SUMMARY OF MAJOR LITERATURE RELATED TO COVID-19 (JUNE 8-22)
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*This is informational and not intended to create variance from VUMC policies/guidance.

STATISTICS - Tennessee and Nashville: June 22 - Nashville enters Phase 3 of Roadmap for Reopening

As of June 21, in TN
- Total cases = 35,102
- Total tests = 685,381
- Total hospitalizations = 2,291
- Total deaths = 526
- Active cases = 11,509
- Upward trends in active cases in TN and Davidson county
- Top three counties:
  - Shelby = 7,916
  - Davidson = 7,668
  - Rutherford = 2,060
- Demographics:
  - Groups
    - Cases
    - %
      - By sex
        - Female 15,383 43.8%
        - Male 18,727 53.4%
      - By race/ethnicity
        - White 14,657 41.8%
        - Black 7,312 20.8%
        - Hispanic 9,404 26.8%
        - Asian 512 1.5%
        - Other 5,779 16.5%
      - By age
        - 0–10 1,584 4.5%
        - 11–20 3,223 9.2%
        - 21–30 7,502 21.4%
        - 31–40 7,267 20.7%
        - 41–50 5,957 17.0%
        - 51–60 4,712 13.4%
        - 61–70 2,626 7.5%
        - 71–80 1,327 3.8%
        - 80+ 840 2.4%

EPIDEMIOLOGY
   - COVID-19 hospitalizations across TN have increased by 30% statewide since early June, particularly in Memphis Delta and southeast TN (including Chattanooga)
     - Represents highest point in the pandemic but without acute stress on healthcare system
     - Increase in hospitalizations has been more gradual than increase in positive cases
   - COVID Case Mix Index (CMI) is a new daily tracking measure derived by the authors to adjust the number of new daily cases by age, thereby accounting for lower or higher hospitalization risks of those new cases
o Age is a risk factor for both hospitalization and death
o Most recent time periods when the reported new cases exceed the COVID CMI (shaded blue) represent periods with a relatively large proportion of infections among low-risk individuals

![Chart showing new cases and COVID CMI adjusted cases](chart.png)

- Nashville's COVID CMI adjusted case growth has been relatively slower than in other areas in TN
  o Hospitalizations have remained below their highest levels seen in early May
- Model projections, which estimate transmission number (R) of 1.13, indicate that if current case trends continue, TN may see >1,000 concurrent COVID-19 hospitalizations in late summer
  o Could stress facilities in some regions with limited ICU and hospital beds available
- **Implications:** Risk of hospitalization among COVID-19 cases diagnosed in TN varies over time and region, so this VUMC model can help predict health system capacity


- Understanding the role of age in transmission and disease severity is critical for determining the impact of social-distancing interventions on SARS-CoV-2 transmission, especially those aimed at schools
- Age-stratified dynamic transmission models demonstrated that observed age distributions in COVID-19 cases can be explained by children having both lower susceptibility to infection and lower probability of showing clinical symptoms
- **Susceptibility to infection in individuals <20y of age is approximately half that of adults aged >20y**
- **79% (95% CI: 69–88%) of infections are asymptomatic in 10- to 19-year-olds, compared to 31% (18–43%) in people aged over 70y**
- Estimates are consistent across countries and intervention contexts
- **Limitations:** Unknown contribution to transmission of asymptomatic or subclinical infections among children; questionable generalizability to populations (including low- and middle-income countries) with younger age profiles and/or other underlying comorbidities (e.g., HIV) or undernutrition, which may alter case severity/transmissibility
- **Implications:** Despite higher contact rates among children, interventions aimed at children (e.g. school closings) are likely to have a relatively small impact on overall transmission or final size of the epidemic; however, **relative timing of epidemic peaks** (holding R0 constant) does differ with schools closing vs. schools remaining open in this modeling exercise


- Bayesian modeling study of major interventions across 11 European countries from start of COVID-19 through May 4, 2020 when lockdowns began to be lifted
  o Model back-calculates infections (attack rates) from observed deaths
- Initial reproduction number averaged across all countries was 3.8 (2.4-5.6)
• Across all 11 countries:
  o Combined non-pharmaceutical interventions (lockdown, banning public events, school closures, self-isolation, social distancing) have been sufficient to drive the reproduction number \( R_t \) below 1 (probability \( R_t < 1.0 \) across all countries is 99.9%)
  o Lockdown had the largest impact on transmission (81% [75% - 87%] reduction)
  o 3,100,000 [2,800,000 - 3,500,000] deaths have been averted due to interventions
  o Model estimated 12-15 million individuals have been infected with SARS-CoV-2, representing between 3.2% and 4.0% of the population
• Limitations: Model relies on fixed estimates for parameters such as onset to death and infection fatality rate; interventions are assumed to have same relative impact on \( R_t \) across countries; model uncertainty increased by very dissimilar early interventions
• Implications: Major non-pharmaceutical interventions and lockdown in particular have had a substantial effect on reducing transmission

Asymptomatic infection
• Study of 37 asymptomatic individuals in Wanzhou District who were diagnosed with confirmed SARS-CoV-2 infections but with no clinical symptoms in the preceding 14 days, identified through screening for close contacts under quarantine
• Compared to symptomatic group (37 sex-, age- and comorbidity-matched symptomatic patients), asymptomatic group had:
  o Significantly longer duration of viral shedding [median 19 d (IQR 15-26) vs 14 d (IQR 9-22)] \( (P = 0.028) \)
  o Significantly lower levels of virus-specific IgG levels (median S/CO, 3.4 vs 20.5) \( (P = 0.005) \) during acute phase (when viral RNA found in respiratory specimen)
  o Lower levels of 18 pro- and anti-inflammatory cytokines
• During early convalescent phase (8 weeks after hospital discharge):
  o 93% and 81% of asymptomatic group had reduction in IgG and neutralizing antibody levels, respectively, as compared to 97% and 62% of symptomatic group
  o 40% of asymptomatic individuals became seronegative for IgG vs 13% of symptomatic group
• Implications:
  o Asymptomatic individuals may have a weaker immune response to SARS-CoV-2 infection
  o Decrease in IgG and neutralizing antibody levels within 2-3 months after infection might suggest short duration of immunity (compared to 1-2 years for SARS and MERS-CoV) and have implications for timing of seroprevalence surveys
• Limitations: Measurable virus RNA shedding may not reflect virus infectivity; IgG and IgM assays focused on recombinant nucleocapsid protein and a single peptide of the spike protein; all neutralization assays were with pseudovirus expressing spike protein

Blood type
• Genome-wide association study (GWAS) for development of SARS-CoV-2 respiratory failure, including 835 cases and 1,255 blood donor controls from Italy and 775 cases and 950 controls from Spain
  o Results from the two case-control analyses were combined by meta-analysis
Two cross-replicating associations were identified: rs11385942 (chr3p21.31) and rs657152 (9q34) with odds ratios of 1.77 (95% CI: 1.48 to 2.11; P=1.14×10⁻¹⁰) and 1.32 (95% CI, 1.20 to 1.47; P=4.95×10⁻⁸), respectively.

Fine mapping implicated 22 variants in six genes on chromosome 3, including SLC6A20, a known interaction partner with angiotensin converting enzyme 2 (ACE2), the SARS-CoV-2 cell surface receptor, and 38 variants in the ABO gene on chromosome 9.

Analysis of genetically inferred blood type indicated that type A individuals have 45% higher risk than non-A, while type O have 45% lower risk than non-O of COVID-19 respiratory failure.

Limitation: Cases of severe respiratory failure were compared to general population controls, rather than to COVID-19 patients without respiratory failure, so reported associations are for risk of having severe disease versus no disease or asymptomatic disease.


The pooled frequency of blood groups A, B, O, and AB among COVID-19 infected individuals was estimated as 36.22%, 24.99%, 29.67%, and 9.29% respectively.

The odd ratio of COVID-19 infection for blood group A versus other blood groups was 1.16 (CI 95%: 1.02-1.33) and for blood group O versus other blood groups was 0.73 (CI 95%: 0.60-0.88).

CLINICAL MANAGEMENT


Meta-analysis of 25 randomized clinical trials (3804 participants) to examine the association between noninvasive oxygenation strategies and all-cause mortality or endotracheal intubation among adults with acute hypoxemic respiratory failure:
- Studies with >50% of population with COPD, CHF, in immediate post-extubation period, or post-op from cardiovascular surgery were excluded
- Compared with standard oxygen therapy:
  - There was a significant 60% and 17% lower risk of death with helmet noninvasive ventilation and face mask noninvasive ventilation, respectively
  - Helmet noninvasive ventilation (RR=0.26), face mask noninvasive ventilation (RR=0.76) and high-flow nasal oxygen (RR=0.76) were associated with lower risk of endotracheal intubation
- Additional sensitivity analyses altered the association of face mask but not helmet noninvasive ventilation with reduced rate of intubation and reduced mortality
- Limitations: Patients had a range of severity of respiratory failure; patient-level characteristics potentially associated with likelihood of response to any of the individual therapies were not assessed
- Implications: Noninvasive oxygen support strategies may fit into the algorithm of providing respiratory support for patients with COVID-19, but questions remain regarding when and for which patients


Large national study of insured patients (either Medicare Advantage or commercial insurance) with hypertension, all of whom were receiving at least one anti-hypertensive agent
- Propensity-score matched analyses
- Outpatient cohort of 2,263 people who had a positive outpatient SARS-CoV-2 test
  - 32% used ACE inhibitors, 32% used ARBs
12.7% were hospitalized, median of 30 days after testing positive
Overall, compared with use of other anti-hypertensive medications, neither ACE inhibitors nor ARBs was associated with risk of hospitalization
  • In the Medicare sub-population, use of ACE inhibitors was associated with nearly 40% lower risk of hospitalization, but no change in mortality

• Inpatient cohort of 7,933 patients who were hospitalized with COVID-19
  o 30% used ACE inhibitors, 28% used ARBs
  o 14% died, 60% survived to discharge, and 26% had ongoing hospitalization
  o Compared with use of other anti-hypertensive medications, neither ACE inhibitors nor ARBs was associated with increased risk of in-hospital mortality

• Limitation: Observational study; lower risk of hospitalization with use of ACE inhibitors among older individuals with hypertension requires confirmation
• Implications: Findings do not support a change to current use of ACE inhibitors or ARBs

TREATMENT
8. **Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19.** June 16.
• 2104 COVID-19 patients were randomized to receive dexamethasone (anti-inflammatory steroid) 6 mg once per day for 10 days and were compared with 4321 patients randomized to usual care alone
• In usual care arm, 28-day mortality was 41% in patients who required ventilation, 25% in those who required oxygen only, and 13% among those who did not require any respiratory intervention
• Dexamethasone reduced deaths by one-third in ventilated patients \[\text{rate ratio 0.65 (95\% CI 0.48 to 0.88); } p=0.0003\] and by one fifth in patients receiving oxygen only \[0.80 (0.67 to 0.96); p=0.0021\]
• There was no benefit among patients who did not require respiratory support
• Implications: Dexamethasone is inexpensive and widely available, and provides substantial survival benefit among COVID-19 patients with severe respiratory complications
• Limitations: Press release of unadjusted data; trial stopped early due to reported findings, full study results anticipated soon

• Elevated bruton tyrosine kinase (BTK) activity (autophosphorylation and increased IL-6) was detected in blood monocytes from 3 patients with severe COVID-19 compared to 4 healthy volunteers
• Treatment of whole blood samples with small molecule R848, a mimic of TLR7 and TLR8 activation by single strand RNA, increased the percentage of IL-6+ blood monocytes, with significantly higher levels in samples from COVID-19 patients compared to healthy controls
• In a prospective off-label clinical study, the BTK inhibitor (acalabrutinib) was administered to 19 hospitalized patients with severe COVID-19 (11 on supplemental oxygen, 8 on mechanical ventilation)
  • Patients in the supplemental oxygen cohort significantly increased their oxygen uptake efficiency and absolute lymphocyte count, and decreased their CRP levels
  • Blood IL-6 levels decreased during acalabrutinib treatment
• Limitations: Small study, no control group
• Implications: A hypothetical model suggested that BTK may participate in the cytokine storm response to COVID-19; opportunity to improve outcomes in severe COVID-19 by modulating the host inflammatory response; RCT is planned

TESTING
10. **Swabs Collected by Patients or Health Care Workers for SARS-CoV-2 Testing.** Tu et al. NEJM. June 2.
- Comparison of RT-PCR SARS-CoV-2 positivity for self-collection of tongue, nasal, and mid-turbinate swab samples to a nasopharyngeal sample collected by a health care worker
  - Compared to the nasopharyngeal sample, sensitivities of the tongue, nasal, and mid-turbinate samples were 89.8%, 94.0%, 96.2%
- Compared to nasopharynx, viral load may be higher in the middle turbinate and equivalent in the nose
- **Limitations:** Based on ~50 positive cases; lack of statistical significance
- **Implication:** Self-collection of samples for SARS-CoV-2 testing could reduce exposure of health care workers, preserve PPE

**IMMUNOLOGY/VACCINE DEVELOPMENT**

- Mice were made susceptible to SARS-CoV2 through exogenous delivery of human ACE2 with a replication-deficient adenovirus (Ad5-hACE2).
- Ad5-hACE2 treated and SARS-CoV2 intranasally challenged mice developed weight loss, severe pulmonary pathology, and high-titer virus replication in lungs
- Using genetically modified mice, the data indicate type I interferon and STAT1 were critical for virus clearance and disease resolution (IFNg was less critical)
- Antibody depletions of T cells in the mouse model reduced viral clearance; CD4+ and CD8+ T cell epitopes were predominantly located in the N protein and the S1 region of the S protein
- Immunization with Venezuelan equine encephalitis replicon particles (VRPs) expressing the SARS-CoV-2 spike reduced SARS-CoV-2 titers by greater than 3 logs in the mice. (VRPs expressing other proteins including transmembrane, nucleocapsid, and envelope did NOT change kinetics of viral clearance)
- Pooled convalescent plasma from SARS-CoV2 patients (NT50 >1:1000) or remdesivir administered one day PRIOR to challenge with SARS-CoV2 reduced weight loss, accelerated clearance of virus, and reduced pathological lung changes
- **Limitations:** Mice transduced with Ad5-hACE2 do not develop severe disease or extrapulmonary manifestations of disease. Treatment studies were a prophylactic design.
- **Implication:** Adenoviral vector strategy allows sensitization of all mouse strains and all genetically modified mice to SARS-CoV-2 infection providing immediate utility to investigate COVID-19 lung pathogenesis, to determine host factors necessary for optimal virus clearance, and to evaluate new therapies and vaccines

- Transduction of replication-defective adenoviruses encoding human ACE2 via intranasal administration into BALB/c mice and established receptor expression in lung tissues
- hACE2-transduced mice were productively infected with SARS-CoV-2, and this resulted in high viral titers in the lung, lung pathology, and weight loss.
- Viral titers in this model were low in the heart, spleen and brain and not detected in the GI tract, kidney or serum
- Transient type I IFN blockade was not necessary or sufficient for SARS-CoV-2 infection in mice, but with blockade, the mice exhibited greater weight loss and lung pathology
• Passive transfer of a neutralizing monoclonal antibody (B107, mAb recognizes the SARS-CoV-2 RBD) reduced viral burden in the lung and reduced levels of several pro-inflammatory cytokines and chemokines in the lungs

• **Limitations:**
  o Passive immunization was performed only on cohort of mice with anti-Type I response arm and was prophylactic (1 day prior to SARS-CoV2 challenge)
  o Adenoviral-vector method to transduce expression of hACE2 results in variable expression in different mice and is transient

• **Implication:** The availability of SARS-CoV2 small animal models can speed up screening, identification, and development of therapeutics and vaccines for advancement to human studies