Summary of Major Literature Related to COVID-19 (May 25-June 7)

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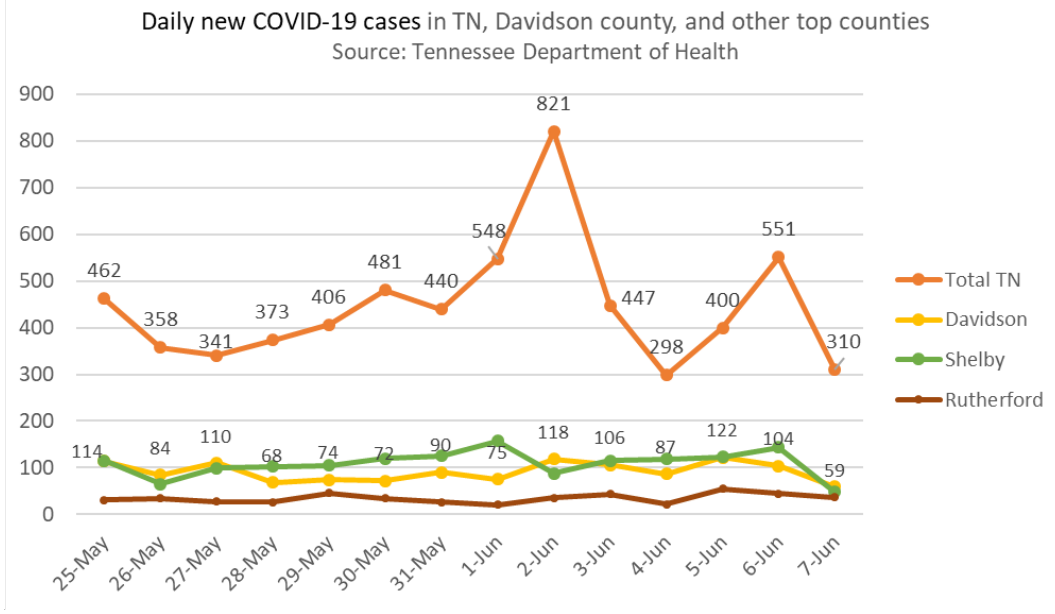
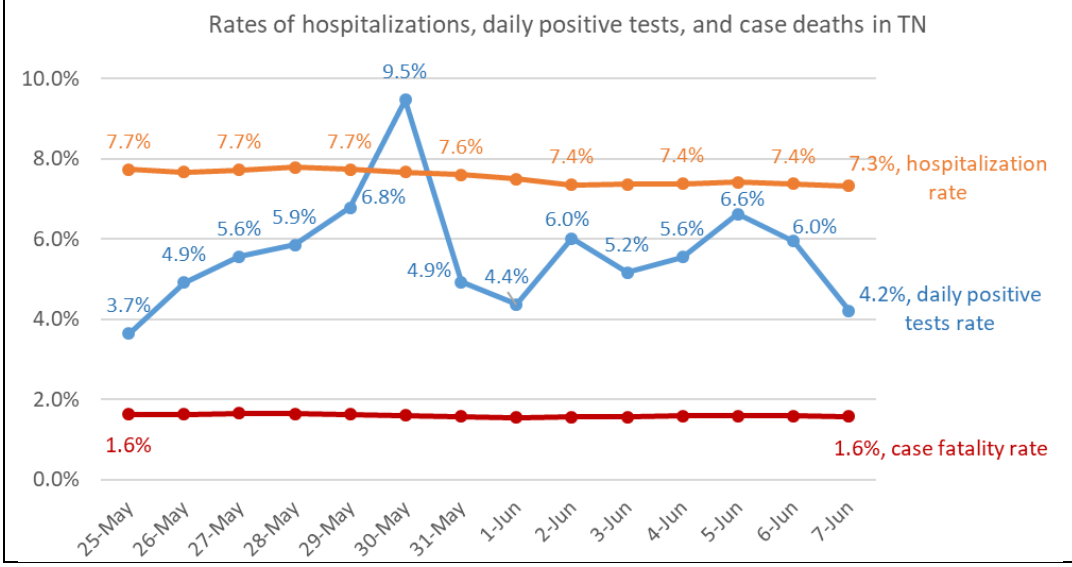
***This is informational and not intended to create variance from VUMC policies/guidance.**

STATISTICS - Tennessee and Nashville: Nashville will remain in Phase 2 of Roadmap for Reopening





As of June 7,

- Total cases = 26,381
- Total tests = 498,768
- Total test positive rate = 5.3%
- Top three counties:
  - Shelby = 5,860
  - Davidson = 5,801
  - Rutherford = 1,479
- Demographics:

Groups	Cases	%
By sex		
Female	11,155	42.3%
Male	14,268	54.1%
By race/ethnicity		
White	11,315	42.9%
Black	5,858	22.2%
Hispanic	6,273	23.8%
Asian	441	1.7%
Other	3,837	14.5%
By age		
0–10	1,020	3.9%
11–20	2,170	8.2%
21–30	5,483	20.8%
31–40	5,388	20.4%
41–50	4,500	17.1%
51–60	3,713	14.1%
61–70	2,120	8.0%
71–80	1,027	3.9%
80+	689	2.6%

EPIDEMIOLOGY

1. **Comparison of Clinical Characteristics of Patients with Asymptomatic vs Symptomatic Coronavirus Disease 2019 in Wuhan, China.** Yang et al. JAMA. May 27.

- Case series of 78 confirmed COVID-19 patients identified through contact tracing of transmission clusters in Wuhan; 33 patients were asymptomatic and 45 were symptomatic
- Compared to symptomatic cases, asymptomatic COVID-19 cases:
  - were younger (median age=37 vs 56 years) and more likely to be female (67 vs 31%)
  - had a lower proportion of liver injuries (3 vs 20%), lower CD4+T lymphocyte counts (median 719 vs 474 per µL), faster lung recovery in CT images (9 vs 15 days), and shorter duration of viral shedding from nasopharynx swabs (8 vs 19 days)

- lower likelihood of recurring positive test
- Implications: Findings suggest milder damage to immune system in asymptomatic infections, but importance of identifying and isolating individuals with asymptomatic infection to control transmission

Racial disparities

2. **Hospitalization and Mortality among Black Patients and White Patients with Covid-19.** Price-Haywood et al. NEJM. May 27.

- 3,481 COVID-19 positive patients with known race/ethnicity (70.4% black non-Hispanic) in a Louisiana health system
- 1,382 patients (40%) were hospitalized, 77% of whom were black
  - Factors independently associated with hospitalization are black, older age, public health insurance, residence in a low-income area, obesity, male sex, higher Charlson Comorbidity Index
- In-hospital mortality
  - Higher mortality was independently associated with age, presentation with an elevated respiratory rate, elevated venous lactate, creatinine, procalcitonin, and low platelet or lymphocyte counts
  - Black race was not associated with higher mortality but a higher proportion of blacks who died had been treated with mechanical ventilation than were whites (74% vs 37%)
- Limitation: Incomplete laboratory data

Cancer

3. **COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study.** Lee et al. Lancet. May 28.

- Prospective cohort study using the UK Coronavirus Cancer Monitoring Project (UKCCMP) database aimed to describe clinical and demographic characteristics and COVID-19 outcomes (all-cause mortality) in cancer patients
  - UKCCMP is the first and largest clinical registry for COVID-19 patents with cancer
  - Included patients who had a positive test for COVID-19 on RT-PCR from a swab
- From March 18 to April 26, authors analyzed the first 800 patients with a diagnosis of cancer and symptomatic COVID-19; 226 (28%) died
  - Patients who died were significantly older and more likely to be male and have comorbidities including cardiovascular disease and hypertension
- 281 patients (35%) had received chemotherapy within 4 weeks of testing positive for COVID-19
  - After adjusting for age, gender, and comorbidities, cytotoxic chemotherapy in the past 4 weeks was not associated with mortality from COVID-19 when compared to patients with cancer who did not receive chemotherapy (OR: 1.18; 95% CI: 0.81, 1.72)
- Implication: No evidence that cancer patients on cytotoxic chemotherapy or other treatment are at increased risk of mortality from COVID-19 compared with those not on active treatment

4. **Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study.** Kuderer et al. Lancet. May 28.

- Aimed to identify potential prognostic factors for mortality and severe illness among patients with cancer and COVID-19
- Analysis of de-identified data from patients from the USA, Canada, and Spain from the COVID-19 and Cancer Consortium (CCC19) from March 17 to April 16
  - Primary outcome was all-cause mortality within 30 days of diagnosis of COVID-19
  - Included patients with active or previous malignancy, aged 18 years or older, and with confirmed SARS-CoV-2

- Among 928 patients, 30% were aged 75 years or older, 50% were male, 39% were on active anticancer treatment, 43% had active cancer, and at analysis 121 (13%) had died
- Factors associated with increased 30-day mortality were older age (OR: 1.84; 95% CI: 1.53, 2.21), being male (OR: 1.63; 1.06, 2.48), smoking status (OR: 1.60; 1.03, 2.47), number of comorbidities (OR: 4.50; 1.33, 15.28), active cancer (OR: 5.20; 2.77, 9.77), and receipt of azithromycin plus hydroxychloroquine (OR: 2.93; 1.79, 4.79)
- Race/ethnicity, obesity, cancer type, type of anticancer therapy, and recent surgery were not associated with mortality
- Implication: Among patients with cancer and COVID-19, 30-day all-cause mortality was high and associated with general risk factors not unique to patients with cancer

Impact of COVID-19 pandemic on health care

5. **Impact of the COVID-19 Pandemic on Emergency Department Visits – United States, January 1, 2019-May 30, 2020.** Hartnett et al. MMWR. June 3**.**

- Study of weekly number of emergency departments (ED) visits during Jan 1, 2019-May 30, 2020 at 3,552 EDs in 47 states in National Syndromic Surveillance Program (represents 66-73% of US ED visits)
- ED visits were 42% lower during early pandemic period (March 29-April 25, 2020) than same period in 2019
    - visits declined for every age group with largest declines in children ≤14 years (>70%)
    - largest decline in Northeast (49%)
    - visits declined 37% among males and 45% among females
- Largest declines in visits were for abdominal pain, musculoskeletal pain, essential hypertension, nausea and vomiting, upper respiratory infections, sprains and strains, and superficial injuries
- Proportion of infectious disease-related visits was four times higher during the early pandemic period
- Visits decreased for nonspecific chest pain and acute myocardial infarction
- Implication: Wider access to triage telephone and virtual visits is needed as well as messages that reinforce importance of not delaying care for serious conditions

Clinical risk scores

6. **A clinical risk score to identify patients with COVID-19 at high risk of critical care admission or death: an observational cohort study.** Galloway et al. Journal of Infection. May 19.

- Retrospective cohort study of patients admitted to two London hospitals (N=1,157) with COVID-19 between 3/1/20 and 4/17/20; 28-day cumulative incidence of death, transfer to critical care, or discharge from the hospital was 26.1%, 12.8%, and 63.9%, respectively
- To assist clinicians in identifying hospitalized patients with potentially worse prognosis (critical care admission or death), a risk score was created from twelve parameters: age greater than 40, male gender, nonwhite ethnicity, oxygen saturation less than 93%, radiological severity score greater than 3, neutrophil count greater than 8.0 $x10^9$/L, CRP greater than 40 mg/L, albumin less than 34 g/L, creatinine greater than 100 µmol/L, diabetes mellitus, hypertension, and chronic lung disease
- Race/ethnicity but not social deprivation was a predictor of ICU admission
- Patients with a risk score of 4 or more had a higher 28-day cumulative incidence of either transfer to critical care or death than those with a lower risk score (40.7% versus 12.4%, respectively)
- Chest radiography severity was a striking predictor of poor outcome; this novel finding has potential utility, as each unit of radiographic assessment of lung edema (RALE) was associated with a 35% greater risk of transfer to critical care or death
- Implication: Risk score may inform clinical care and stratify patients for clinical trials

- Limitations: generalizable only to hospitalized patients in London

7. **Development and validation of the COVID-19 severity index (CSI): a prognostic tool for early respiratory decompensation. Haimovich et al. medRxiv preprint. May 14**.
   See also Quick COVID-19 Severity Index *derived from a dataset of hospitalized COVID-19 patients; uses data from first 4 hours of admission to predict critical respiratory illness at 24-hours as defined by high oxygen requirements, non-invasive ventilation, invasive ventilation, or death*

- EHR data from 9 hospitals in the Northeastern US. Included adult patients (≥ 18 years) admitted from the emergency department who tested positive for COVID-19 up to 24 hours after initial presentation. Excluded patients meeting criteria for respiratory critical illness within 4 hours of arrival.
    - Main outcome: composite endpoint of critical illness as defined by oxygen requirement (greater than 10 L/min by low-flow device, high-flow device, non-invasive, or invasive ventilation) or death within the first 24 hours of hospitalization
    - Area under receiver operating characteristic (AU-ROC), precision-recall curves (AU-PRC), and calibration metrics were used to compare predictive models to three illness scoring systems: Elixhauser comorbidity index, qSOFA, and CURB-65
- Data from 932 patients was used for model development and data from 240 patients was used for external validation. 12.3% (n=144) met composite endpoint within the first 24 hours.
- Developed a bedside quick COVID-19 severity index (qCSI), a twelve-point scale using nasal cannula flow rate, respiratory rate, and minimum documented pulse oximetry. Also developed a machine-learning gradient boosting model (CSI) using 12 additional variables. Both the qCSI and CSI outperformed the comparator models and performed well on external validation.
    - Additional variables included in the CSI highlight the associations between liver chemistries and inflammatory markers with patient risk
- A qCSI score of 0-3 was associated with a less than 5% risk of critical respiratory illness, while a score of 9-12 was associated with a 57% risk of progression to critical illness
- Implications: The qCSI requires only three variables that are all accessible at the bedside.

SEROPREVALENCE

8. **SARS-CoV-2 IgG Antibody Responses in New York City.** Reifer et al. medRxiv preprint. May 26**.**

- SARS-CoV-2 antibody response was described in 11,092 COVID-19 patients from an urgent care facility in Brooklyn, NY, many from a tight-knit religious community
- Estimated sensitivity and specificity of the semi-quantitative assay [DiaSprin LIAISON] used is 97.6% and 99.3%, respectively
- 5,208 were SARS-CoV-2 IgG positive, indicating a 47% positivity rate
    - higher in males (53%) than females (41%)
    - highest in ages 11-15 (58%) and 16-20 (61%)
    - lowest in age 0-5 (28%)
- Among 240 patients with data on illness severity (Severity Symptom Index, SSI; scored by healthcare provider using this de-novo tool), 70% were asymptomatic with or without known exposure to SARS-CoV-2 positive patients and 30% ranged from mildly to severely symptomatic
    - Linear regression analysis showed that semi-quantitative SARS- CoV-2 IgG antibody levels were positively correlated with SSI (p-value < 0.01)
- Implications:
    - High positivity rate compared to some other studies based on random samples, but a third of study sample were symptomatic and another 35% had known exposure to an infected patient

- Higher positivity rates in young age groups may indicate more robust immune response in this generally healthy age group

- Limitations: extent and duration of immunity conferred by SARS-CoV-2 IgG antibodies remains unknown; time-course of infection unknown, but data suggest all patients were infected within one week of each other

9. Are SARS-CoV-2 seroprevalence estimates biased? Takahashi et al. OSF preprint. May 30.

- Growing evidence suggests that asymptomatic and mild SARS-CoV-2 infections, together comprising >95% of all infections, may be associated with lower antibody titers than severe infections
- In addition, antibody levels peak a few weeks after infection and decrease gradually
- However, positive controls used for determining the sensitivity of serological assays are usually limited to samples from hospitalized patients with severe disease, leading to what is commonly known as spectrum bias in estimating seroprevalence in the general population
- Based on simulation analyses, assays with imperfect sensitivity will underestimate the true seroprevalence, but this can be corrected if assay sensitivity in the general population is known
- Implications: Optimization and validation of serological assays should involve samples from across the spectrum of severity and time since infection, and performance characteristics should be stratified by these factors

TREATMENT

10. Lancet and NEJM retracted two papers on hydroxychloroquine and ACE inhibitors. Concerns have been raised by the authors and the scientific community regarding data access and integrity
Retraction—Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Mehra et al. June 5.
Retraction: Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. Mehra et al. June 4.

11. A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19. Boulware et al. NEJM. June 3.

- Randomized, double-blind, placebo-controlled trial testing hydroxychloroquine (HCQ) as post- SARS-CoV-2 exposure prophylaxis
- Enrolled 821 adults who had exposure to someone with confirmed Covid-19 at a distance of less than 6 ft for more than 10 minutes while wearing neither a face mask nor an eye shield (high-risk exposure, 88%) or while wearing a face mask but no eye shield (moderate-risk exposure, 12%)
    - Within 4 days after exposure, participants were randomly assigned to receive either placebo or HCQ (800 mg once, followed by 600 mg in 6 to 8 hours, then 600 mg daily for 4 additional days)
- Incidence of new illness compatible with COVID-19 or confirmed infection did not differ significantly between the two groups
    - 11.8% in HCQ group vs. 14.3% in placebo group
- Side effects were more common with hydroxychloroquine than with placebo (40.1% vs. 16.8%), but no serious adverse reactions were reported

IMMUNOLOGY/VACCINE DEVELOPMENT

12. Targets of T Cell Responses to SARS-CoV-2 Coronavirus in Humans with COVID-19 Disease and Unexposed Individuals. Grifori et al. Cell. May 14.

- SARS-CoV2-specific CD4+ T cells were found in 100% of convalescent patients with specificity to spike protein epitopes as well as many other SARS-CoV-2 proteins. CD4+ T cell responses were measured by expression of activation markers (OX40 and CD137) and cytokines production in response to the megapool and spike protein epitopes

- CD4+ T cells were Th1 type producing IL-2 and IFNg; little expression of IL-4, IL-5, IL-13 or IL-17. CD4+ T cell responses specific to the spike protein correlated with spike IgG responses
- The majority (~70%) of recovered COVID-19 patients generated a CD8+ T cell response against SARS-CoV-2. CD8+ responses were measured by investigating expression of CD69 and CD137 and expression of IFNg, granzyme B, TNF and IL-10
- Non-spike-specific CD4+ T cell responses were above the limit of detection in 50% of unexposed donors
- Limitations: The prediction strategy used to generate the megapool of potential CD4+ T cell epitopes utilized is geared to capture ~50% of the total response. For CD8+ responses targeted prominent HLA class I A and B alleles allowing for broad coverage (>85%) of population
- Implications: T cell response in COVID-19 cases were directed against many highly expressed SARS-CoV-2 open reading frames suggesting that spike may not be the only good vaccine target. Cross-reactivity is relatively widely distributed in unexposed individuals suggesting pan-coronavirus T cells do exist and are capable of recognizing SARS-CoV-2 epitopes.

13. **SARS-CoV-2 infection protects against rechallenge in rhesus macaques.** Chandrashekar et al. Science. May 20.

- Rhesus macaque model of SARS-CoV-2 infection was developed. Three different doses were administered to 3 groups of 3 animals
- Macaques had high viral loads in the upper and lower respiratory tract detected by PCR of BAL (out to 10-14 days) and nasal swabs (out to 21-28 days).
- All 9 macaques developed binding antibody responses to the S protein by ELISA and neutralizing antibody responses using pseudovirus and a live virus
- Spike-specific T cell IFNg responses were detected in most macaques.
- Pathologic evidence of viral pneumonia was observed in 4 macaques in a separate cohort at day 2 post challenge necropsy
- Rechallenge (at day 35) with matching doses significantly reduced viral loads compared with viral loads in macaques receiving primary challenge at the same time. 7-days after rechallenge there were significant increases in Ab responses NAb responses
- Limitations: Study groups are small and there are differences between SARS-CoV-2 infection in macaques and humans, i.e. macaques did not develop fever. Durability of the protective immune response is not addressed
- Implications: SARS-CoV-2 infection induced protective immunity against re-exposure in nonhuman primates and may do the same in humans

14. **Immunogenicity of a DNA vaccine candidate for COVID-19.** Smith et al. Nature Communications. May 20.

- A synthetic DNA vaccine targeting the SARS-CoV-2 S protein was engineered and induced robust RNA and protein expression of the S protein in cell lines
- Mice and guinea pigs immunized with this DNA vaccine make functional Abs which neutralize SARS-CoV-2 infection in both pseudovirus (Balb/c mice) and live virus assays (C57Bl/6 mice)
- Sera from immunized animals blocks the viral spike protein from binding to the ACE2 receptor
- Immunized animals have significant increases in Spike-binding Abs in their lung-washes
- Cellular T cell responses (IFNg producing) which develop in immunized mice have some cross-reactivity to SARS-CoV but not MERS-CoV
- Limitations: Durability of the response not measured. No challenge/protection experiments can be performed with these models.
- Implications: Further evaluation of this DNA vaccine (INO-4800) as a vaccine candidate should be considered.