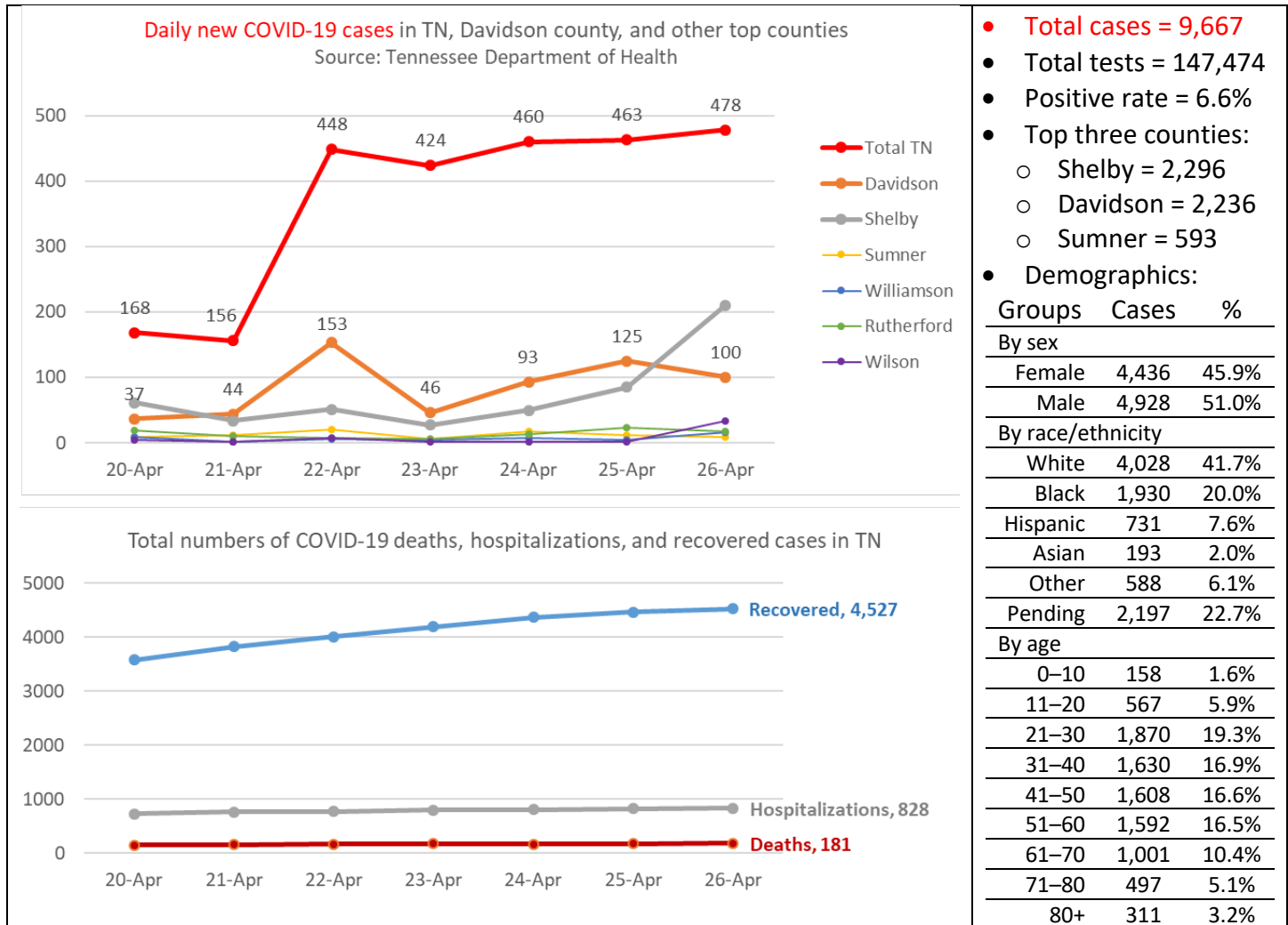**Summary of Major Literature Related to COVID-19 (Week of April 20-26)**
Led by Loren Lipworth and Qi Dai, with contribution from XO Shu, D Yu, M Shrubsole, S Sudenga, J
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*This is informational and not intended to create variance from VUMC policies/guidance.

STATISTICS - Tennessee and Nashville

Daily new COVID-19 cases in TN, Davidson county, and other top counties
Source: Tennessee Department of Health

Total numbers of COVID-19 deaths, hospitalizations, and recovered cases in TN

- Total cases = 9,667
- Total tests = 147,474
- Positive rate = 6.6%
- Top three counties:
  - Shelby = 2,296
  - Davidson = 2,236
  - Sumner = 593
- Demographics:

Groups	Cases	%
By sex		
Female	4,436	45.9%
Male	4,928	51.0%
By race/ethnicity		
White	4,028	41.7%
Black	1,930	20.0%
Hispanic	731	7.6%
Asian	193	2.0%
Other	588	6.1%
Pending	2,197	22.7%
By age		
0–10	158	1.6%
11–20	567	5.9%
21–30	1,870	19.3%
31–40	1,630	16.9%
41–50	1,608	16.6%
51–60	1,592	16.5%
61–70	1,001	10.4%
71–80	497	5.1%
80+	311	3.2%

EPIDEMIOLOGY

1. **The association between age, COVID-19 symptoms, and social distancing behavior in the United States**. Canning et al. medRxiv preprint. April 23**.**
- Open online survey of 4,676 adults (April 4-7) was conducted to model effects of age and common COVID-19 symptoms on going out of the home for non-medical reasons and on number of close contacts with non-household members
- 20.4% reported common symptoms of COVID-19 (fever, dry cough, shortness of breath) during past two weeks
- 52% went out of home the day before survey
- 38.5% had $\geq$1 and 9.7% had $\geq$5 close contacts with non-household members
- Those experiencing shortness of breath or flu-like symptoms in past two weeks, but not those with dry cough or fever, practiced more intense social distancing
- Older people were just as likely to leave their homes as younger people but had fewer close contacts
- Limitations: concerns about selection bias and generalizability; sample skewed toward those with higher education, younger adults, and women; no data on comorbid risk factors except for age

- <u>Implications</u>: Public health message about symptoms that indicate high likelihood of having COVID-19 should be clearer; social distancing recommendation should be stronger for symptomatic individuals

2. **Estimating the Prevalence of COVID-19 in the United States: Three Complementary Approaches**. Lu et al. medRxiv preprint. April 23.
- Official positive COVID-19 case counts are under-reported because asymptomatic cases and symptomatic cases who did not seek testing or medical attention are not counted
- Four predictive models were developed, relying on different data sources and assumptions, and were applied to estimate COVID-19 cases from March 1 to April 4 on the state and national level
- The lowest and highest model estimates for the number of COVID-19 cases nationally are 2.7 to 8.3 million, 9 to 27 times greater than the 311,000 positive cases officially reported in that time period
- At the state level, COVID-19 prevalence estimates range from 10 to 100 times greater than reported
    - All four methods generally agree on the ordering of states by case count
- <u>Limitation</u>: Potential for uncertainty and bias in each method
- <u>Implication</u>: Influenza-like illness surveillance systems can be leveraged to estimate COVID-19 burden and to guide public health response

3. **Time course quantitative detection of SARS-CoV-2 in Parisian wastewaters correlates with COVID-19 confirmed cases**. Wurtzer et al. medRxiv preprint. April 17.
- RT-qPCR analysis of SARS-CoV2 in sampled sewage across greater Paris for more than 1 month
- All raw and 75% of treated wastewater samples were positive for SARS-CoV2
    - Treated wastewater showed a 100 times reduction in viral load compared to raw wastewater
- The increase of viral load in raw wastewater corresponded to the increase in fatal cases observed
    - Detection of viral genome in wastewater occurred before the beginning of the exponential growth of the epidemic
- <u>Implication</u>: Monitoring wastewater may be an early, cheap tool to warn about COVID-19 outbreaks

Homelessness
4. **Assessment of SARS-CoV-2 Infection Prevalence in Homeless Shelters — Four U.S. Cities, March 27–April 15, 2020**. CDC COVID-19 Response Team. April 22.
    COVID-19 outbreak at a large homeless shelter in Boston: Implications for universal testing. Baggett et al. medRxiv preprint. April 15.
- PCR testing for SARS-CoV-2 of 1,192 residents and 313 staff members at 19 homeless shelters in Boston, San Francisco, Seattle and Atlanta, irrespective of symptoms
- At 5 sites where testing followed identification of a cluster of 2 or more COVID-19 cases in preceding 2 weeks, the proportion with positive test results for SARS-CoV-2 was high
    - Seattle: 17% of residents, 17% of staff members; Boston: 36%, 30%; San Francisco: 66% 16%.
- Lower infection prevalence reported at shelters with <u><</u>1 reported case: 4-5% of residents, 1-2% of staff
- Symptom assessment for 408 participants from the Boston shelter only
    - mean age 51.6 years, 71.6% male, 33.1% Black, ad 18.6% Hispanic or Latino
    - cough (7.5%), shortness of breath (1.4%), and fever (0.7%) were all uncommon among SARS-CoV-2 positive individuals
- <u>Limitation</u>: Testing at single time point, incomplete testing uptake (56% in San Francisco)
- <u>Implication</u>: Universal testing may be a better strategy than screening at symptom onset

THROMBOEMBOLIC DISEASE/HYPERCOAGULABILITY
5. **Incidence of thrombotic complications in critically ill ICU patients with COVID-19.** Klok et al. Thrombosis Res. April 10.

- COVID-19 may predispose to both venous and arterial thromboembolic disease due to excessive inflammation, hypoxia, and hypercoagulability
- Study of a composite outcome of symptomatic acute pulmonary embolism (PE), deep-vein thrombosis, ischemic stroke, myocardial infarction or systemic arterial embolism in 184 ICU patients with COVID-19 pneumonia in 3 Dutch hospitals
  - All patients received at least standard doses of thromboprophylaxis
- The cumulative incidence of the composite outcome was 31%
  - PE was the most frequent thrombotic complication (n=25, 81%)
- Age and coagulopathy were independent predictors of thrombotic complications.
- Limitation: 76% of patients still in ICU at end of study, so results could be underestimates
- Implication: Evaluation and risk stratification for thromboembolic disease are critical
- **See also: Pulmonary Embolism in COVID-19 Patients: Awareness of an Increased Prevalence**. Poissy et al. Circulation. April 24.
  - Cumulative incidence of PE in 107 COVID-19 ICU patients in France was estimated at 20%
    - 91% were receiving prophylactic anticoagulation per guidelines for critically ill
  - D-Dimers, plasma factor VIII activity, and factor Willebrand antigen levels at admission were associated with greater PE risk

6. **Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy**. Tang et al. JTH. March 27.
- Study of the effect of anticoagulant therapy on mortality among 449 consecutive patients with severe COVID-19 in Wuhan
  - 99 (22%) received heparin (94/99 got low molecular weight heparin, LMWH) for 7+ days
  - Doses were those typically used for less mobile hospitalized US patients
- LMWH treatment was associated with significantly lower 28-day mortality among patients with sepsis-induced coagulopathy (SIC) score $\geq$4 (40% vs 64%) and patients with D-dimer >3.0 ug/mL (33% vs 52%)
- Limitation: possible confounding by indication for LMWH use
- Implication: Heparin is associated with better prognosis in severe COVID-19 patients with coagulopathy

CLINICAL MANAGEMENT
7. **Expert U.S. panel develops NIH treatment guidelines for COVID-19**.
- A panel of U.S. physicians, statisticians, and other experts has developed treatment guidelines for COVID-19. Guidelines are intended for healthcare providers and based on published and preliminary data and the clinical expertise of the panelists; will be updated often as new data are published
Summary recommendations
- The COVID-19 Treatment Guidelines Panel (the Panel) **does not recommend** the use of any agents for pre-exposure prophylaxis (PrEP) against SARS-CoV-2 outside of the setting of a clinical trial
- The Panel **does not recommend** the use of any agents for post-exposure prophylaxis (PEP) against SARS-CoV-2 infection outside of the setting of a clinical trial
- The Panel recommends no additional laboratory testing and no specific treatment for persons with suspected or confirmed asymptomatic or presymptomatic SARS-CoV-2 infection
- At present, no drug has been proven to be safe and effective for treating COVID-19. There are insufficient data to recommend either for or against the use of any antiviral or immunomodulatory therapy in patients with COVID-19 who have mild, moderate, severe, or critical illness.

8. **Association of Renin-Angiotensin System Inhibitors With Severity or Risk of Death in Patients With Hypertension Hospitalized for Coronavirus Disease 2019 (COVID-19) Infection in Wuhan, China.** Li et al. JAMA Cardiol. April 23.

- In this single-center case series involving 362 patients with hypertension hospitalized with COVID-19 infection, no difference in severity of disease, complications, and risk of death was found in patients who were taking ACEIs/ARBs compared with those not treated with these medications.
- Results support no change in current guidelines for treating hypertension among COVID-19 patients

9. **Covid-19 and Kidney Transplantation.** Akalin et al. NEJM. April 24.
- Study of 36 consecutive kidney transplant patients positive for the COVID-19 test at Montefiore Medical Center; 28 were hospitalized, 11 of whom received mechanical ventilation
- Median age 60y, most common initial symptom was fever (58%)
- 94% had hypertension, 69% had diabetes, 36% were former or current smokers, 17% had heart disease
- Antimetabolites were withdrawn in 24/28, and tacrolimus withdrawn in 6/28 severely ill patients
- 68%, 71% and 29% had low CD3, CD4 and CD8 cell counts, respectively
- Patients had lower CD3, CD4, and CD8 cell counts and more rapid clinical progression (28% mortality at 3 weeks) than those with Covid-19 in the general population.
- Implication: Results support the need to decrease doses of immunosuppressive agents in patients with Covid-19, especially in those who have recently received antithymocyte globulin, which decreases all T-cell subsets for many weeks

10. **Bacterial and fungal infections in COVID-19 patients: A matter of concern.** Zhou et al. Infection Control Hospital Epidemiol. April 2020.
- Bacterial and fungal infections in COVID-19 patients have been inadequately investigated and reported
- In the few studies with data available, the antibiotic use rate (94%-100%) was much higher than the reported incidence of secondary infection (13-15% among non-survivors, and 0-25% among survivors)
- Implication: Diagnosis of bacterial or fungal infection should be included in prognostic analyses for COVID-19, but shortage of PPE has hampered routine microbiological examination

TREATMENT/EMERGING DRUG TARGETS
11. **Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19.** Magagnoli et al. medRxiv preprint. April 23.
- Retrospective EHR study of 368 Veterans hospitalized with confirmed SARS-CoV-2 infection, classified by exposure to hydroxychloroquine alone (HC; n=97), HC with azithromycin (HC+AZ; n=113) or no HC (n=158) during their hospitalization
- Compared to the no HC group:
  - there was a 2.6-fold increased risk of death in the HC group but not in the HC+AZ group
  - there was no significant difference in the risk of ventilation or in the risk of death after ventilation in either the HC or the HC+AZ group
- Limitation: HC, with or without AZ, was more likely to be prescribed to patients with more severe disease, as assessed by baseline ventilatory status and metabolic and hematologic parameters; thus, potential for residual confounding remains even with propensity score adjustment
- Implication: Suggests caution in using HCQ in hospitalized COVID-10 patients, but clinical trials needed
- **FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems**

12. **Depriving Iron Supply to the Virus Represents a Promising Adjuvant Therapeutic Against Viral Survival.** Liu et al. Current Clinical Microbiology Reports. April 20.
- Iron-containing enzymes are required for viruses, likely including coronaviruses, to complete their replication process. Poor prognosis has been reported under conditions of iron overload among patients with viral infections

- Deferiprone has been shown to induce cell death in HIV-infected cells
- It could be deduced from other viral infections that iron chelation might be a promising beneficial adjuvant in treating COVID-19, through oral uptake or venous injection of iron chelators, or through manipulation of key iron regulators
- <u>Limitation</u>: No clinical trial data for COVID-19 are currently available

MENTAL HEALTH

13. **Coronavirus Disease 2019 (COVID-19) and Mental Health for Children and Adolescents.** Golberstein et al. JAMA Pediatr. April 14.
- School closures may have unintended and severe consequences for mental health care of children and adolescents
  - based on past surveys, 14% of adolescents (~3 million) receive mental health services at school and 35% of these adolescents receive the services solely at school
- Potential for increasing disparities: adolescents in racial/ethnic minority groups, with lower family income, or with public health insurance are disproportionately more likely to receive services at school
- Tele-mental health services are an important strategy and are similarly effective to in-person services; however, reliance on this as sole strategy may increase disparities
- Models such as schools coordinating with community mental health agencies to deliver services in schools are also needed

IMMUNOLOGY/VACCINE DEVELOPMENT

14. **Human leukocyte antigen susceptibility map for SARS-CoV-2**. Nguyen et al. J Virol [Epub]. April 17.
- Human leukocyte antigen (HLA) alleles, which are critical components of the viral antigen presentation pathway, have been shown to confer differential viral susceptibility and severity of disease
- The investigators used major histocompatibility complex (MHC)-peptide binding affinity predictors to *in silico* evaluate per-allele viral proteome presentation across 145 HLA -A, -B, and -C genotypes for all SARS-CoV-2 peptides
- They examined distribution of HLA allelic presentation of highly conserved human coronavirus peptides with potential to elicit cross-protective immunity to COVID-19
- HLA-B*46:01 had the fewest predicted binding peptides for SARS-CoV-2, suggesting individuals with this allele may be particularly vulnerable to COVID-19 and could have more severe infection, as was previously shown for SARS
  - Global allelic frequency of HLA-B*46:01 is ~6.1%, with higher frequency in China, Thailand and Vietnam.
- HLA-B*15:03 showed the greatest capacity to present highly conserved SARS-CoV-2 peptides, suggesting it could enable cross-protective T-cell based immunity
  - Global allelic frequency of HLAB*15:03 is low at ~0.63%, with higher frequency in parts of Africa
- <u>Limitation</u>: This is an *in silico* study. Studies conducted in COVID-19 patients with individual-level HLA typing and clinical outcomes data are needed to confirm the findings
- <u>Implication</u>: If confirmed, pairing HLA typing with COVID-19 testing may help to predict viral severity, and HLA typing could be used to tailor future vaccination strategies to genotypically at-risk populations

15. **Microneedle array delivered recombinant coronavirus vaccines: Immunogenicity and rapid translational development**. Kim et al. EBioMedicine (in press). April 2.
- Microneedle array (MNA) subunit vaccines were developed against MERS and SARS-CoV2. Utilized respective spike (S) protein as the antigen, a trimerization domain and agonists of TLR4 and 5.
- Pre-clinical immunogenicity of the vaccines was tested in mouse models.

- MNA delivery of MERS-S1 subunit vaccines generated strong antibody-mediated neutralizing activity that approaches that induced by live adenovector immunization and exceeds that observed by s.c. delivery (traditional needle)
- MNA delivery of MERS-S1 subunit vaccines produced long lasting (>55 week) IgG levels independent of choice of TLR agonist, but s.c. immunization of only the rMERS-S1+TLR4 agonists induced increasing levels of IgG that were sustained up to 55 weeks after immunization
- MNA delivery of 2 SARS-CoV2-S1 vaccines (with or without TRL4 agonist) lead to detectible SARS-CoV-2 specific IgG responses by two weeks post-immunization.
- A timeline for the rapid development of clinic grade MNA SARS-CoV-2 subunit vaccines is presented.
- Limitation: No preclinical model is available to investigate efficacy in vivo (neutralizing antibody)
- Implication: MNA delivery of coronaviruses-S1 subunit vaccines as an immunization strategy against SARS-CoV-2 infection should be considered. MNA delivery systems are in a clinical trial for delivery of chemo-immunotherapy (ClinicalTrials.gov Identifier: NCT02192021)

16. **Imbalanced host response to SARS-CoV-2 drives development of COVID-19**. Blanco-Melo et al. Cell (in press). April 26.
- Utilizing epithelial cells, the ferret model and COVID19 patients (post-mortem lung), the transcriptional immune profile to SARS-CoV2 was assessed
- A549 cells (engineered to express ACE2) & normal bronchial epithelial cells infected with SARS-CoV2 produced a limited IFN type I/III response but increased expression of many chemokines
- The ferret model facilitated viral replication and transcriptional responses to SARS-CoV2 at 4 time points up to 14 days. Peak viral gene expression was observed in nasal washes at day 3 (and undetectable by day 14); peak host gene expression was at day 7. Significant expression of CXCL9, CCL2, CCL8 as well as IL-6 and IL-1RA were reported (sustained to 14 days post infection). Type I/III interferons were not detected
- Serum analysis of COVID19 patients detected no IFNβ or IFNλ but high levels of IL-6, CXCL9, CCL8 and IL-1RN compared to control serum. While post-mortem analysis of lungs was limited (2 controls and 2 patients), signature of limited IFN I/III was observed
- Limitations: In addition to low numbers of COVID19 patient samples and only being able to assess post-mortem, the timeline for serum analysis may be too late to see Type I/III interferon
- Implications: Further evidence that immune modulatory drugs could be considered for treatment of patients with COVID19