Summary of Major Literature Related to COVID-19 (June 8-22)

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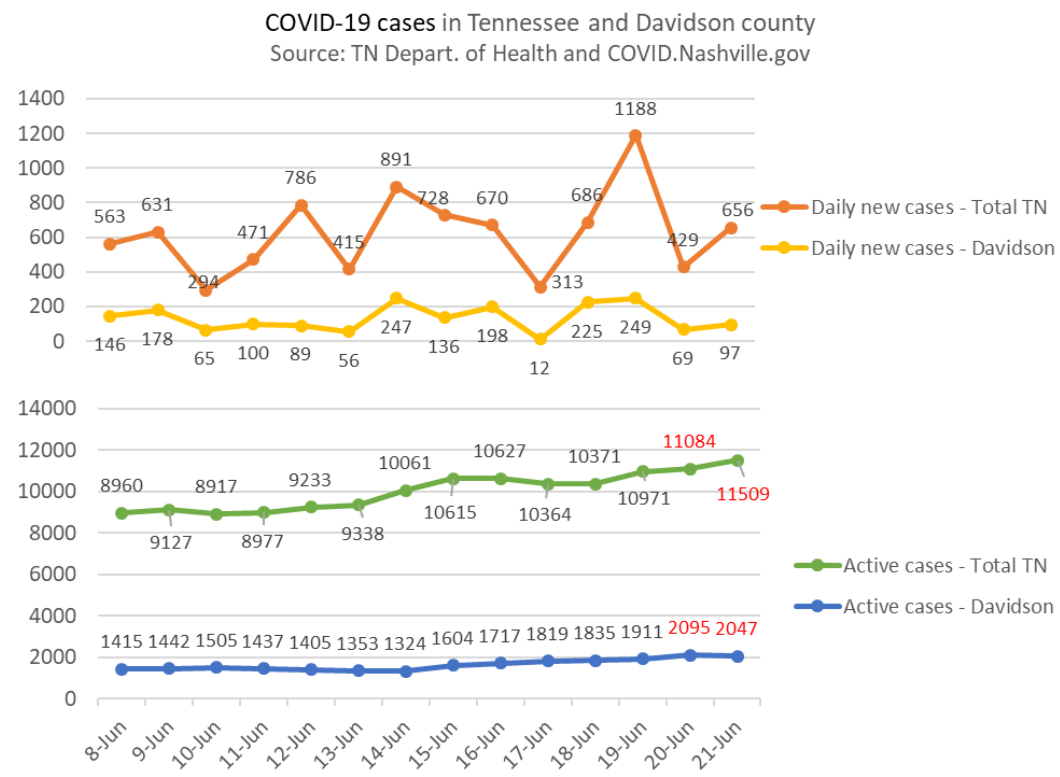
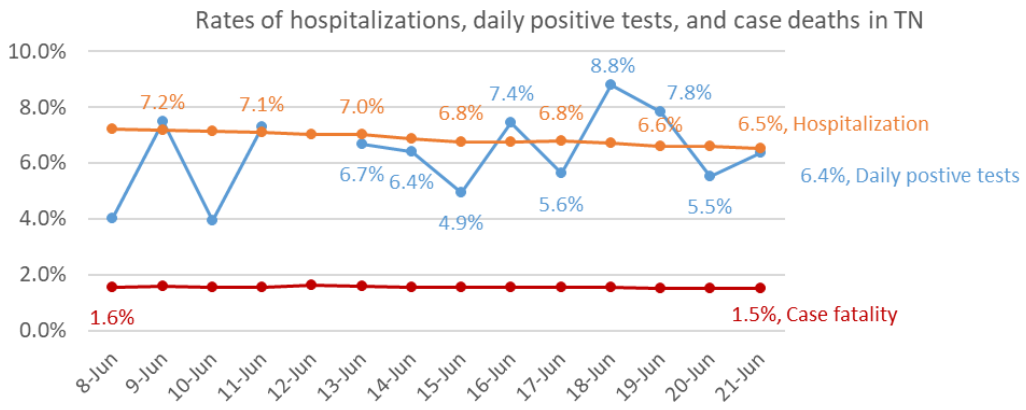
***This is informational and not intended to create variance from VUMC policies/guidance.**

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:

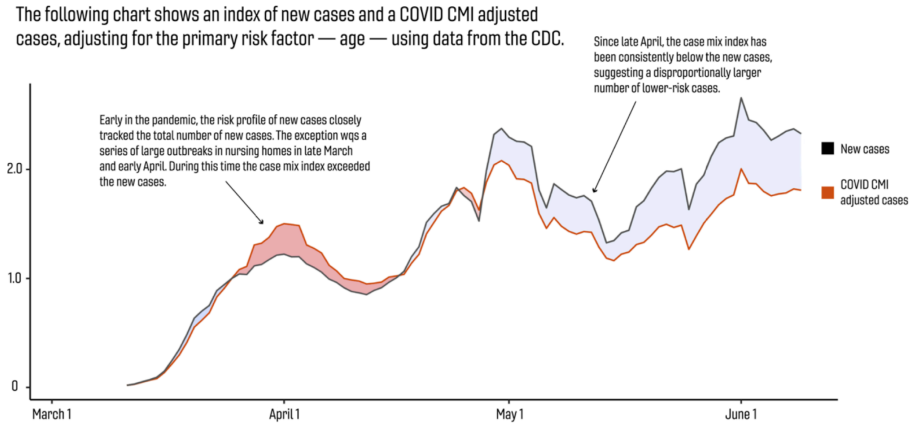
Groups	Cases	%
By sex		
Female	15,383	43.8%
Male	18,727	53.4%
By race/ethnicity		
White	14,657	41.8%
Black	7,312	20.8%
Hispanic	9,404	26.8%
Asian	512	1.5%
Other	5,779	16.5%
By age		
0–10	1,584	4.5%
11–20	3,223	9.2%
21–30	7,502	21.4%
31–40	7,267	20.7%
41–50	5,957	17.0%
51–60	4,712	13.4%
61–70	2,626	7.5%
71–80	1,327	3.8%
80+	840	2.4%

EPIDEMIOLOGY

1. **Vanderbilt COVID-19 Modeling Report for Tennessee**. Graves et al. June 16**.**

- 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

- Age is a risk factor for both hospitalization and death
- 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



- Nashville's COVID CMI adjusted case growth has been relatively slower than in other areas in TN
  - 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
  - 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

2. Age-dependent effects in the transmission and control of COVID-19 epidemics. Davies et al. Nature Medicine. June 16.

- 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

3. Estimating the effects of non-pharmaceutical interventions on COVID-19 in Europe. Flaxman et al. Nature. June 8.

- 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
  - 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:
    - 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%)
    - Lockdown had the largest impact on transmission (81% [75% - 87%] reduction)
    - 3,100,000 [2,800,000 - 3,500,000] deaths have been averted due to interventions
    - 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

4. **Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections.** Long et al. Nature Medicine. June 18.

- 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:
    - Significantly longer duration of viral shedding [median 19 d (IQR 15-26) vs 14 d (IQR 9-22)] (P = 0.028)
    - 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)
    - Lower levels of 18 pro- and anti-inflammatory cytokines
- During early convalescent phase (8 weeks after hospital discharge):
    - 93% and 81% of asymptomatic group had reduction in IgG and neutralizing antibody levels, respectively, as compared to 97% and 62% of symptomatic group
    - 40% of asymptomatic individuals became seronegative for IgG vs 13% of symptomatic group
- Implications:
    - Asymptomatic individuals may have a weaker immune response to SARS-CoV-2 infection
    - 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

5. **The *ABO* blood group locus and a chromosome 3 gene cluster associate with SARS-CoV-2 respiratory failure in an Italian-Spanish genome-wide association analysis.** Ellinghouse et al. medRxiv preprint. June 2.

- 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
    - 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

See also: Relationship Between Blood Group and Risk of Infection and Death in COVID-19: a live Meta-Analysis. Pourali et al. medRxiv preprint. June 8.

- 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

6. **Association of Noninvasive Oxygenation Strategies With All-Cause Mortality in Adults With Acute Hypoxemic Respiratory Failure: A Systematic Review and Meta-analysis.** Ferreyro et al. JAMA. June 4**.** **Editorial: Alternatives to Invasive Ventilation in the COVID-19 Pandemic.** Bhakti et al.

- 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 [risk ratio (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

7. **Association of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers with the Risk of Hospitalization and Death in Hypertensive Patients with Coronavirus Disease-19.** Khera et al. medRxiv preprint. May 19**.**

- 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
    - 30% used ACE inhibitors, 28% used ARBs
    - 14% died, 60% survived to discharge, and 26% had ongoing hospitalization
    - 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 [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

9. **Inhibition of Bruton tyrosine kinase in patients with severe COVID-19.** Roscheweski et al. Science Immunology. June 5**.**

- 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

11. **Generation of a Broadly Useful Model for COVID-19 Pathogenesis Vaccination, and Treatment.** Sun et al. Cell. June 10.

- 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 (NT_{50} >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

12. **A SARS-CoV-2 infection model in mice demonstrates protection by neutralizing antibodies.** Hassan et al. Cell. June 10.

- 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:
    - 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)
    - 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