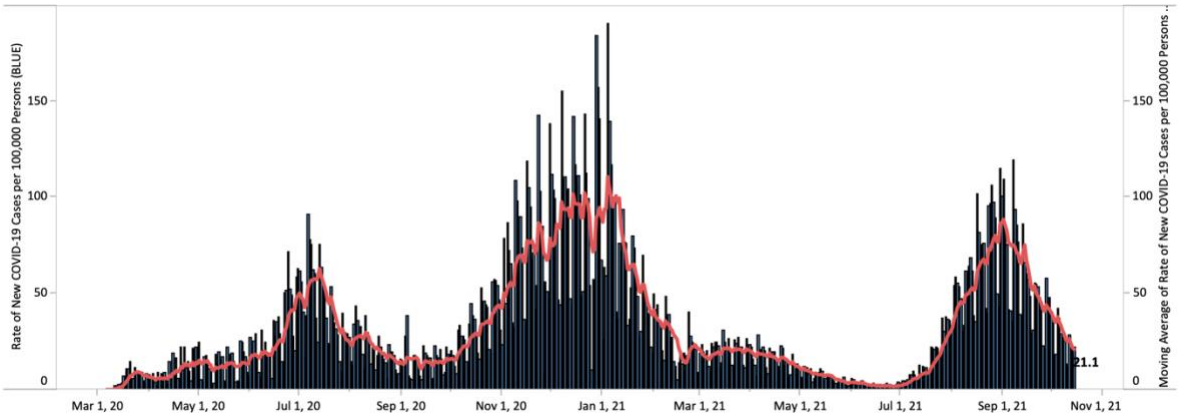
***This is informational and not intended to create variance from VUMC policies/guidance**

Tennessee

Daily Trends in Number of Cases and 7-Day Cumulative Incidence Rate of COVID-19 Cases in Tennessee Reported to CDC, per 100,000 population.



Davidson county



EPIDEMIOLOGY

Post-acute COVID-19 syndrome (Long-COVID)

1. **Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study.** Evans et al. Lancet Respir Med. 7 Oct 2021.

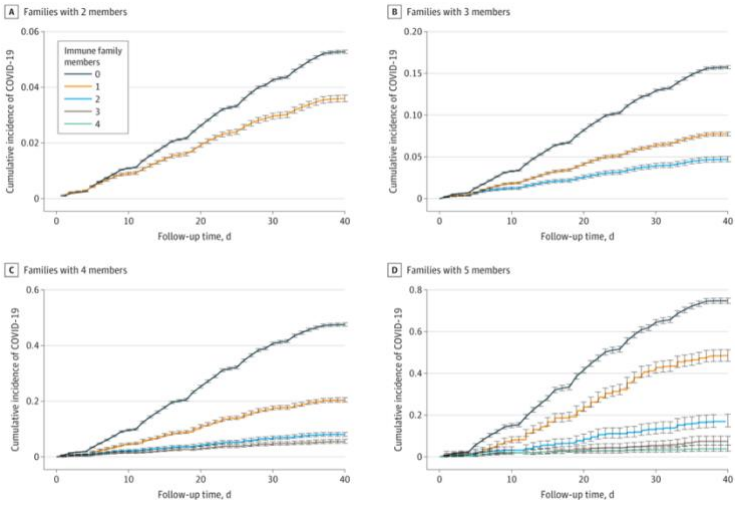
- This is the first report from the PHOSP-COVID prospective follow-up consortium study, which was established to examine long-term health outcomes among adults discharged from hospital in the UK with a clinical diagnosis of COVID-19 between March-Nov 2020
- Follow up research visits to record clinical data and symptoms and to conduct physiological and biochemical testing occurred between 2 and 7 months after discharge
- This analysis included 1077 individuals
    - Mean age 58y, 36% female, 69% White race, 27% had received mechanical ventilation, 50% had 2+ comorbidities

- Primary outcomes were health status and patient-perceived recovery using validated questionnaires
- At follow up (median 5.9 months):
    - 29% of participants felt fully recovered
    - 20% had a new disability
    - 19% experienced a health-related change in employment status
    - 93% had at least one persistent symptom, with a median of 9 symptoms; most common were muscle aches, fatigue, physical slowing down, impaired sleep quality, joint pain/swelling, limb weakness, breathlessness, short-term memory loss, slowed thinking
- Four post-hoc "recovery phenotypes" were identified using cluster analysis, with different severities of mental and physical health impairment; cognitive impairment was independent of the four clusters
- Factors related to worse recovery were female sex, 2+ comorbidities, and requiring invasive mechanical ventilation during hospitalization and suggestively middle age (40-59y) and BMI≥30
- Limitations: Potential selection biases in both directions (most severely affected patients may be underrepresented or more willing to participate); no data on health status prior to COVID-19; unknown whether the post-hoc cluster phenotypes have different underlying mechanisms or justify stratified post-hospital care
- Implications: This consortium study report confirms a large burden of symptoms persisting at 5 months after COVID-19 hospitalization; while likelihood of recovery in this hospitalized cohort is lower than that reported among those with less severe COVID-19 illness, severity of the acute illness was inconsistently related to severity of persistent health impairments, suggesting that post-hospital care should include symptom assessment and should not be limited to those who received ventilatory support

Family transmission

2. **Association Between Risk of COVID-19 Infection in Nonimmune Individuals and COVID-19 Immunity in Their Family Members.** Nordstrom et al. JAMA Intern Med. 11 Oct 2021.

- Nationwide registry-based cohort study of incident COVID-19 infection from April 15 to May 26, 2021 among non-immune members of mixed immunity families, which represent a high-risk transmission setting
- Analysis included almost 1.8 million individuals from 814,806 families, with 2 to 5 family members each; immunity was defined as either a prior natural COVID-19 infection or full vaccination before the index data
- During mean (range) follow-up of 26.3 (1-40) days, 5.7% (88,797/1,549,989) of nonimmune family members were diagnosed with COVID-19



- There was a significant inverse dose-response association between the number of immune family members and the risk of incident COVID-19 infection in nonimmune family members (see Figure)
    - Compared to families with 0 immune family members, risk reductions were 45 to 61%, 75 to 86%, 91 to 94%, and 97% (all $P < .001$) in families with 1, 2, 3 or 4 immune family members, respectively
    - Results were similar for the outcome of severe COVID-19 infection requiring hospitalization

    - Similar pattern of risk reduction was observed in sensitivity analyses in which immunity was restricted to that acquired from previous infection (vaccinated individuals excluded)
- Limitations: Absence of a mandatory quarantine in Sweden may limit generalizability of estimates; study period prior to Delta variant predominance; most of the immunity in family members was due to natural infection, so sample size was insufficient to draw conclusions specifically for those who had received 2 doses of vaccine
- Implications: Vaccination is important not only for individual protection but also for reducing infection within families that include non-immune individuals; these data may have important implications for vaccination strategies in countries with limited vaccine supply

Medical care disruption

3. **Effect of COVID-19 pandemic lockdowns on planned cancer surgery for 15 tumour types in 61 countries: an international, prospective, cohort study.** COVIDSurg Collaborative. Lancet Oncology. 5 Oct 2021. (NCT04384926).

- Study compared delivery of elective cancer surgery during periods of lockdown versus light restriction during the early stages of the pandemic
- Cohort study of 20,006 adult patients from 466 hospitals in 61 countries (including high-income, UMIC and LMIC) with 15 cancer types who had a decision for curative surgery during the pandemic and were followed until date of surgery or end of follow up (Aug 31, 2020)
    - Primary outcome was "non-operation rate", or proportion of patients who did not undergo planned surgery
    - Median follow up 23 weeks
- Proportion of patients awaiting surgery in full lockdowns was higher in UMICs and LMICs than in high-income countries
- 2003 (10%) patients did not receive surgery, all with a COVID-19 related reason for non-operation
    - After multivariable adjustment, both moderate (HR 0.81; 95% CI 0.77-0.84) and full lockdowns (HR 0.51; 95% CI 0.50-0.53) were associated with a lower likelihood of receiving planned surgery compared to light restrictions
    - Surgery beyond 12 weeks from diagnosis in patients without neoadjuvant therapy increased from 9.1% in light restrictions, to 10.4% in moderate lockdowns, to 23.8% in full lockdowns
- Being in an LMIC, increasing frailty, comorbidity, and having advanced disease were all independently associated with increased likelihood of non-operation
- Limitations: Relatively short follow up; definition of "lockdown" may not capture all policy changes; may be additional specialty-specific implications not addressed in this study
- Implications: One in seven patients in regions with full lockdowns did not undergo planned cancer surgery and experienced longer preoperative delays; these delays and non-operations may adversely impact long-term survival; policy implications include consideration of protected elective surgical pathways and staffing during a pandemic, particularly in LMIC settings, as well as enhanced surveillance for metastatic disease

VACCINES

Effectiveness in adolescents

4. **Effectiveness of Pfizer-BioNTech mRNA Vaccination Against COVID-19 Hospitalization Among Persons Aged 12–18 Years — United States, June–September 2021**. Olson et al (**Halasa NB, VUMC author**). MMWR. 19 Oct 2021.

- Real-world study of effectiveness of 2 doses of Pfizer-BioNTech vaccine against COVID-19 hospitalization among adolescents 12-18y at 19 pediatric hospitals in 16 states, June 1-Sept 30, 2021

- Test-negative case-control design, included 179 case patents hospitalized with symptomatic confirmed COVID-19 and 285 hospitalized controls without COVID-19
    - Median age 15y; 72% had ≥1 underlying condition, including obesity; 68% attended in-person school; 61% of case-patients were from the South
    - Compared to controls, case-patients were significantly more likely to have diabetes (12% vs. 5%) and to reside in areas with higher social vulnerability index scores
    - Partially vaccinated patients were excluded
- 3% of case-patients and 33% of controls were vaccinated
    - VE against COVID-19 hospitalization was 93% (95% CI 83%-97%)
    - VE was similar for age 12-15y (91%) and 16-18y (94%)
    - All 77 case-patients admitted to ICU, all 29 critically ill (requiring life support) case-patients, and both deaths occurred among unvaccinated
- Limitations: Small sample size precluded assessment of VE by underlying conditions
- Implications: Real world evidence during the time of Delta variant predominance demonstrates that vaccination of adolescents provides strong protection against severe COVID-19
- **See also: Effectiveness of BNT162b2 Vaccine against Delta Variant in Adolescents.** Reis et al. NEJM. 20 Oct 2021.
    - Study of 94,354 vaccinated Israeli adolescents and matched controls with no prior COVID-19 infection, June to Sept 2021; median follow up 27 days
    - Vaccine effectiveness against infection was 90% (95% CI 88-92%) and against symptomatic COVID-19 was 93% (95% CI 88-97%) on days 7 to 21 after second dose

Influenza/COVID-19 (animal model)

5. **Increased lethality in influenza and SARS-CoV-2 coinfection is prevented by influenza immunity but not SARS-CoV-2 immunity**. Achdout et al. Nature Communications. 5 Oct 2021.

- Examined the disease outcome of influenza A virus (IAV) and SARS-CoV-2 co-infection in K18-hACE2 mouse model (and in supplemental data, using the hACE2-expressing human Ad5 mice)
- In a susceptibility assay comparing K18-hACE2 mice infected with IAV and then infected with SARS-CoV2 to mice infected with SARS-CoV-2 alone or IAV alone
    - If SARS-CoV2 was administered 2 dpIi (days post influenza infection) there was significant susceptibility (more weight loss and almost complete mortality by 8 dpIi). This becomes the time point they focused on for subsequent studies
    - A significant increase in the IAV RNA levels was observed in the lungs of the coinfected mice at 4 dpIi, but not at 6 dpIi; significant increase in the IAV RNA levels in nasal turbinate of the coinfected mice at 4 dpIi and 6 dpIi, compared to those in the mice with IAV infection alone
    - SARS-CoV-2 load was reduced in the coinfected mice compared to that in the SARS-CoV-2-infected mice in both the lungs and the N.T. (not significantly) at 4 and 6 dpIi
    - Co-infected mice did have exacerbated lung pathology including severe necrosis of the bronchiolar epithelium and infiltration of PMNs and lymphocytes and involvement of the lung parenchyma
    - IAV and SARS-CoV-2 coinfection resulted in a significantly increased gene expression in several genes (complement genes, antigen presentation genes, *Il6, il1a, ccl5*) compared to expression in IAV infection or SARS-CoV2 infection alone
    - SARS-CoV2 infection at 5dpIi still an impacted weight loss negatively but no significant difference in survival was observed; SARS-CoV-2 infection at 8 dpIi had no effect on the body weight or survival rate of the mice
- To assess how immunization would impact disease progression during co-infection, mice were immunized against either influenza or SARS-CoV2 and then challenged with mono-infection or co-infection
    - preexisting immunity to SARS-CoV-2 completely prevented the mortality caused by SARS-CoV-2 infection, but had no effect on the morbidity or mortality caused by coinfection

    - preexisting immunity to IAV prevented the weight and mortality caused by the IAV-SARS-CoV2 co-infection
    - passive transfer of anti-IAV sera to coinfected mice rescued them, indicating the protection was antibody dependent
- Limitations: a previous study showed IAV infection enhanced SARS-CoV2 infectivity - this cannot be compared because the study design was different (lower dose of SARS-CoV2 in this study and no IAV alone arm in that study); small numbers (gene expression data was only on 4 mice per group); does not address the reverse co-infection model where infection with SARS-CoV2 occurs before IAV infection
- Implications: Supports the necessity of seasonal influenza vaccination for reducing the risk of severe influenza/COVID-19 comorbidity during the COVID-19 pandemic

Immune response

6. **Cross-reactive CD4+ T cells enhance SARS-CoV-2 immune responses upon infection and vaccination**. Loyal et al. Science. 8 Oct 2021.

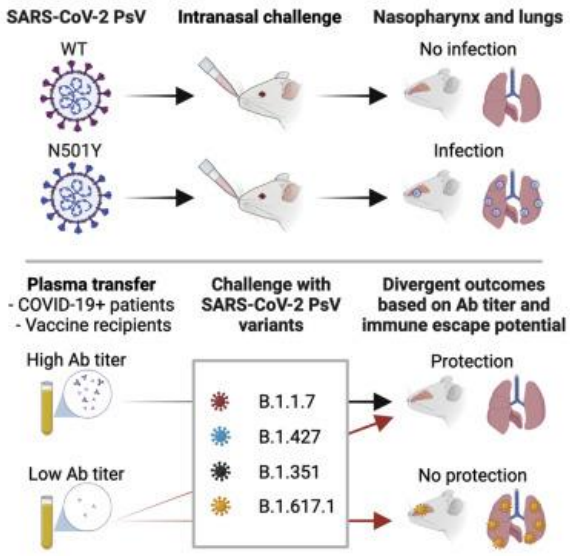
- The functional role of preexisting SARS-CoV-2–cross-reactive and HCoV-reactive CD4+ T cells was performed to determine their contribution to host response; reactivity was defined by increased expression of CD40L and CD137 on CD4+ T cells in response to peptide antigen.
- COVID-19 convalescents (n=59) did not show significantly increased CD4+ T cell reactivity against the nonstructural proteins compared with unexposed individuals (60 tested). The spike S-I (N-terminal portion) and S-II (C-terminal portion) pools alone elicited T cell reactivity in all COVID-19 convalescents and in a subset of unexposed individuals
- Examining SARS-CoV-2 spike–specific CD4+ T cell responses in 568 unexposed individuals and 174 COVID-19 convalescents; Reactivity to the peptide pool from the S-II was more frequent and mostly higher in unexposed individuals compared to the S-I- but the CD137+IFNg+TNF+ cells cross-reactive cells significantly decreased with age; T cell cross-reactivity to peptide pools from the SI part of spike was rare (close to the limit of detection)
- High functional avidity (defined as $CD3^{lo}$ expression after stimulation) was observed in COVID-19 convalescents when PBMCs were stimulated by either S-I or S-II peptide pools; high functional avidity was markedly lower in unexposed individuals compared to convalescents, but higher against the S-II peptide pools compared to S-I peptide pools; high functional avidity in HCoV spike reactive T cells decreases with age
- A universal immunodominant coronavirus peptide located within the fusion peptide domain of spike (S816-830) was recognized by CD4+ T cells in 20% of unexposed individuals (n=568), 50-60% of convalescents (n=174) and 97% of vaccinated individuals (Pfizer/BioNTech); This fusion peptide domain was identified from a peptide pool derived from the HCoV-homologous C-terminal section of the spike glycoprotein
- The healthy, previously unexposed study participants were monitored for primary SARS-CoV-2 infection, 17 cases of acute primary SARS-CoV-2 infection were identified
    - Individuals with preexisting cross-reactive CD4+ T cells showed higher functional avidity and a rapid increase in the magnitude of cross-reactive T cells and anti-spike antibody during their responses
- Humoral and T cell responses against SARS-CoV-2 and HCoV spike glycoproteins were monitored in 31 healthy adults who underwent primary (day 0) and booster (day 21) vaccination with BNT162b2
    - The kinetics of the S-II reactive T cells were that of a secondary response (baseline to day 7); whereas S-I reactive T cells increased later (day 7-14)
    - High-functional-avidity ($CD3^{lo}CD40L^{+}4\text{-}1BB^{+}CD4^{+}$ T cells) increased more rapidly in cross-reactive donors
    - Humoral response to S809-826 (overlapping with S816-830) was detectable as early as 7 days after primary vaccination and this was distinct from the slower anti–SARS-CoV-2-S1-IgG response
- Limitations: A limited number of healthy individuals developed primary infection (17) and all had mild disease not allowing for any stratification of the data based on preexisting cross-reactive T cells and disease
- Implications: The S816-830 peptide may serve as a conserved universal coronavirus target in the S2 portion of spike for both B cells and T cells. Enhancing the immune response to S816-830 may induce efficient protection and should be a focus of future studies.

VARIANTS

Infectivity, immune escape

7. **Ten emerging SARS-CoV-2 spike variants exhibit variable infectivity, animal tropism, and antibody neutralization.** Zhang et al. Communications Biology. 13 Oct 2021.

- Investigation into the infectivity and antigenicity of ten emerging SARS-CoV-2 variants—B.1.1.298, B.1.1.7(Alpha), B.1.351(Beta), P.1(Gamma), P.2(Zeta), B.1.429(Epsilon), B.1.525(Eta), B.1.526-1(Iota), B.1.526-2(Iota), B.1.1.318 (and, 7 corresponding single amino acid mutations in the RBD using SARS-CoV-2 pseudovirus)
- Infectivity of pseudoviruses (PsVs) – of the variants' spikes – was tested in human (Huh-7, and Calu-3), primate (LLC-MK2 and Vero) and mouse ACE2-overexpressing cell lines; results were variable for different cell lines infectivity was compared to the D614G ref. strain; most variants had increased infectivity (<4 fold) in at least 1 cell line



- The L452R single mutation PsV and B.1.526-2 PsV led to increased infectivity in 4 cell lines, but B.1.1.298 variant exhibited significantly decreased infectivity (this variant PsV is shown to have reduced spike expression)
- 14 ACE2s from different species (including pangolin, bat, mink, ferret, civet, ect) were overexpressed in 293 T cells to address animal tropism;
    - the infectivities of the B.1.1.7, B.1.351, P.1, B.1.525, and B.1.1.318 were significantly increased (>4 fold, compared to ref)
    - K417T, K417N, E484K, and N501Y single mutations led to increased infectivity
- Neutralizing activity of 13 mAbs targeting different areas of the receptor-binding domain were tested against the 10 SARS-CoV2 variant PsVs
    - highest escape frequencies were B.1.351 and P.1, which escaped from 10 of 13 mAbs
    - B.1.1.7, against which seven of 13 mAbs
    - B.1.525, P.2, B.1.526-2 (E484K), B.1.1.318 exhibited significantly reduced neutralization activity among 3 mAbs; others only showed reduced susceptibility to one or two mAb
- Sera was collected from several immunized animals to test neutralization against PsV variants [(trimer spike protein (in mice), pseudotyped virus (in guinea pigs), recombinant DNA containing full-length spike gene (in guinea pigs) or purified RBD protein (in horses)]; Of the 10 variants, only B.1.351, P1, P2, B.1.525, B.1.526-2, and B.1.1.318 displayed reduced sensitivities to immunized sera; these variants all harbor the E484K mutation
- Compared convalescent plasma and vaccine elicited sera (two vaccines approved in China) against variants; E484K was found to be the key mutation that caused the most obvious neutralization insensitivity
- Limitations: sample sizes were relatively small for immune sera assays (both animal and human specimens); cell lines may not all be the best representative cell lines to use for infectivity assays
- Implications: mutations in the RBD enabled to escape from various mAbs and this was consistent with the activities of SARS-CoV-2 variants carrying the corresponding mutations; specific mAbs are likely more effective against specific variants, implying that cocktail therapy might be appropriate in clinical practice; these data may help determine vaccine candidate for new generations of vaccines and suggest that focusing only on the RBD may not produce cross-reactive antibody in the face of emerging variants

8. **In vivo characterization of emerging SARS-CoV-2 variant infectivity and human antibody escape potential.** Lam et al. Cell Reports. 4 Oct 2021

- Vesicular stomatitis virus (VSV) pseudoviruses (PsVs) incorporating spike variants were generated to address infectivity and immune escape *in vivo* in the AdV5-hACE2 transduction model in mice- creating an Animal Biosafety Level 2 (ABSL-2) system for study
- N501Y RBD SARS-CoV-2 PsVs achieve high-level infection in murine respiratory tract (this mutation is found in alpha, beta and kappa variants)
- Infection with South Africa and India variant PsVs leads the highest infection levels in the airways in this model (South Africa is AKA beta and has N501Y + K417N + E484K + D614G mutations; India is AKA kappa and has N501Y + L452R + K417N + E484Q + D614G mutations)
- A mouse re-infection model was established, and the primary outcomes measured was infection in the nasopharynx after secondary challenge. SARS-CoV-2 variants carrying E484 perturbations exhibit immune escape in vivo
- In vitro neutralization assays with variant PsVs were performed with plasma from several donors (45 samples from plasma donors with confirmed SARS-CoV2+ infection, with <10% requiring hospitalization and 15 samples from healthy HCW >14 days after vaccination with mRNA vaccine); markedly lower reciprocal $\log_{10}$IC50 values were noted for the South Africa PsV
- When mice received a transfer of human plasma samples (intranasal) from the COVID-19+ and vaccinated donors and were then challenged with the variant SARS-CoV-2 VSV PsV, plasma from high-titer COVID-19+ or vaccinated individuals control emerging variants the strongest; partial immune escape was observed for the South Africa and the India variants
- Limitations: SARS-CoV-2 PsVs are used as a model leading to a model with lack of spread, a single round of infection, and inability to model clinical pathogenesis of SARS-CoV-2; intranasal plasma administration is artificial in nature
- Implications: Study draws similar conclusions regarding the dose dependency of immune escape to emerging spike variants, but this study is the first to demonstrate immune escape in vivo; Use of VSV PsVs permits infection in the nasopharynx and lungs of animals, anatomically closely mimicking human infection and can be used as a model in the future for study of immunity

9. **Impact of circulating SARS-CoV-2 variants on mRNA vaccine-induced immunity**. Lucas et al. Nature. 11 Oct 2021.

- This study is an analysis of plasma neutralization using 16 authentic isolates of distinct locally circulating SARS-CoV-2 variants (198 samples from 40 individuals; some recovered from SARS-CoV2 infection)
- No differences were observed in antibody levels between vaccinated participants of different sexes and after stratification by age; virus-specific IgG levels were significantly higher in the previously infected vaccinated group than the uninfected vaccinated group
- The data are consistent with other studies summarized above and revealed a range of reduction in the neutralization capacity associated with specific mutations in the spike gene:
    - lineages with E484K and N501Y/T (e.g., B.1.351 and P.1) had the greatest reduction in neutralization capacity, followed by lineages with L452R (e.g., B.1.617.2, AKA Delta)
    - Plasma from previously infected then vaccinated individuals exhibited better neutralization capacity when compared to plasma from uninfected, vaccinated individuals; but both groups had some neutralization capacity against all variants

- Differences in neutralization activity between individual vaccinated HCWs were much larger (up to ~2 log PRNT50 titers) than differences among virus isolates (<1 log) suggesting host-response may be more influential than virus-specific factors
- Limitations: How neutralization capacity translates to protection from infection or disease is still unknown
- Implications: Vaccine boosters should be considered to reduce immune escape and increase neutralization capacity against some variants; these data suggest that Delta many be a less concerning variant in terms of NAb escape

IMMUNOLOGY

10. **SARS-CoV-2 infection generates tissue-localized immunological memory in humans**. Poon et al. Science Immunology. 7 Oct 2021.

- 4 SARS-CoV-2 seropositive organ donors (ages 10 – 74) and controls from organ donors pre-pandemic were used to investigate populations of virus specific memory cells across blood, BM, spleen, lung, lung-associated lymph nodes (LN), and gut-associated LNs (all donors died of non-infectious related causes)
- CD4+ T, CD8+ T, and B cell memory was generated in response to infection is present in bone marrow, spleen, lung, and multiple lymph nodes (LNs) for up to 6 months post-infection
    - SARS-CoV-2-specific CD4+ T cells were identified using the activation-induced marker (AIM) assay; restimulation of cells with SARS-CoV2 peptide pools and measuring upregulation of OX40, CD137 and CD40L; significant CD4+ T cell responses to S were found in all tissues from seropositive donors compared to control; there were also increased in frequency of non-S SARS-CoV-2 specific-CD4+ T cells in the BM, lung-associated LNs, and gut-associated LNs
    - The AIM assay for CD8+ T cells measured upregulation of CD137 and CD25; SARS-CoV-2-specific CD8+ T cell frequencies were lower compared to CD4+ T cells and more variable between donors
    - Defining central memory T cells (TCM; CD45RA-CCR7+), effector memory T cells (TEM; CD45RA-CCR7-), terminally differentiated effector T cells (TEMRA; CD45RA+CCR7-), and naïve or stem-like memory cells (CD45RA+CCR7+) - the majority of SARS-CoV-2-specific CD4+ T cells were maintained as TEM (≥75%) in the blood and lung, and as TEM or TCM (≥80%) in lymphoid sites. For SARS-CoV-2-specific CD8+ T cells, the majority were maintained as TEM and TEMRA cells (≥50%) for all sites
    - Antigen-binding B cells among IgM+, IgG+, or IgA+ memory B cells were identified with fluorescently-labeled, biotinylated, and multimerized probes of full-length S and RBD proteins; IgG+ was the dominant isotype; memory B cells were present at significantly higher frequencies in lung and lung-associated LNs than in the spleen or gut-associated LNs
- Lungs and lung-associated LNs were the most prevalent sites for SARS-CoV-2-specific memory T and B cells
    - significant correlations were found between circulating and tissue-resident memory T and B cells
    - SARS-CoV-2-specific germinal centers were identified in the lung-associated LNs up to 6 months post-infection; GC B cells were defined as Bcl6+Ki67+CD19+ B cells
    - SARS-CoV-2-specific follicular helper T cells (co-expressing CXCR5 and PD-1) were abundant in lung-associated LNs and lungs (20-50% of SARS-CoV2- reactive T cells in an AIMs assay)
- Limitations: unable to know if these responses would be protective in future re-infection; while 50 immune mediators were quantified from culture supernatants of peptide-stimulated mononuclear cells- the small sample size combined with the heterogeneity in the response did not allow for further analysis of these results
- Implications: Addresses distribution of SARS-CoV-2 specific memory cells across tissues (which has been a challenge as most studies have used easily accessible PMBCs); this study provides evidence of a local tissue coordinated effort to develop cellular and humoral immune memory against SARS-CoV-2 in the lungs and local LN