Summary of Major Literature Related to COVID-19 (Week of May 4–10)

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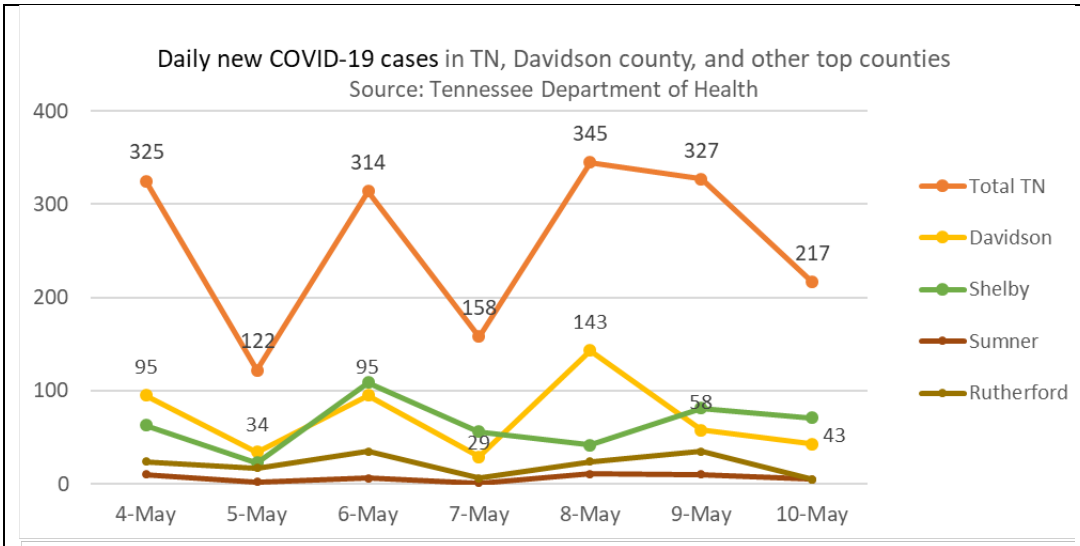
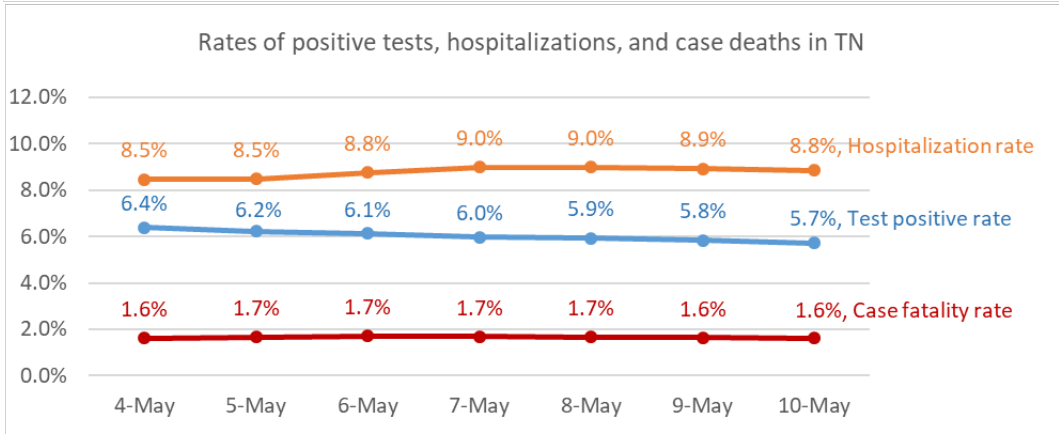
***This is informational and not intended to create variance from VUMC policies/guidance.**

STATISTICS - Tennessee and Nashville





- A trend of decline in the rate of positive tests

- Total cases = 14,985
- Total tests = 261,869
- Top three counties:
  - Davidson = 3,401
  - Shelby = 3,260
  - Rutherford = 725
- Demographics:

Groups	Cases	%
By sex		
Female	6,299	42.0%
Male	7,851	52.4%
By race/ethnicity		
White	6,016	40.1%
Black	3,087	20.6%
Hispanic	1,715	11.4%
Asian	342	2.3%
Other	1,062	7.1%
Pending	2,763	18.4%
By age		
0–10	348	2.3%
11–20	969	6.5%
21–30	2,939	19.6%
31–40	2,886	19.3%
41–50	2,632	17.6%
51–60	2,402	16.0%
61–70	1,462	9.8%
71–80	706	4.7%
80+	445	3.0%

EPIDEMIOLOGY

1. **Assessing Differential Impacts of COVID-19 on Black Communities**. Millett et al. amfAR preprint. May 2. **See also**: **COVID-19 Racial Disparities in U.S. Counties**.

- Reporting by state health departments of cumulative COVID-19 data by race/ethnicity is incomplete
- Using publicly available county-level data, COVID-19 cases and deaths were compared between disproportionately (>13%) black and all other (<13% black) counties in the US
  - 91% (616/677) of disproportionately black counties are located in the southern US
  - disproportionately black counties had higher comorbidity rate, higher proportion uninsured or unemployed, more crowded living conditions, and higher levels of air pollution
- 49% and 55% of COVID-19 cases and deaths, respectively, occurred in the 22% of counties that are disproportionately black
- Counties with higher proportions of black residents had more COVID-19 diagnoses (RR 1.24, 95% CI 1.17-1.33) and deaths (RR 1.18, 95% CI 1.00-1.40), after adjusting for county-level characteristics such as age, poverty, comorbidities, and epidemic duration

- COVID-19 deaths were higher in disproportionally black rural and small metro counties
- Limitations: ecologic analysis based on county-level data; potential for residual confounding by comorbidities, as well as socioeconomic and behavioral factors including social distancing practices

2. **Obesity could shift severe COVID-19 disease to younger ages.** Kass et al. Lancet. May 4**.**
Obesity a Risk Factor for Severe COVID-19 Infection: Multiple Potential Mechanisms. Sattar et al. Circulation. April 22

- Early reports suggested obesity may be an underappreciated risk factor for COVID-19 in the US
- Study examined the correlation between BMI and age among 265 COVID-19 patients (58% males, age 15-90 years) admitted to ICUs in the US
    - Median BMI was 29 kg/m^2, with 25% exceeding a BMI of 35 kg/m^2
- Younger individuals admitted to ICU were more likely to be obese
- In an earlier study among individuals with COVID-19 aged less than 60 years in New York City, those with a BMI between 30-34 and >35 Kg/m were 1.8 times and 3.6 times more likely to be admitted to critical care, respectively, than individuals with a BMI <30
- Obesity can restrict ventilation and reduce forced expiratory volume, impair immune responses, increase basal inflammatory status, and induce oxidant stress
- Implication: Obesity shifts severe COVID-19 to younger ages

3. **Covid-19 in Immune-Mediated Inflammatory Diseases — Case Series from New York.** Haberman et al. NEJM. April 29**.**

- Case series of 86 confirmed or highly suspected symptomatic COVID-19 patients at NYU Langone Health with known immune-mediated inflammatory disease and receiving anticytokine biologics or other immune-modulatory therapies
    - 62 (72%) were receiving biologics or JAK inhibitors
    - Incidence of hospitalization was 16%
- Compared to non-hospitalized patients, hospitalized patients:
    - were older (50 vs 46 years)
    - had higher percentage of hypertension (36 vs 8%), diabetes (14 vs 4%), or COPD (7 vs 4%)
    - had 30-40% higher odds of use of oral glucocorticoids, hydroxychloroquine or methotrexate, but not biologics or JAK inhibitors, after adjusting for comorbidities
- Implications:
    - incidence of hospitalization among patients with immune-mediated inflammatory disease is consistent with general population in NYC
    - baseline use of biologics is not associated with worse COVID-19 outcomes in this study

Children

4. **Hyperinflammatory shock in children during COVID-19 pandemic.** Riphagen et al. Lancet. May 7**.**

- Case cluster of 8 children with hyperinflammatory shock, showing features similar to atypical Kawasaki disease, in pediatric intensive care unit in London, UK
    - Four (50%) children had known family exposure to COVID-19
    - All children tested SARS-CoV-2 negative while inpatient
    - No pathological organisms were identified in 7 of the children
    - All but one were in the 75% for weight
- Clinical presentation was similar with unrelenting fever, variable rash, conjunctivitis, peripheral edema, and generalized extremity pain with significant gastrointestinal symptoms
- Since discharge, two children tested positive for SARS-CoV-2 (one postmortem). All children are receiving ongoing surveillance for coronary abnormalities

- Authors suggest this clinical picture represents a new phenomenon that children with asymptomatic SARS-CoV-2 infection may manifest as a hyperinflammatory syndrome with multiorgan involvement similar to Kawasaki syndrome
- Update states authors have now treated more than 20 children with similar clinical presentation, 10 of these are antibody positive for SARS-CoV-2.
- **See also: NYC Department of Health Advisory Statement.** Similar hyperinflammatory syndrome among 64 children and teens in NYC has been reported

5. **Atypical presentation of COVID-19 in young infants.** Nathan et al. Lancet. April 27**.**

- Trousseau Hospital in Paris observed an increase in number of young (< 3 months) infants presenting with SARS-CoV-2 infections one week after quarantine began
- Admitted 14 infants with 5 (all boys) testing positive for SARS-CoV-2. All 14 infants presented with fever and/or respiratory symptoms
- 4 of the COVID-19 positive boys showed neurological symptoms at admission. Their clinical course was rapidly favorable, which allowed for discharge after 1-3 days.
- All infants' parents showed mild signs of viral infection that could be related to undiagnosed COVID-19 with no mention of testing
- Implication: infants younger than 3 months with isolated fever should be tested for SARS-CoV-2

TRANSMISSION/PPE

6. **Universal Masking is Urgent in the COVID-19 Pandemic: SEIR and Agent Based Models, Empirical Validation, Policy Recommendations.** Kai et al. arXiv preprint. April 21**.**

- Two modeling approaches for predicting the impact of universal face mask wearing on the spread of SARS-CoV-2
- Significant impact when at least 80% of the population wears masks
- Minimal impact when only 50% or less of the population wears masks
- Significant impact when universal masking is adopted early (by Day 50 of a regional outbreak) compared to late
- Effects hold for homemade masks
- Empirical data showed strong correlation between early universal masking and successful suppression of daily case growth rates and/or reduction from peak daily growth rates, consistent with model predictions
- Implication: **Universal masking is a key non-pharmaceutical intervention** for containing or slowing the spread of the COVID-19 pandemic as governments exit society lockdowns
    - combined with social distancing and mass contact tracing, this is more sustainable from economic, social and mental health perspectives than full lockdown
    - depends on strong public health messaging and the acceptance of masking in the population
    - proper masking techniques and norms need to be taught

7. **Changes in contact patterns shape the dynamics of the COVID-19 outbreak in China.** Zhang et al. Science. April 29.

- Mathematical models were used to address age differences in susceptibility and how altered social patterns affect transmission of COVID-19
- Using a mean time between successive generations of cases of 5.1 days, strict social distancing measures were found to significantly reduce R_0 to below an epidemic threshold
    - Findings were robust across a variety of sensitivity analyses
- School closures also impacted disease dynamics. However, models indicated that this approach alone would not be sufficient to prevent an outbreak

- Limitations:
    - contact testing and rapid quarantine of suspected and confirmed positive cases was also in place, which could influence model results
    - differences in population structures and age-mixing behavior patterns limit generalizability

TREATMENT/EMERGING DRUG TARGETS

8. **Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial.** Hung et al. Lancet. May 8.

- Multicenter, prospective, open-label, randomised, phase 2 trial in adults with COVID-19 admitted to six hospitals in Hong Kong (NCT04276688)
- Patients were randomly assigned (2:1) to a 14-day triple combination of lopinavir 400 mg and ritonavir 100 mg every 12 h, ribavirin 400 mg every 12 h, and three doses of 8 million IUs of interferon beta-1b on alternate days (combination group, N=86) or to 14 days of lopinavir 400 mg and ritonavir 100 mg every 12 h (control group, N=41)
- Primary endpoint was time to providing a nasopharyngeal swab negative for SARS-CoV-2 RT-PCR
- Median number of days from symptom onset to start of study treatment was 5 days (IQR 3–7)
- The combination group had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab (7 days [IQR 5–11]) than the control group (12 days [8–15]; hazard ratio 4.37 [95% CI 1.86–10.24], p=0.001)
- Combination group also showed improvements in secondary outcomes, including shorter time to complete resolution of symptoms and shorter hospital stay
- Adverse events included self-limited nausea and diarrhea with no significant difference between the two treatment groups. One patient in the control group discontinued treatment because of biochemical hepatitis
- Limitations:
    - Open label, no placebo group
    - Subgroup (n=34) within combination group who started treatment 7 days or more after symptom onset omitted interferon beta-1b because of concerns about proinflammatory side-effects
- Implications: Early treatment with the triple combination of antiviral therapy with interferon beta-1b, lopinavir–ritonavir, and ribavirin is safe and highly effective in shortening duration of virus shedding, alleviating symptoms, and facilitating the discharge of patients with mild to moderate COVID-19

9. **Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study.** Cavalli et al. Lancet Rheum. May 7.

- A small retrospective study conducted in Italy to evaluate clinical outcomes of patients treated with anakinra in addition to standard treatment (hydroxychloroquine + lopinavir + ritonavir)
- At 21 days, 29 patients who received anakinra (5 mg/kg twice a day intravenously) showed reductions in serum CRP; 21 (72%) of 29 patients showed improvements in respiratory function vs. 8 (50%) of 16 patients who received standard treatment only
- Survival was 90% in anakinra group vs. 56% in standard treatment group (p=0.009); ventilation-free survival was 72% in anakinra group vs. 50% in standard treatment group (p=0.15)
- Discontinuation of anakinra was not followed by inflammatory relapses
- A phase 2 trial of intravenous anakinra in COVID-19 is ongoing (NCT04324021).
- Implication: Treatment with anakinra in addition to standard treatment was safe and associated with better clinical outcomes
- Limitations: Small and non-randomized study

VIROLOGY

10. **The coronavirus proofreading exoribonuclease mediates extensive viral recombination.** Gribble et al. bioRxiv preprint. April 25.

- Extensive RNA recombination is performed by SARS-CoV-2, MERS-CoV, and murine hepatitis virus (MHV) in culture – determined by combining both short- and long-read RNA sequencing
- These divergent β-CoVs generate similar patterns of recombination junctions and diverse populations of defective viral genomes (DVG) and subgenomic mRNAs (sgmRNA)
- Inactivating the proofreading nonstructural protein (nsp14) 3'-to-5' exoribonuclease (nsp14-ExoN) in MHV decreased recombination events and patterns of recombination suggesting nsp14-ExoN is required not just for high fidelity replication and also recombination
- Limitation: no proofreading-deficient nsp14-ExoN catalytic mutant has been rescued in MERS-CoV or SARS-CoV-2 limiting the genetic inactivation study to MHV at this time.
- Implications:
    - nsp14-ExoN represents a highly-conserved and vulnerable target for virus inhibition and attenuation
    - treatment of SARS-CoV-2 infection with small molecules that target the replicase proteins including nsp14-ExoN may result in an altered recombination landscape and perturb viral fitness