Summary of Major Literature Related to COVID-19 (July 27-Aug 10)

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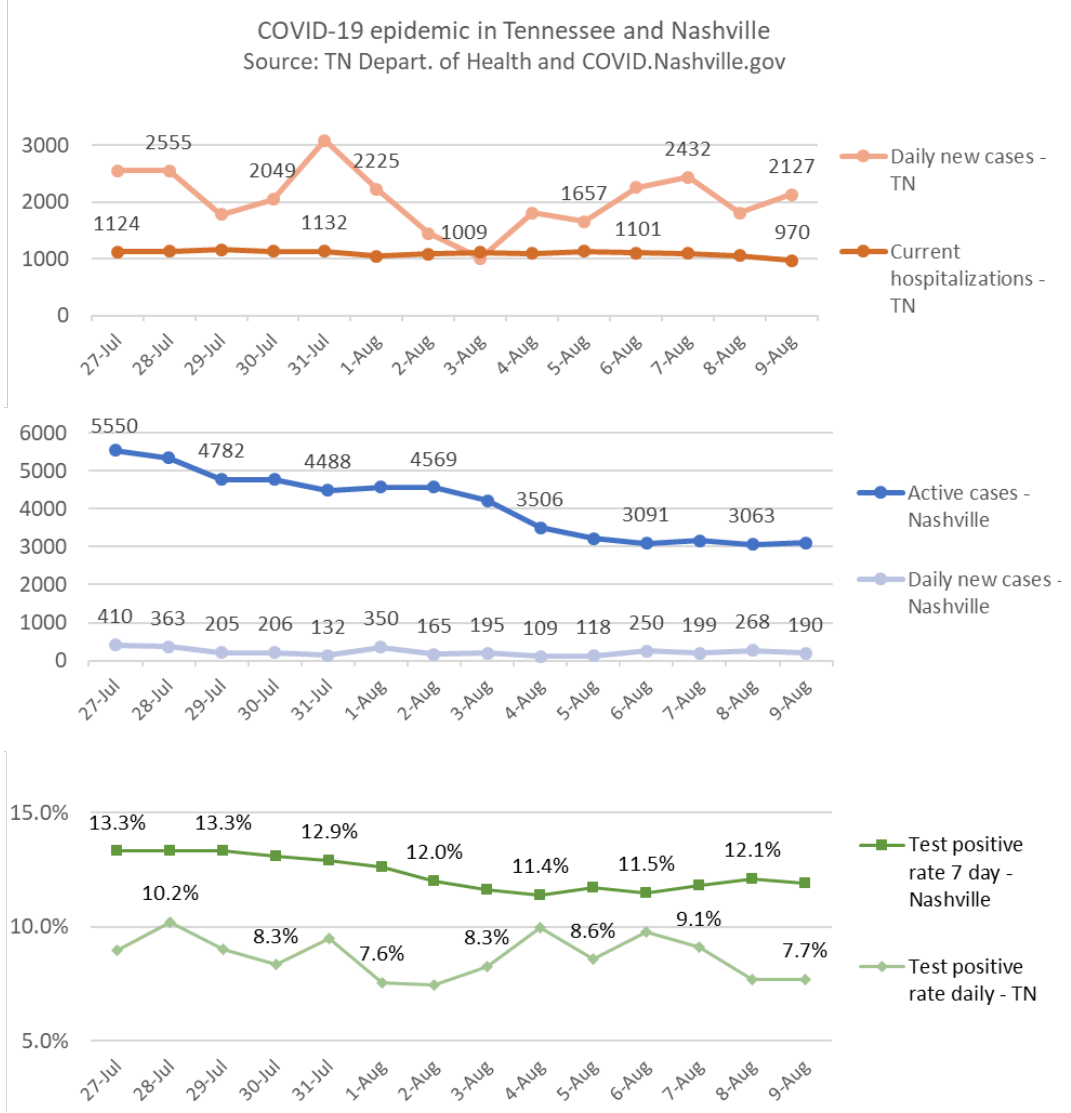
***This is informational and not intended to create variance from VUMC policies/guidance.**

STATISTICS – Tennessee and Nashville



As of Aug 9, in TN

- Total cases = 122,712
- Total hospitalizations = 5,304
- Total deaths = 1,223
- Top counties:
  - Shelby = 23,238
  - Davidson = 22,904
- Downward trends of current active cases and test positive rate in Nashville
- Demographics:

Groups	Cases	%
By sex		
Female	61,562	50.2%
Male	59,804	48.7%
By race/ethnicity		
White	55,187	45.0%
Black	23,066	18.8%
Hispanic	19,175	15.6%
Asian	1,085	0.9%
Other	17,790	14.5%
By age		
0–10	5,908	4.8%
11–20	14,226	11.6%
21–30	28,066	22.9%
31–40	22,075	18.0%
41–50	18,900	15.4%
51–60	15,444	12.6%
61–70	9,779	8.0%
71–80	5,230	4.3%
80+	2,873	2.3%

EPIDEMIOLOGY

1. **Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network – United States, March-June 2020.** Tenforde et al. MMWR. July 31**.**

- 274 symptomatic adults with a positive outpatient SARS-CoV-2 test at one of 14 U.S. academic health care systems in The Influenza Vaccine Effectiveness in the Critically Ill (IVY) Network, April 15-June 25
- Telephone interviews 14-21 days from the test date on demographic characteristics, chronic medical conditions, symptoms present at testing and interview date, and self-reported return to usual health
- 35% had not returned to usual state of health by time of interview (median: 16 days from test date)
  - 19% aged 18-34 years with no chronic condition reported not having returned to usual health
- Factors significantly associated with higher odds of not returning to usual health:
  - Age ≥50 (odds ratio [OR] = 2.29)

    - ≥3 chronic conditions (OR = 2.29)
    - Obesity (OR = 2.31)
    - Reported psychiatric condition (OR = 2.32)
- Among those returning to usual health, 34% still reported one or more symptoms at interview
    - Symptoms least likely to have resolved were fatigue (71%), cough (61%) and headache (61%)
- Implication: Non-hospitalized COVID-19 illness can result in prolonged illness and persistent symptoms, even in young adults and persons without underlying medical conditions
- Limitation: 44% of eligible patients could not be reached for interview

Healthcare workers

2. **Risk of COVID-19 among front-line health-care workers and the general community: a prospective cohort study.** Nguyen et al. Lancet Public Health. July 31**.**

- Prospective observational study of 2,035,395 community individuals and 99,795 front-line health-care workers in the UK and US who were voluntary users of the COVID Symptom Study smartphone application (NCT04331509) from March 24-29 to April 23
- 5545 incident positive COVID-19 tests were reported over 34,435,272 person-days
- Compared with the general community, front-line health-care workers were at increased risk for reporting a positive COVID-19 test (adjusted HR 11.61)
    - An inverse probability-weighted model adjusting for the likelihood of receiving a COVID-19 test showed aHR=3.40
    - Both Black, Asian, & minority general community members (aHR 2.49) and healthcare workers (aHR 21.7) were at increased risk of COVID-19 infection compared to Non-Hispanic Whites
- Adequacy of PPE and clinical setting were also important factors
    - Reuse of PPE (aHR 1.46) or inadequate PPE (aHR 1.31) increased risk compared to healthcare workers who reported adequate PPE
    - Highest risk among those working in inpatient settings (aHR 24.3) and nursing homes (aHR 16.2) relative to the general community members
- Limitation: Possible selection bias

3. **Hospital-Wide SARS-CoV-2 Antibody Screening in 3056 Staff in a Tertiary Center in Belgium.** Steensels et al. JAMA. June 15**.**

- A hospital-wide screening study evaluated SARS-CoV-2 antibodies among hospital staff (n=3056) in Belgium, April 22-30
- 6.4% of the staff (95% CI, 5.5%-7.3%) had IgG antibodies for SARS-CoV-2
- Neither being involved in care for patients with COVID-19 nor exposure to COVID-19-positive coworkers increased the odds of being seropositive, while having a suspected or confirmed COVID-19 household contact did [odds ratio 3.15 (95% CI, 2.33-4.25)]
- The high availability of PPE, high standards of infection prevention, and PCR screening in symptomatic staff, coupled with contact tracing and quarantine, might explain a relatively low seroprevalence
- Limitations: Single-center design and testing of only 74% of staff; seroconversion may have been missed if testing was too early, especially without IgM results which were excluded due to low sensitivity and specificity

COVID inequities

4. **Assessment of Community-Level Disparities in Coronavirus Disease 2019 (COVID-19) Infections and Deaths in Large US Metropolitan Areas.** Adhikari et al. JAMA Netw Open. July 28**.**

- Rates of COVID-19 infections and related deaths by neighborhood race/ethnicity and poverty in 158 urban US counties

- Counties were categorized as 1) substantially White (3.0%-17.9% non-White), less diverse (18.0%-29.4%), more diverse (29.5%-44.5%), and substantially non-White (>44.5%) based on quartiles among all counties and 2) less poverty (<10.7% below poverty level) or more poverty
- Regardless of poverty status of the county, rates of infection (RR 2.8 to 7.8) or death (RR 2.6 to 9.3) were higher in counties with 30% or more non-White residents compared to substantially White counties
- Among more-poverty counties, the disparity between substantially White and substantially non-White counties was greatest – (RR 7.8 for infection and RR 9.3 for mortality)
- Implications: Excess burden of COVID-19 infections and deaths in racially/ethnically diverse counties cannot be explained by neighborhood differences in income alone so other sources of inequities should be evaluated

5. **Comparison of Weighted and Unweighted Population Data to Assess Inequities in Coronavirus Disease 2019 Deaths by Race/Ethnicity Reported by the US Centers for Disease Control and Prevention.** Cowger et al. JAMA Netw Open. July 28**.**

- Comparison of two different methods for evaluating rates of COVID-19 by race/ethnicity
    - Weighted population & US census unweighted population
- "Use of the CDC's weighted population distributions to evaluate racial/ethnic inequities in COVID-19 mortality underestimates the excess burden of COVID-19 among Black and Latinx individuals compared with analyses conducted using the total population (unweighted) in the US Census data."
    - Unweighted pop: Blacks accounted for 10% greater and Whites 8% less COVID deaths than would be expected based on their share of population
    - Weighted pop: Whites accounted for 11% greater and Blacks 4% greater COVID deaths than their share of population
- Implications: Current methods fail to account for social segregation as a result of structural racism and may underestimate inequities in COVID-19 mortality

Healthcare during the pandemic

6. **The Invisible Epidemic: Neglected Chronic Disease Management During COVID-19.** Wright et al. J Gen Intern Med. July 14. [**VUMC PAPER**]

- Analysis of outpatient LDL cholesterol and HbA1c testing (screening) and initiation of statin and metformin therapy (treatment) at two healthcare institutions (including VUMC) from February-May 2020
- During February-March, screening decreased by 81-90% and new treatment by 52-60%, with only modest rebounding during April
- Implications: Primary care services should resume; potential need for alternative insurance coverage of non-traditional lab options to address backlog; need to identify populations most likely to have gaps related to COVID-19 care deferrals

Genetic associations

7. **Immune complement and coagulation dysfunction in adverse outcomes of SARS-CoV-2 infection.** Ramlall et al. Nat Med. Aug 3**.**

- Between Feb 1 and April 25, 11,116 patients presented to New York-Presbyterian/Columbia University Irving Medical Center, 6,398 of whom tested positive for SARS-CoV-2
- History of macular degeneration (a proxy for complement-activation disorders) and history of coagulation disorders (thrombocytopenia, thrombosis and hemorrhage) were risk factors for SARS-CoV-2-associated morbidity and mortality, independent of age, sex and smoking history

- SARS-CoV-2 infection induced higher expression of IFNs, IL-6 and the complement cascade (false discovery rate (FDR) $P < 0.001$)
- Genetic variants regulating expression or splicing of genes in complement or coagulation cascades were associated with poor SARS-CoV-2-associated clinical outcome among 388 UK Biobank patients
- Implication**:** Genetic variants may regulate complement function, which may modulate clinical outcome associated with SARS-CoV-2 infection

8. **Investigation of the genetic variation in ACE2 on the structural recognition by the novel coronavirus (SARS-CoV-2).** Guo et al. J Translational Med. In press. **[VUMC paper]**

- Systematic evaluation of non-silent genetic variants of the Angiotensin-converting enzyme 2 (ACE2) in humans. This gene encodes the receptor recognized by the surface spike glycoprotein (S-protein) of SARS-COV-2
- Using data from the Genome Aggregation Database, 12 putative deleterious missense variants were identified in specific populations that may affect the structure/function of ACE2
    - p.His378Arg could directly weaken the binding of catalytic metal atom to decrease ACE2 activity and p.Ser19Pro could distort the most important helix to the S-protein
    - Another seven missense variants may affect ACE2 secondary structures (i.e. p.Gly211Arg; p.Asp206Gly; p.Arg219Cys; p.Arg219His, p.Lys341Arg, p.Ile468Val, and p.Ser547Cys).
- Limitation: Lack of experimental validation of findings
- Implications: Genetic variation in ACE2 may affect SARS-CoV-2 recognition and infection, and may contribute to discrepancies in COVID-19 morbidity and mortality in distinct populations

Long-term cardiovascular effects

9. **Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19).** Valentina et al. JAMA Cardiol. July 27**.**

- Prospective study of the presence of myocardial injury in 100 unselected patients recently recovered from COVID-19 illness identified from the University Hospital Frankfurt COVID-19 Registry between April and June 2020
    - Most patients (67) recovered at home with asymptomatic/mild disease, while 33 required hospitalization
    - Preexisting cardiovascular conditions included hypertension, diabetes, and known coronary artery disease but no previously known heart failure or cardiomyopathy
- The median (IQR) time interval between COVID-19 diagnosis and cardiovascular magnetic resonance (CMR) was 71 (64-92) days.
- Compared with 50 healthy, normotensive volunteer controls (sex- and age-matched) and 57 risk factor–matched patients, patients recently recovered from COVID-19 had lower left ventricular ejection fraction, higher left ventricle volumes, higher left ventricle mass, and raised T1 and T2 measures
- 78% of patients recently recovered from COVID-19 had abnormal CMR findings, most commonly myocardial inflammation, defined by raised native T1 and T2 (60%), followed by regional scar and pericardial enhancement
    - Native T1 and T2 provided the best discriminatory ability to detect COVID-19–related myocardial pathology
- Implication: Evidence of cardiac inflammatory involvement in the early convalescent stage of COVID-19 among those with generally non-severe disease and in the absence of preexisting cardiovascular conditions
- Limitations: Small study; most patients had new or persistent symptoms at time of CMR

10. **Association of Cardiac Infection With SARS-CoV-2 in Confirmed COVID-19 Autopsy Cases.** Lindner et al. JAMA Cardiol. July 27**.**

- Evaluation of the presence of SARS-CoV-2 in the myocardial tissue and a possible cardiac response to infection in 39 consecutive autopsy cases of COVID-19 in Germany, April 8-18
    - Median (IQR) age of patients was 85 (78-89) years, 23 (59.0%) were women, and comorbidities such as hypertension, diabetes and coronary artery disease were common
- SARS-CoV-2 was documented in cardiac tissue in 24/39 patients (61.5%)
- 16 of 39 (41%) patients had high viral load (above 1000 copies per µg RNA) in cardiac tissue; these patients had higher gene expression in the myocardium of a cytokine response panel of 6 genes compared to 15 patients with no SARS-CoV-2 in the heart
- Virus presence was not associated with increased infiltration of mononuclear cells into the myocardium
- Limitation: Autopsy study with limited clinical information, including about cardiac dysfunction during or after COVID-19 illness
- Implication: The presence of SARS-CoV-2 in cardiac tissue does not necessarily cause an inflammatory reaction consistent with clinical myocarditis

TRANSMISSION/VIRAL SHEDDING

11. **Contact tracing during Phase I of the COVID-19 pandemic in the Province of Trento, Italy: key findings and recommendations.** Fateh-Moghadam, et al. medRxiv pre-print. July 29.

- Contract tracing results for COVID-19 from Trento, Italy, March-April 2020, which was mostly under lockdown with schools closed
    - Cases were defined as being laboratory-confirmed or probable based on symptoms following contact with a known case
    - Contacts were linked to each case in the time frame ranging from 48 hours before to 14 days after the onset of symptoms of the case
- After excluding 1,101 contacts linked with institutional setting (e.g., hospitals, nursing homes), 6,690 contacts were linked to 2,812 cases and placed in self-isolation.
    - 70% of the cases were laboratory confirmed for COVID-19
    - 890 (13%) of the contacts developed symptoms and became cases
- Secondary attack rate (proportion of contacts who themselves became cases) increased with the age of the contacts and ranged from 8.4% among contacts aged 0-14 to 18.9% among contacts 75+
- Contagiousness among the 1,489 index cases was assessed
    - 14 were aged 0-14 years and 22% of their contacts became positive for COVID-19
    - Second highest proportion of contacts to become positive was among index cases age 75+ (17%)
    - Overall, secondary attack proportion was higher in workplace contacts (16%) than cohabitants (14%) or non-cohabitating family and friends (13%)
- Limitations: Testing was largely based on symptoms so could be underestimating transmission among contacts; schools were closed during this time so there were a small number of contacts for children

HUMAN IMMUNOLOGY

12. **Selective and cross-reactive SARS-CoV-2 T cell epitopes in unexposed humans. Mateus et al. Science. Aug 4.**

- Human blood samples collected in March 2015 and March 2018 were used to map T cell epitopes across the SARS-CoV-2 genome; samples were seronegative for SARS-CoV-2
- 474 SARS-CoV-2 peptides were screened; a total of 142 SARS-CoV-2 CD4+ T cell epitopes were identified, 66 from the spike protein and 76 from the remainder of the genome

- Comparing the sequences of the immunogenic SARS-CoV-2 peptides to sequences of the 4-common cold human coronaviruses (HCoV), there was significantly higher sequence similarity in those peptides which were immunogenic in two or more individuals than those which were immunogenic in only one individual
- The CD4+ T cells from unexposed individuals which respond to SARS-CoV-2 peptides were cross-reactive with comparable affinity also to common cold HCoVs. The phenotype of those cross-reactive T cells were predominantly effector or central memory T cells.
- Limitations: No data yet to determine if pre-existing cross-reactive T cells impact pathogenesis of the response
- Implications: Pre-existing cross-reactive T cells could explain aspects of differential COVID-19 clinical outcomes, influence epidemiological models of herd immunity, or affect the performance of COVID-19 candidate vaccines. Some of the more common epitopes could be useful for tracking CD4+ T cell response in COVID disease or SARS-CoV2 vaccine trials

13. Acute SARS-CoV-2 infection impairs dendritic cell and T cell responses. Zhou et al. Immunity. Aug 3.

- Seventeen patients were evaluated during their acute phase of SARS-CoV-2 infection (AP); they exhibited lymphocytopenia [including ↓ T, NK, monocyte and dendritic cells (DC)] and an ↑ in myeloid-derived suppressive cells compared to healthy donors (HD)
- 24 convalescent patients (CP) were also assessed; T cell and NK cell numbers were generally recovered compared to AP; DCs and monocytes numbers were significantly lower than HD
- DCs from AP exhibited functional impairment compared to HD with reduced co-stimulatory marker expression, reduced type I interferon upon stimulation, and inability to stimulate T cells activation; conventional DC: plasmacytoid DC ratios were increased among acute severe patients.
- CD4+ T cells from AP had reduced proliferative capacity and reduced ability to become dual IFNg/TNFa producing cells compared to HD; CD8+ T cells from AP had reduced ability to produce cytokines and reduced expression of cytolytic proteins.
- Neutralizing antibodies developed by 30 days in all the CP samples; only 61% and 83% had developed T cells specific for the receptor binding domain (RBD)- and nucleocapsid protein (NP)
- Limitations: Relatively small sample size; acute patient samples were collected at various times within 3 weeks of the onset of symptoms (not a set time); work evaluating the timing of development of T cells specific for the RBD and NP from the onset of symptoms was too small to be powered for analysis
- Implications: Impaired DCs together with weak CD8 T cell responses may contribute to acute COVID-19 pathogenesis development

THERAPEUTIC DEVELOPMENT

14. Structural basis for neutralization of SARS-CoV-2 and SARS-CoV by a potent therapeutic antibody. Lv et al. Science. July 23.

- The main goal of this study was to identify receptor binding domain (RBD) -targeting cross-neutralizing NAbs that might block cellular entry of both SARS-CoV and SARS-CoV-2
- A phage antibody library created from RNAs extracted from peripheral lymphocytes of mice immunized with recombinant SARS-CoV RBD allowed for identification of antibodies with high binding affinity for SARS-CoV-2 RBD; H014 is a humanized antibody derived from murine antibody clone 014 with potent neutralizing activity against SARS-CoV-2 and SARS-CoV in their VSV pseudovirus based neutralization assay (at nM level).
- A ~10-fold reduction of viral titers was observed in the lungs of hACE2 humanized mice that received H014 treatment post infection; mice that received two doses of H014 before and post challenge showed ~100-fold reduction of viral titers

- Cryo-EM data shows that H014 recognizes a conformational epitope on one side of the open RBD, which is distinct from the receptor-binding motif (RBM). That is why SARS-CoV-2 S trimer can only bind to H014 if at least one RBD is at open state. H014 epitope is 81% identical between SARS-CoV-2 and SARS-CoV, which explains the cross-reactivity and comparable binding affinities
- The competitive binding assays at both protein (ELISA) and cellular levels (expressed on the surface of 293T cells) showed that H014 was able to block the binding of ACE2 to RBDs of SARS-CoV-2 and SARS-CoV. Surface plasmon resonance (SPR) assays further verified that ACE2 could be displaced from trimeric S and be replaced by H014
- Limitations: Although they show the potency of their humanized H014 antibody, human antibodies originating from the memory B cells of Covid-19 survivors may provide better alternatives for therapy. In addition, according to their mouse study, H014 antibody is much more potent in prophylactic setting compared to therapeutic setting- limiting its utility
- Implications: An antibody-based therapeutic could be effective in treating COVID-19 infections by blocking attachment of the virus to the host cell. In addition, the molecular features of H014 epitopes can help with the discovery of broad cross-neutralizing epitopes and structure-based rational vaccine design.

ANIMAL MODELS/VACCINE DEVELOPMENT

15. Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques. Mercado et al. Nature. July 31.

- Study investigates the use of 7 different single dose (10^{11} viral particles) of adenovirus serotype 26 (Ad26) vector-based vaccines expressing variants of the SARS-CoV-2 spike (S) protein in rhesus macaques (N=4-6 per vaccine, N=20 for sham control)
- Vaccination induced neutralizing Ab titers in most animals; Abs were functional in assays measuring antibody-dependent phagocytosis, complement deposition, NK cell activation and Fc binding; IFNg producing T cells were detected in vaccinated animals
- 6 weeks post-vaccination, macaques were challenged with SARS-CoV2
    - Among the 32 vaccinated macaques, 17 animals had no detectable subgenomic RNA (sg RNA) in BAL or nasal swab (NS) following challenge, and 5 additional animals had no sgRNA in BAL but showed some virus in NS
    - All vaccinated animals had no detectible virus in their NS (using plaque assays) after challenge
- The Ad26-S.PP variant stimulated the strongest response of the 7 variants tested
    - Ad26-S.PP contained the wildtype leader sequence with full-length Spike with a mutation in the furin cleavage site and 2 proline stabilizing mutations
    - Ad26-S.PP induced strong neutralizing Ab responses after a single immunization (4-fold that of convalescent macaques and humans) and provided complete protection against SARS-CoV-2 challenge in 5 of 6 animals, whereas one animal had low levels of virus in NS.
- Limitations: The timeline from vaccination to challenge is limiting; durability of the vaccine response is not addressed.
- Implications: Serum antibody titers (especially neutralizing antibody) may prove a useful immune correlate of protection for SARS-CoV-2 vaccines; pairing NAb data with another measure (Ab functionality) may provide better immune correlates of protection

16. Adaptation of SARS-CoV-2 in BALB/c mice for testing vaccine efficacy. Gu H et al. Science. July 30.

- A mouse-adapted strain of SARS-CoV-2 was generated by serial passaging (6 times) of a clinical isolate in the respiratory tract of aged BALB/c mice (termed MASCp6)
- When young (6wk) and aged mice (9mo) were intranasally inoculated with MASCp6, club cells and AT2 cells are the major target cells of the lung and the mice developed interstitial pneumonia and

inflammatory responses (by 3 dpi); aged-mice had more severe pneumonia and strong inflammatory responses; Improvements in pathology by 5dpi suggesting self-resolving (no weight loss)

- Deep sequencing revealed a panel of adaptive mutations predicted to be associated with the observed increased virulence of MASCp6; i.e. the N501Y mutation in the RBD of the spike protein.
- A recombinant RBD vaccine candidate (SARS-CoV-2 RBD of spike fused with a human IgG Fc at the C-terminal) was administered twice at 2 week intervals to naïve Balb/c mice and elicited neutralizing Ab; Both immunized and sham (PBS) treated animals were challenged with MASCp6; vaccinated animals had significantly lower viral RNA load, less CoV protein detection, and no pathological damage compared to the PBS control
- Limitations: The mouse-adapted strain was not plaque purified. No definitive evidence that the N501Y mutation drives the virulence of the adapted strain. Animal model uses a relatively low dose of MASCp6 and the durability of the model is not investigated (neither natural immunity or with induced immunity)
- Implications: This mouse-adapted strain and associated challenge model should be of value in evaluating vaccine platforms and antivirals against SARS-CoV-2