Summary of Major Literature Related to COVID-19 (Sept 22-Oct 12)

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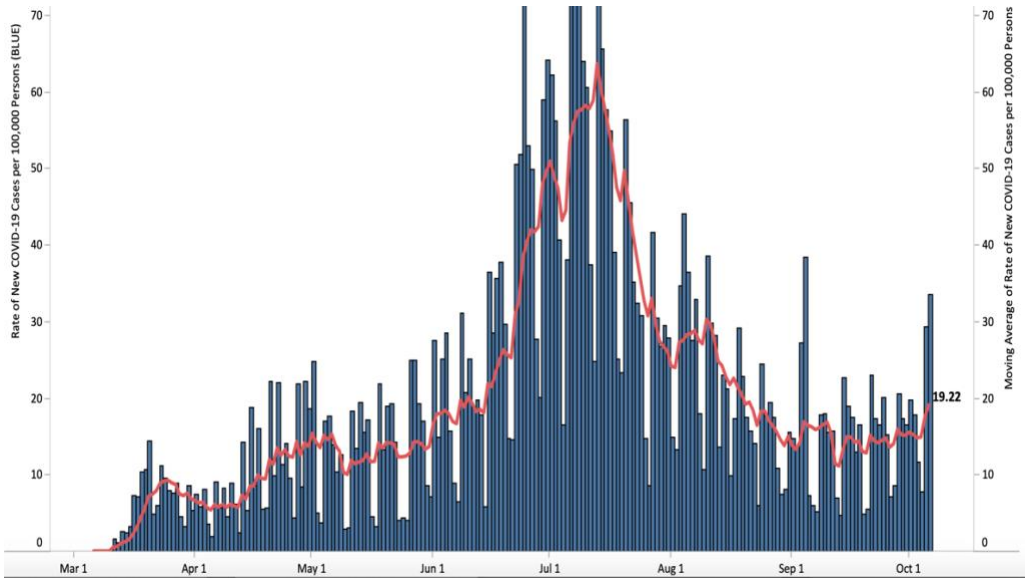
***This is informational and not intended to create variance from VUMC policies/guidance.**

STATISTICS – Daily new cases per 100,000 population

Tennessee

Davidson county



As of October 11, in TN

- Total cases = 214,717 (surpassed 200,000 cases on October 4)
- Active cases = 18,101
- Current hospitalizations = 985
- Total deaths = 2,767
- Top counties:
  - Shelby = 32,722
  - Davidson = 30,575 (active cases = 1,405)
- Active cases in Davidson county and TN both ↑ since early October
- Demographics:

Groups	Cases	%
By sex		
Female	110,166	51.3%
Male	102,716	47.8%
By race/ethnicity		
White	119,806	55.8%
Black	37,697	17.6%
Hispanic	26,047	12.1%
Asian	1,920	0.9%
Other	29,247	13.6%
By age (average: 40 years)		
0–10	10,627	4.9%
11–20	28,598	13.3%
21–30	44,027	20.5%
31–40	35,182	16.4%
41–50	31,892	14.9%
51–60	27,931	13.0%
61–70	19,001	8.8%
71–80	11,067	5.2%
80+	6,061	2.8%

EPIDEMIOLOGY

Clinical

1. **Patient Trajectories Among Persons Hospitalized for COVID-19: A Cohort Study.** Baribaldi et al. Ann Intern Medicine. September 22.

- Evaluated factors at hospital admission between March and April that are predictive of severe disease or death from COVID-19 in a single health care system in Maryland/Washington DC (5 hospitals)
- Developed a prediction model based on study results: The COVID Inpatient Risk Calculator (CIRC)
- Factors at hospital admission associated with death: older age, age-nursing home interaction (admission from nursing home if younger than 75y), Charlson Comorbidity Index (CCI), and SaO_2/FiO_2

- Factors at admission associated with time to severe disease OR death:
    - Higher BMI; higher CRP level, respiration rate, albumin level, and temperature > 38.0°C
    - Higher CCI was only associated with progression among those younger than 60
    - Detectable troponin level was only associated among patients between 60-74
    - Prediction model using these factors had good performance (area-under-the-curve (AUC) between 0.85 to 0.78 for first week with best performance in first two days)
- Limitations: Small number of cases in some categories; early in the pandemic when treatment decisions may have been different; DNR/DNI orders were common among those who died without mechanical ventilation which could affect prediction; overfitting is likely for the prediction model

2. Relation of Statin Use Prior to Admission to Severity and Recovery Among COVID-19 Inpatients. Daniels et al. Am J Cardiol. September 16**.**

- Retrospective study of the association between use of statin/ACE inhibitor/ARB in the month before hospital admission, with risk of severe outcome (death or ICU admission) and with time to discharge without severe disease among patients hospitalized for COVID-19 at UCSD Hospital
    - 170 patients hospitalized for COVID-19; severe disease occurred in 53%
    - 27% were taking statins on admission, 21% were on ACE inhibitors, and 12% were on ARBs
- After controlling for comorbid conditions and concomitant use of ACE inhibitors or ARBs, statin use prior to admission was associated with significantly reduced risk of severe COVID-19 (aOR 0.29, 95%CI 0.11 to 0.71) and faster time to recovery among those without severe disease (aHR for recovery 2.69, 95%CI 1.36 to 5.33)
- Use of ACE inhibitors (aOR 1.31, 95%CI 0.55 to 3.19) or ARBs (aOR 1.77, 95%CI 0.60 to 5.59) were not significantly associated with risk of severe disease
- Implications: A potential impact of statins on COVID-19 severity and recovery is important given their high prevalence of use among individuals at risk for severe COVID-19
    - biologic plausibility for a protective role of statins: through known anti-inflammatory and immunomodulator effects or direct effects on the virus
- Limitations: Small study; potential for residual confounding - sensitivity analysis of COVID-negative hospitalized patients also showed a comparable strong beneficial effect of statins on severe outcomes (aHR 0.21, 95% CI 0.07-0.34)
- **See also: Cholesterol 25-Hydroxylase inhibits SARS-CoV-2 and other coronaviruses by depleting membrane cholesterol.** Wang et al. EMBO J. October 5.

Children/adolescents

3. Transmission Dynamics by Age Group in COVID-19 Hotspot Counties — United States, April–September 2020. Oster et al. MMWR. October 9**.**

- Analysis of temporal trends in percentage of positive SARS-CoV-2 RT-PCR test results (percent positivity) by age group in COVID-19 hotspot counties before and after their identification as hotspots
- 767 hotspot counties (>100 cases in preceding 7 days) were identified during June and July, representing 24% of counties and 63% of US population
- In these 767 hotspot counties, particularly those in the South and West, early increases in percent positivity among persons aged ≤24 years began 31 days before hotspot identification, followed by several weeks of increasing percent positivity in older persons
    - among adults aged 25–44, 45–64, and ≥65 years, increases began 28 days, 23 days, and 20 days, respectively, before hotspot identification
    - percent positivity in older age groups continued to increase for 21–33 days after hotspot detection

- Implications: Percent positivity is an important indicator of community transmission, and increases among younger age groups (particularly age 18-24y) could serve as a signal of upcoming increases in hospitalizations, severe illnesses, and deaths among older age groups

4. **COVID-19 Trends Among School-Aged Children — United States, March 1–September 19, 2020.** Leeb et al. MMWR. September 28.

- During March 1–September 19, a total of 277,285 laboratory-confirmed cases of COVID-19 in school-aged children were reported in the United States, including 101,503 (37%) in children aged 5–11 years and 175,782 (63%) in adolescents aged 12–17 years
- Among school-aged children with COVID-19:
    - 42% were Hispanic/Latino (Hispanic), 32% were non-Hispanic White (White), and 17% were non-Hispanic Black (Black)
    - 58% reported at least one symptom, 5% reported no symptoms, and information on symptoms was missing or unknown for 37%
    - Overall, 3,240 (1.2%) were hospitalized, including 404 (0.1%) who required ICU admission. 45% of those hospitalized were Hispanic and 25% Black
    - 3% reported at least one underlying condition. This percentage increased to 16% of children who were hospitalized, 27% of those admitted to an ICU, and 28% of those who died
    - Fifty-one (<0.01%) school-aged children died of COVID-19
- Weekly SARS-CoV-2 laboratory test volume among school-aged children more than tripled, from 100,081 tests performed during the week beginning May 31 to a peak of 322,227 during the week beginning July 12, then decreased to approximately 260,000 during August and rebounded in September; test volume was higher among adolescents than younger children
- Limitations:
    - May be an underestimate of actual disease incidence since testing was prioritized among symptomatic persons and data are from a single reporting system which may not capture total cases and deaths
    - Missing data was common for race/ethnicity, symptom status, underlying conditions, outcomes
    - Delays in reporting may affect trend data
    - State reporting of laboratory data and case surveillance is not uniform

5. **Susceptibility to SARS-CoV-2 Infection Among Children and Adolescents Compared with Adults A Systematic Review and Meta-analysis.** Viner et al. JAMA Pediatrics. September 25.

- Included published or preprint studies that provided data on confirmed SARS-CoV-2 infection (by PCR or serology) and reported either rate of secondary infections in children and adolescents compared with adults or infection prevalence/seroprevalence in children and adolescents separate from adults
    - 32 studies from 21 countries were included; 18 assessed contract-tracing with 3 of these occurring in schools, and 14 were population screening studies (prevalence/seroprevalence)
- Based on evidence from 15 contact-tracing studies, children and adolescents younger than 20y were less likely to be an infected contact than adults, with a pooled OR of 0.56 (95%CI, 0.37-0.85)
    - When studies were categorized by age, lower susceptibility appeared to be confined to those younger than 10-14y, who had 48% lower odds of infection compared with those >20y
- Data from population screening studies were heterogenous and not suitable for meta-analysis
    - Two virus prevalence studies reported lower infection rates in those younger than 20 years. In contrast, other studies reported no age-related differences
    - Lower seroprevalence in children (but not in adolescents) compared to adults

- Limitations: some included studies were low quality and open to bias; many of the contract tracing studies occurred during strict social distancing which reduced potential contacts outside of the home; population screening studies only tested a small number of children and results could be biased in unknown direction; high heterogeneity between studies

6. Conclusions: Children younger than 10 to 14 years appear to have lower susceptibility to SARS-CoV-2 infection than adults, with adolescents appearing to have similar susceptibility to adults

Genetics

7. **Inborn errors of type I IFN immunity in patients with life-threatening COVID-19.** Zhang et al. Science. Sept 24.

- Study of 659 patients with COVID-19 pneumonia who developed critical disease, 14% of whom died
  - 75% men, mean age 51.8y (1mo-99y)
  - ancestry confirmed by principal components analysis
- Controls were 534 individuals infected with SARS-CoV-2 who remained asymptomatic/had mild disease
- Whole exome sequencing/whole genome sequencing was performed
- Rare loss-of-function (LOF) variants located in 13 human loci known to govern TLR3- and IRF7-dependent type 1 interferon (IFN) immunity to human influenza virus were enriched among severe COVID-19 cases relative to asymptomatic or mild COVID-19 cases
- At least 23 of the 659 (3.5%) unrelated patients of varying ages (17-77y) and ancestries have known or new genetic deficiency at one of eight loci among the 13 tested: *IRF7*, *IFNAR1, TLR3, TICAM1, TBK1, IRF3*, *UNC93B1*, *IFNAR2*
- Implication: Loss-of-function variants in human loci involved in type I or II IFN immunity, which induces innate immunity against coronaviruses, were identified with significant prevalence in severe COVID-19 patients, suggesting that pathogenic variants in these loci may significantly contribute to the pathogenesis of COVID-19

8. **Genetic variants mimicking therapeutic inhibition of IL-6 receptor signaling and risk of COVID-19.** Bovijn et al. Lancet Rheumatol. September 25.

- Early evidence from observational studies and open-label, uncontrolled trials has suggested that IL-6 receptor (IL6R) blockers might confer benefit, particularly in patients with severe COVID-19
  - More than 40 clinical trials of anti-IL-6 receptor antibodies (including tocilizumab and sarilumab) in the setting of SARS-CoV-2 infection are ongoing
- This study investigated whether an instrument of seven genetic variants in or close to *IL6R* were associated with COVID-19 hospitalization and other related outcomes using data from the COVID-19 Host Genetics Initiative
- IL6R genetic variants were associated with lower serum C-reactive protein concentrations and with lower risk of hospitalization for COVID-19 (0·88; 0·78–0·99)
- No association observed with very severe COVID-19 requiring respiratory support or death
- Limitation: Genetic analysis of very severe COVID-19 was based on only 536 cases
- Implication: Provides genetic evidence to support potential efficacy of IL6R blockade in COVID-19 and study of IL6R inhibitors in randomized controlled trials

COVID-19 inequities

Important considerations

- Differential testing frequency and testing algorithms/protocols across racial/ethnic groups in different populations could influence observed disease burden and findings related to COVID-19 outcome
- Each study was conducted within a single healthcare system (Bronx, NY and Milwaukee, WI)

- Observed racial disparities in COVID-related outcomes in some populations may be attributable to greater incidence of COVID-19 among Black residents rather than to worse survival
- **See also: Invited Commentary: Racism, not race, drives inequity across the COVID-19 continuum.** Khazanchi et al. JAMA Netw Open. September 25.

9. Association of Race and Ethnicity With Comorbidities and Survival Among Patients With COVID-19 at an Urban Medical Center in New York. Kabaritti et al. JAMA Netw Open. September 25**.**

- Study of 5902 COVID-19 patients at Montefiore Medical Center in Bronx, NY
    - 3231 (54.7%) required inpatient admission, of whom 470 (14.5%) required an ICU stay
    - Among 3912 (77%) with complete comorbidity information, 33% and 45% had diabetes and hypertension, respectively
- 918 patients (15.5%) died during the study period
    - Median (range) time from COVID-19 diagnosis to death was 6 (0.2-40) days
    - Death rates were 27% for hospitalized patients, 44% for ICU patients, 3% for those treated in the emergency department only, and 0.6% for those treated in outpatient setting
- Higher proportion of non-Hispanic Black (40%) and Hispanic (34%) patients had more than 2 medical comorbidities compared to Whites (29%), and non-Hispanic Black patients had higher rates of inpatient admission
- Adjusting for age, sex, socioeconomic status, and comorbidities, non-Hispanic Black (aHR 0.69; 95% CI, 0.55-0.87) or Hispanic patients (aHR 0.77; 95% CI, 0.61-0.98) had slightly improved survival compared with non-Hispanic White patients
- Across ethnic and racial groups, male sex, BMI > 35, comorbidities such as diabetes, kidney disease, and dementia were associated with increased risk of death
- Limitations: relatively small sample size of non-Hispanic Whites; approximately 5% of non-Hispanic Whites were transferred from chronic nursing facilities and thus may not be representative sample (but excluding them did not materially alter observed associations)
- Implication: Non-Hispanic Black and Hispanic patients who tested positive for SARS-CoV-2 and received care at this *single urban academic medical center* did not experience worse outcomes compared with their White counterparts, suggesting that an integrated, comprehensive health care environment may attenuate racial/ethnic disparities in mortality

10. Racial Disparities in Incidence and Outcomes Among Patients With COVID-19. Munoz Price et al. JAMA Netw Open. September 25**.**

- Cross-sectional study of all 2,595 consecutive patients tested for COVID-19 in a large healthcare system in Milwaukee from March 12-31
    - 785 (30%) African American, 1617 (62%) White, and 193 (7%) belonging to other racial groups
    - 716 (28%) met the definition of poverty (ie, uninsured or Medicaid beneficiary)
    - Nearly 80% had at least 1 comorbid condition associated with higher COVID-19 risk, and 24% had 3 or more
- In multivariable analyses adjusting for demographics, comorbidities, presenting symptoms and clustering within socially disadvantaged zip codes:
    - Black individuals were greater than five times more likely to test positive for SARS-CoV-2 (OR 5.37; 95% CI, 3.94-7.29)
    - Both Black race (OR 1.85; 95% CI, 1.00-3.67) and poverty (OR 3.84; 95% CI, 1.20-12.30) were significantly associated with increased likelihood of hospitalization among the 369 individuals with COVID-19

    - Poverty, but not race, was associated with increased risk of ICU admission, and neither poverty nor race was associated with risk of mechanical ventilation or death
- Zip code explained 79% of the variance of COVID-19 positivity, indicating that where a patient lived was strongly associated with testing positive

TREATMENT

11. **Remdesivir for the Treatment of Covid-19 — Final Report.** Beigel et al. (**VUMC, Creech co-author**). NEJM. October 9.

- **FINAL REPORT of ACTT-1** (NCT0428) double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults hospitalized with COVID-19 who had evidence of lower respiratory tract infection
    - 541 patients were randomly assigned to intravenous remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) arm, and 521 to placebo for up to 10 days
    - 73 sites around the world (45 in the US)
    - ~85% had severe disease
- Primary outcome was time to recovery, defined as the first day, during the 28 days after enrollment, on which a patient met the criteria for category 1, 2, or 3 on an eight-category ordinal scale
- Patients in the remdesivir group had a shorter time to recovery than patients in the placebo group (median, 10 days vs. 15 days; rate ratio (RR) for recovery, 1.29; 95% CI 1.12 to 1.49; P<0.001)
    - A benefit was *not* observed among those receiving mechanical ventilation or high-flow oxygen or ECMO at enrollment (RR for recovery, 0.98; 95% CI, 0.70 to 1.36)
- Patients randomized during the first 10 days after symptom onset had a RR for recovery of 1.37 (95% CI, 1.14 to 1.64), whereas no significant benefit was observed among those with longer duration of symptoms prior to randomization
- Kaplan–Meier estimates of mortality were 11.4% with remdesivir and 15.2% with placebo by day 29, (hazard ratio, 0.73; 95% CI, 0.52 to 1.03), suggestive of a mortality benefit, albeit not statistically significant
- Implications: Remdesivir benefit is apparent among COVID-19 patients who have had symptoms for <10 days

12. **Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial.** Recovery Collaborative Group. Lancet. October 5.

- Randomized, controlled, open-label platform trial at 176 hospitals in the UK (ISRCTN 50189673 and ClinicalTrials.gov NCT04381936)
- Between March 19-June 29, 1616 hospitalized COVID-19 patients were randomly allocated to receive lopinavir– ritonavir (400 mg and 100 mg, respectively, by mouth for 10 days or until discharge) and 3424 patients to receive usual care; primary outcome was 28-day mortality
    - Mean age 66.2y, 60% male; ~75% White
    - At randomization, 26% patients had no ventilatory support, 70% were receiving oxygen only, and only 4% were on invasive mechanical ventilation
- Overall, 374 (23%) patients in lopinavir–ritonavir arm and 767 (22%) patients allocated to usual care died within 28 days (rate ratio 1·03, 95% CI 0·91–1·17)
    - Similar results across all prespecified subgroups o age, sex, ethnicity, level of respiratory support, days since symptom onset, and predicted 28-day mortality risk
- There was no significant difference in time until discharge alive from hospital (median 11 days [IQR 5 to >28] in both groups)

- Among patients not on invasive mechanical ventilation at baseline, there was no significant difference in the risk of progressing to composite endpoint of invasive mechanical ventilation or death (risk ratio 1·09, 95% CI 0·99–1·20).
- Implications: These findings do not support the use of lopinavir–ritonavir monotherapy for treatment of patients admitted to hospital with COVID-19
    - In line with interim results of SOLIDARITY trial, which halted the lopinavir–ritonavir monotherapy and the lopinavir–ritonavir plus interferon beta combination groups

HUMAN IMMUNE RESPONSE

13. **Ultrapotent human antibodies protect against SARS-CoV-2 challenge via multiple mechanisms .** Tortorici et al. Science. September 24**.**

- Report on the isolation and characterization of 2 SARS-CoV-2 human monoclonal antibodies (mAb) that were tested in a hamster model for their ability to protect against SARS-CoV-2 challenge
- Two mAb (S2M11 and S2E12) were identified by screening memory B cells from 2 convalescent individuals; B cells were baited with the SARS-CoV-2 S ectodomain trimer; high neutralizing abilities against pseudotyped viruses & authentic SARS-CoV-2 virus
- S2M11 and S2E12 target at partially overlapping RBD epitopes; S2M11 binds to a quaternary epitope of the S leading to locking the S trimer in a closed state; S2E12 interactions only with the RBD when its 'open' but also binds to the prefusion S trimer (cryo-EM data on this interaction is available)
- Both mAbs inhibit SARS-CoV-2 binding to immobilized ACE2, binding to ACE2 expressed by CHO cells, and prevent syncytia formation in a SARS-CoV2 transfection Vero6 assay
- S2M11 activated Ab-dependent cell cytotoxicity and Ab-dependent cell phagocytosis (FcRIIIa - mediated); S2E12 did not mediate these activities but did induce signaling through FcRIIa
- In the hamster model, RNA genome copies were significantly reduced at the 4dpi if animals received one or both mAb; replicating virus was detected at 4 dpi in 6/6 controls but only 1/22 animals receiving mAbs
- Implications: use of cocktails of mAb against SARS-CoV-2 could take advantage of different mechanisms of action to inhibit viral binding and neutralization; could circumvent concern that a single mAb could lead to the emergence or selection of viral mutants
- Limitations: mAb were administered 48 h before intranasal challenge therefore prophylactic model was tested; therapeutic model was not addressed

VACCINE DEVELOPMENT

14. **COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T-cell responses.** Sahin et al. Nature. September 30**.**

- This is a second report on vaccine candidate - a lipid nanoparticle formulated nucleoside-modified mRNA encoding the RBD of the SARS-CoV-2 spike protein- with a focus on antibody and T cell responses after vaccination (safety, tolerability and antibody in prior Nature publication)
    - data are from the phase 1/2 German trial (NCT04380701)
- 60 participants (12 per dosing schedule); 1ug, 10ug, 30 ug, or 50ug doses were administered at day 1 and day 22; a 60ug dose was given to one group of 12 at day 1 (no boost)
- Antibody responses were measured at day 7, 21, 29 and 43
    - when 2 doses of vaccine were given RBD-binding IgG concentrations were above those in a COVID-19 human convalescent sample panel (range 0.7-3.5 fold higher)
    - lower ratios of serum neutralizing geometric mean titers to RBD-binding IgG geometric mean concentrations were elicited by the vaccine than by SARS-CoV-2 infection

- Day 43 sera showed high neutralizing titers to 16 SARS-CoV-2 spike variants and the D614G variant in pseudovirion neutralization assays.

- CD4+ and CD8+ T cells responses were measured prior to vaccination on Day 1 and on Day 29
  - 95% of participants receiving the prime-boost regimen (1-50ug doses) had RBD-specific CD4+ T cells responses; 10 fold higher than their memory response to endemic viruses (EBV, CMV, influenza); correlate with IgG and neutralizing titers
  - Increases in IFNg and IL-2 producing T cells are observed; IL-4 producing cells do not increase
  - 76% of participants receiving the prime-boost regimen had strong CD8+ responses; comparable to memory responses against endemic viruses
  - The mean fraction of RBD-specific T cells within total circulating T cells observed in BNT162b1 immunized persons was higher than that observed in 15 convalescents.
- Implications: Boost regimen may be important for eliciting both antibody and T cell responses with this vaccine candidate
- Limitations: 96.7% Caucasian; memory responses are not evaluated (last data of data collection is 43 Days); cannot predict efficacy

15. **Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults.** Anderson et al. NEJM. September 29**.**

- Data presented is from a phase 1, dose-escalation (2 doses 25ug or 100ug; day 0 and 28), open-label trial of a messenger RNA vaccine, mRNA-1273, which encodes the stabilized prefusion SARS-CoV-2 spike protein in healthy adults – including 40 participants ≥56 yo (Moderna/NIAID candidate)
- Adverse events were dose-dependent and were more common after the second immunization.
  - most common solicited adverse events were headache, fatigue, myalgia, chills, and injection-site pain
  - 17/ 71 unsolicited adverse events were considered related to the vaccine
- Antibody responses were assessed by ELISA (days 1, 15, 29, 36, 43 and 57), pseudovirus neutralization assay (day 43) and 3 live-virus neutralization assays (on several days; varied based on assay if both doses and all timepoints)
  - Spike specific IgG titers were dose-dependent & after the 2nd dose, responses reached the upper quarter of the distribution of responses measured in convalescent serum; Responses in 100ug subgroup exceeded the responses measured in convalescent serum
  - Neutralizing responses were undetectable at baseline; by 7 days after dose 2, a significant response was measured and similar to the responses measured in participants 18-55; responses were higher in 100ug dose than 25ug dose and higher in 100ug dose than in convalescent serum.
- Cytokine production by spike -specific T cells was assessed on days 1, 29, and 43.
  - Regardless of age and dose – Th2 cytokines (IL-4 and IL-13) were very low
  - CD4+ T cells responded to the S-specific peptide pools producing TNF>IL-2>IFNg; greater responses in subgroups receiving 100ug (compared to 25ug); the ≥71 yo subgroup receiving the 25ug dose had the lowest cytokine response
  - CD8+ T cell responses were only observed after the 2nd dose in those receiving the 100ug dose
- Implications: With this vaccine candidate there were no systematic differences in the reactogenicity profile between the older cohort and participants between the ages of 18 and 55 years who had received the mRNA-1273 vaccine
- Limitations: Limited diversity; small study (10 participants in each group when stratifying by age groups and dose); only early responses assessed, so cannot predict sustainability of the response

Animal models

16. **A Mouse-adapted SARS-CoV-2 induces Acute Lung Injury (ALI) and mortality in Standard Laboratory Mice.** Leist et al. Cell. September 23**.**

- Serial in vivo passage (10 passages) of SARS-CoV-2 MA selected for a lethal mouse-adapted SARS-CoV-2 MA10 variant; SARS-CoV-2 MA was previously described as mouse adapted (MA) strain in which the spike and RBD were engineered to bind mACE2
  - SARS-CoV-2 MA10 included 5 additional nucleotide changes, all resulting in amino acid changes in 3 nonstructural proteins, 1 in spike and 1 in ORF6
- SARS-CoV-2 MA10 shows a strain- dose- and age-related increase in pathogenesis in mice;
  - Using intranasal inoculating dose of 10^4 PFU in 10wk BALB/c- observations included ~15% mortality; viral antigen peaks at 1-2 dpi; damage to the airway epithelia progressed to accumulation of inflammation and hyperplastic epithelia; ALI scores increased significantly
  - Using the 10^4 PFU dose in 1 yo BALB/c lead to nearly 100% mortality therefore 10^3 PFU was used for standard dose in 1 yo mice – observations included ~15% survival to d7; progressive weight loss; surviving animals had prolonged disturbed lung function and higher ALI scores than 10wk mice with SARS-CoV-2
  - C57Bl/6J mice infected with 10^4 or 10^5 PFU had some weight loss but no mortality; lung function returned to baseline by 5dpi; viral replication was lower and ALI scores were attenuated compared to BALB/c
- Type I and II interferon receptor double knockout mice on C57Bl/6 background infected with SARS-CoV-2 had prolonged weight loss, higher congestion scores and higher viral titers than wild-type mice
- BALB/c mice vaccinated with SARS-CoV-2 spike expressing viral replication particles are protected from disease after challenge
- Implications: This model can utilize existing mouse resources (KO models; inhibitors, antibodies) to elucidate the role of host genetics, underlying molecular mechanisms involved in pathogenesis and immunity; the model can be used for testing vaccines and antiviral drugs
- Limitations: Mapping studies are needed to determine the contribution of each of the nonsynonymous mutations to viral pathogenesis