Summary of Major Literature Related to COVID-19 (Week of April 13-19)

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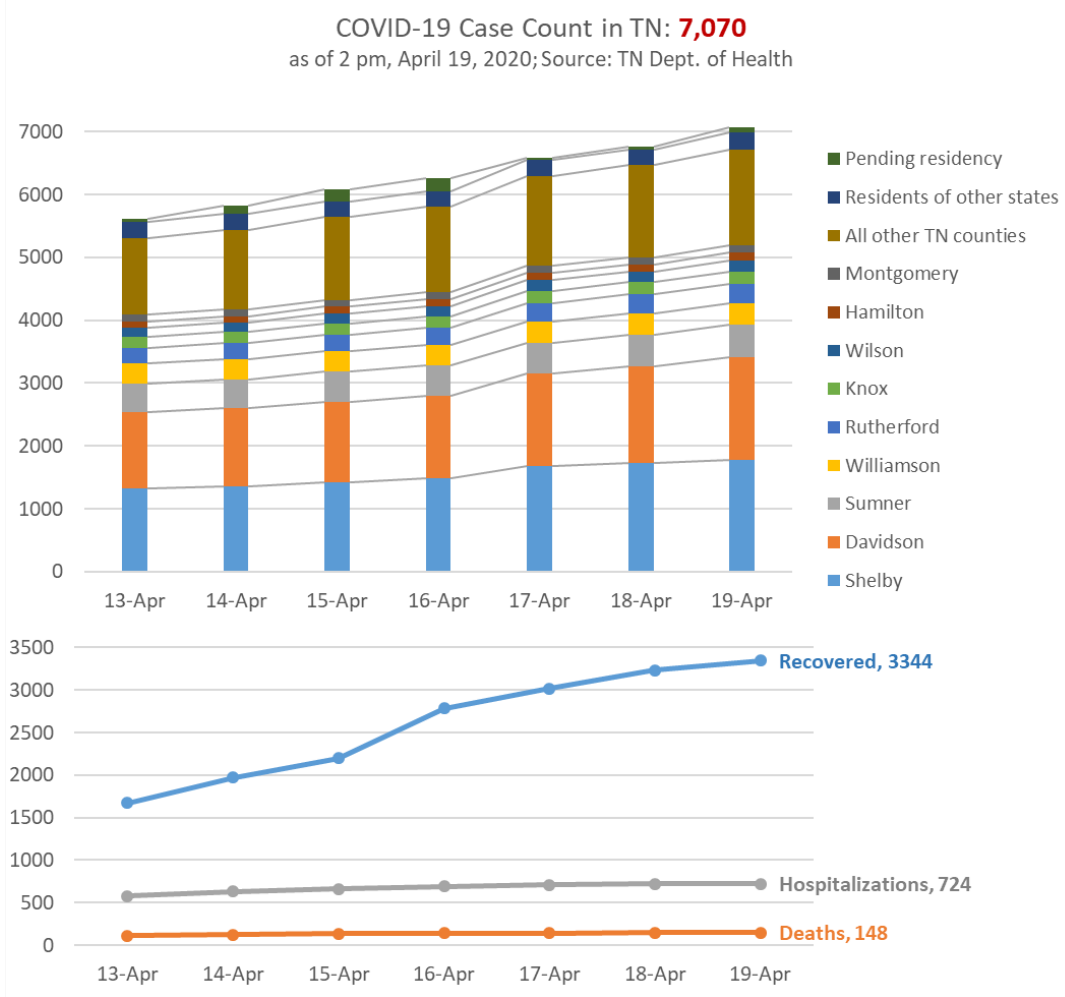
***This is informational and not intended to create variance from VUMC policies/guidance.**

STATISTICS - Tennessee and Nashville



- Total tested = 97,098
- Positive rate = 7.3%
- Hospitalized = 724
- **Recovered = 3,344**
- Deaths = 148
- Top three counties:
  - Shelby = 1,778
  - Davidson = 1,638
  - Sumner = 509
- Demographics:

Groups	Cases	%
By sex		
Female	3,586	50.7%
Male	3,258	46.1%
By race/ethnicity		
White	3,347	47.3%
Black	1,470	20.8%
Hispanic	441	5.9%
Asian	130	1.8%
Other	418	5.9%
Pending	1,264	17.9%
By age		
0–10	98	1.4%
11–20	379	5.4%
21–30	1,422	20.1%
31–40	1,205	17.0%
41–50	1,194	16.9%
51–60	1,282	18.1%
61–70	842	11.9%
71–80	404	5.7%
80+	228	3.2%

MODELING

1. **Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period.** Kissler. Science. April 14**.**

- Estimates of seasonality, immunity, and cross-immunity of human coronaviruses OC43 and HKU1 (causes of the common cold) from US time series data informed a model of SARS-CoV-2 transmission
- The duration of immunity for both OC43 and HKU1 is approximately 45 weeks; while OC43 confers stronger cross-immunity both do provide cross-immunity against the other
- Model projected recurrent wintertime outbreaks of SARS-CoV-2 after initial severe pandemic wave
- Prolonged or intermittent social distancing could be required until 2022 to prevent exceeding US critical care capacity (there is a 3-week lag from start of social distancing to peak critical care demand)
- Model findings showed other key points:
- SARS-CoV-2 can proliferate at any time of year, with winter/spring favoring outbreaks with lower peaks and autumn/winter leading to more acute outbreaks.

- If immunity to SARS-CoV-2 is not permanent, it will likely enter into regular circulation.
- High seasonal variation in transmission leads to smaller peak incidence during the initial pandemic wave but larger recurrent wintertime outbreaks
- If immunity to SARS-CoV-2 is permanent, the virus could disappear for five or more years after causing a major outbreak
- Low levels of cross immunity from the other human coronaviruses against SARS-CoV-2 could make SARS-CoV-2 appear to die out, only to resurge after a few years
- Data on extent and duration of immunity to SARSCoV2 are essential to inform model projections

EPIDEMIOLOGY

2. **Geographic Differences in COVID-19 Cases, Deaths, and Incidence — United States, February 12–April 7, 2020**. CDC COVID-19 Response Team. April 17.

- First community transmission of COVID-19 occurred in Feb, had spread to all 50 states by mid-March
- As of April 7, 395,926 case of COVID-19 and 12,757 related deaths occurred in the US; case fatality ranged from 0.7% in Utah to 5.7% in Kentucky
- Overall cumulative incidence of COVID-19 in the US is 119.6 cases per 100,000 (range: 20.6 to 915.3)
    - Cumulative incidence varied greatly by region; 915.3/100,000 in NYC vs. 61.1/100,000 in TN

3. **Characteristics of Health Care Personnel with COVID-19 — United States, February 12–April 9, 2020.** CDC COVID-19 Response Team. April 17.

- Data from 9,282 health care personnel who tested positive for COVID-19 (3% of all COVID-19 cases)
    - Median age was 42 (IQR: 32 to 54 years); 76% <age 55, 18% aged 55 to 64; 6% age 65+
    - 73% were female
    - 72% were white, 21% black, 5% Asian, 2% other or multiple race; 90% were non-Hispanic/Latino
    - Suspected COVID contact: 55% with a COVID-19 patient only in a health care setting; 27% in household setting only; 13% in community setting only; 5 in more than one of these settings
    - 92% reported having at least one symptom; most common symptom was cough (78%)
    - Limitation: health care personnel status missing for 84% of the cases. In 12 states with more complete reporting, health care personnel made up 11% of COVID-19 cases

4. **Covid-19 Testing, Hospital Admission, and Intensive Care Among 2,026,227 United States Veterans Aged 54-75 Years.** Rentsh. MedRxiv preprint. April 14**.**

- Retrospective EHR study of >2 million Veterans age 54-75
- 585/3,789 (15%) tested positive for Covid-19 between Feb 8-March 30
    - Black Veterans were twice as likely to be tested than non-black Veterans
- Black race was associated with a positive Covid-19 test (after adjusting for urban residence and conditioning on geographic location), but not with hospitalization or intensive care
- Predictors of hospitalization and intensive care among those who tested positive for Covid-19:
    - Laboratory abnormalities (in particular fibrosis-4 score>3.25) and VACS index (validated summary measure of physiologic abnormalities which includes FIB-4, albumin, white blood cell count) were strongly associated
    - Comorbidities (CKD, COPD, DM, HTN, vascular disease) and prior medication use, including NSAIDs and ACE/ARBs, were not important predictors in adjusted analysis
- Implications: Small proportion of Veterans tested; racial differences in VA Healthcare System may not be generalizable to the general population

5. **Factors associated with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York City**. Petrilli. MedRxiv preprint. April 11.

- 4,103 confirmed COVID-19 patients in NY City (NYU Langone Health system: 4 acute care hospitals)
- The strongest risk factor for hospitalization was age≥75y (66.8-fold increased risk), followed by age 65-74y (10.9-fold increase) compared to age of 19-44y; BMI>40 (6.2-fold high risk) and heart failure (4.3-fold increase) were other major risk factors
- Admission oxygen impairment (O2 saturation <88%), d-dimer>2500 and ferritin>2500 (all ORs=6.9) were strongest predictors of critical illness

CLINICAL CHARACTERISTICS

6. **COVID-19, Arrhythmic Risk and Inflammation: Mind the Gap!** Lazzerini. Circulation. April 14.
See also Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the Coronavirus Disease 2019 (COVID-19) Pandemic. Driggin. J Am Coll Cardiol.

- In 138 hospitalized patients, arrhythmias were the leading complication (20%) after acute respiratory distress syndrome
    - Particularly in those admitted to ICU where the prevalence rose to 44%.
- Half of ICU patients with arrhythmia showed acute cardiac injury
- Other factors related to the arrhythmic risk in COVID-19 include:
    - Drugs that increase susceptibility to QT-related VA, such as hydroxychloroquine/chloroquine and lopinavir/ritonavir, and other agents commonly used to treat bacterial pneumonia (quinolones, azithromycin)
    - Pre-existing cardiac diseases, electrolyte imbalances, and other drugs used in critical care
    - High grade, systemic inflammatory state of COVID-19, including elevated IL- 6, TNFα, and IL-1, may promote QT prolongation by impacting K channels and inhibiting cytochrome p450
- Implication: Anti-IL6 targeted therapies (e.g., tocilizumab, sarilumab) may mitigate increased arrhythmic risk

7. **Clinical Features of COVID-19-Related Liver Damage.** Fan. Clin Gastroenterol Hepatol. April 10**.**

- Study of 148 patients; 55 patients (37%) had abnormal liver function, defined as elevated levels of liver enzymes including ALT, AST, GGT, ALP and/or total bilirubin.
- Patients with abnormal liver function were more likely to have high fever (14.5%), prolonged hospital stay (15 days), and receive LPV/R (58%) than those with normal liver function (4.3%, 13 days, 31%)

8. **Clinical characteristics of neonates born to mothers with COVID-19.** Liu. Front Med. April 13**.**

- Study of 19 neonates born in Tongji Hospital in Wuhan in February 2020; neonates were immediately separated from the infected mothers and isolated for 14 days
- SARS-CoV-2 RT-PCR in throat swab, urine, and feces of all neonates were negative. RT-PCR in breast milk and amniotic fluid was negative too
- No vertical transmission of SARS-CoV-2 and no perinatal complications in the 3rd trimester were found

SEROLOGY

9. **A serological assay to detect SARS-CoV-2 seroconversion in humans.** Amanat. MedRxiv preprint. April 16**.**

- Description of a serological enzyme-linked immunosorbent assays (ELISA) that was developed using recombinant antigens derived from the spike protein (SP) of SARS-CoV-2. Antigens included full length trimeric/stabilized version of the SP and the smaller receptor binding domain (RBD)
- The ELISA distinguishes the sera from participants diagnosed with COVID19 (3 recovered, 14 acute patients) from those collected prior to the pandemic (e.g., fall of 2019)
- Pre-pandemic polled immunoglobulin (NHIG) and banked plasma responded to spike proteins from seasonal betacoronaviruses, NL63 and 229E, but not to SARS-CoV-2 RBD and spike

- Seroconversion using human plasma/serum of COVID19 responses were detected as early as 2 days post onset of COVID19 symptoms
- No cross reactivity with another human coronavirus (NL63), but only 1 isolate assessed
- IgG3 was the dominate isotype- which has a stronger affinity to activating Fc-receptors but a shorter half-life than IgG1
- Implication: techniques in this paper (including expression of recombinant spike protein) could be applied for serological assay development
- Limitations:
    - Isotyping and subtyping ELISA was performed on only 4 COVID patients
    - ELISA titers and microneutralization titers used different strains (original Wuhan vs USA-WA1/2020 isolate, an Asian lineage strain) - also only performed on the 4 COVID patients- but they correlated significantly with a Spearman r of 0.9279, suggesting minimal antigenic change
    - No formal assessment of specificity and sensitivity of the assay or correlation of seroconversion and antibody titers with protection

PPE/CLINICAL MANAGEMENT

10. **Assessment of N95 respirator decontamination and re-use for SARS-CoV-2.** Fischer. MedRxiv preprint. April 15. See also **NIH press release on the article**

- Analyzed 4 different decontamination methods: UV Radiation, 70˚C heat, 70% ethanol, and vaporized hydrogen peroxide (VHP) for their ability to reduce contamination with infectious SARS-CoV-2 and their effect on N95 respirator function
- VHP treatment exhibits the best combination of rapid inactivation of SARS-CoV-2 and preservation of N95 respirator integrity. Effective after only a 10-minute treatment.
- N95 respirators can be decontaminated and re-used up to 3 times with UV or VHP and up to 2 times with dry heat, but fit testing should be performed after decontamination to ensure proper functioning
- Ethanol decontamination is not recommended due to loss of N95 integrity

11. **Do chronic respiratory diseases or their treatment affect the risk of SARS-CoV-2 infection?** Halpin. Lancet Respir Med. April 3**. See also: Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury.** Russell. Lancet. Feb 7.

- Patients with chronic respiratory diseases, particularly COPD and asthma, appear to be under-represented in the comorbidities reported for patients with COVID-19, contrary to a common concern that those conditions may increase risk of infection and more severe presentation of COVID-19
- Administration of high-dose corticosteroids during hospitalization has been associated with delayed viral clearance and increased risk of death in patients with severe COVID-19, but may be confounded by disease severity
- The potential benefits or harms of inhaled corticosteroids are unclear at present. No changes to the treatment or management of chronic respiratory conditions, including COPD and asthma, should be considered at this stage

TREATMENT/EMERGING DRUG TARGETS

12. **COVID-19: immunopathology and its implications for therapy.** Cao. Nature Rev Immunol. April 9**.**

- About 15% of COVID-19 patients progress to severe disease characterized by pneumonia, lymphopenia, exhausted lymphocytes and a cytokine storm
- Severe patients frequently had an increased IgG response and a higher titer of total antibodies, which was associated with worse outcome and suggestive of possible antibody-dependent enhancement (ADE) of COVID-19 infection

- A neutralizing monoclonal antibody targeting the receptor-binding domain of the spike protein of MERS virus can enhance viral entry – a potential concern for vaccine development and antibody-based therapies for COVID-19 virus. Studies are needed to evaluate this question for COVID-19 virus
- However, convalescent plasma containing neutralizing antibodies has been used to treat a small number of patients with severe disease, and preliminary results show clinical improvement in critically ill patients with COVID-19 who developed ARDS
- One clinical trial, using the IL-6 receptor-targeted mAb tocilizumab, reported quick control of fever and an improvement of respiratory function in 21 patients with severe COVID-19. A few drugs such as anti-TNF antibodies infliximab or adalimumab are potentially effective, widely available, and have a well-established safety profile (See also: **Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed** Feldmann. Lancet. April 9)
- Other potential anti-inflammatory treatments:
    - Complement inhibitors used at an early stage of the infection
    - Mesenchymal stem cells which can repair pulmonary epithelial cell damage and promote alveolar fluid clearance.
- Implication: Significant antibody production is observed; however, whether this is protective or pathogenic remains to be determined. Defining the immunopathological changes and attenuating pro-inflammatory response is important for clinical management to improve outcome of severe COVID-19

13. Regulators split on antimalarials for COVID-19. Jaffe. Lancet. April 11**.**

- US and French authorities have authorized the use of chloroquine and hydroxychloroquine to treat COVID-19, but the EU regulators and WHO say the science doesn't support the decision. The findings, thus far, have been inconclusive and large-scale randomized trials are ongoing.
- Some estimate 1% of patients will be at increased risk for prolonged QT which can cause arrhythmia and sudden death
- The French drug safety agency (ANSM) recently began its surveillance of trials of drugs against COVID-19, "in particular when they are used outside of clinical trials of chloroquine, hydroxychloroquine, azithromycin, lopinavir/ritonavir (Kaletra), tocilizumab (and) colchicine"
- ANSM reported very recently 43 cases of heart incidents linked to hydroxychloroquine, including 4 sudden deaths plus 3 cardiac arrest in France.

BIOLOGY/PATHOPHYSIOLOGY

14. O-GlcNAc transferase promotes influenza A virus–induced cytokine storm by targeting interferon regulatory factor–5. Wang. Science Advances. April 15**.**

- Patients infected with influenza have higher blood glucose levels than healthy controls and their glucose levels correlate with serum levels of IL-6 and IL-8.
- Patients with influenza have more O-GlcNacylation of the transcription factor interferon regulatory factor-5 (IRF5) than healthy controls.
- Enhancing upstream activation of O-GlcNacylation in vitro by treating primary human alveolar type II (ATII) cells or mice with glucosamine lead to increased production of cytokines (IFNβ, IL-6, IL-8, TNF, CCL2, CCL5) and enhanced viral replication.
- Deletion of the enzyme which facilitates O-GlcNacylation (OGT) of IRF5 or deletion of IRF5 itself, utilizing siRNA in human cells or genetic deletions in mouse models, prevented the inflammatory cytokine response and reduced viral replication.
  *Discussion on how this same pathway of cellular metabolism may be relevant in COVID19 patients is presented in, **Discovered: Metabolic Mechanism of Cytokine Storms**