Summary of Major Literature Related to COVID-19 (May 11-24)

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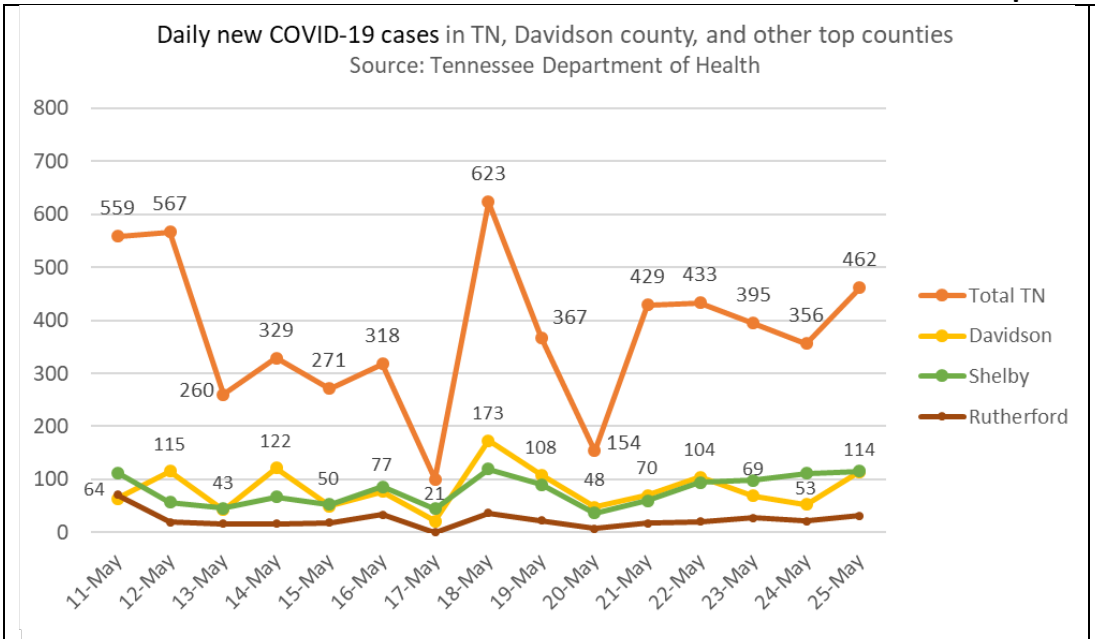
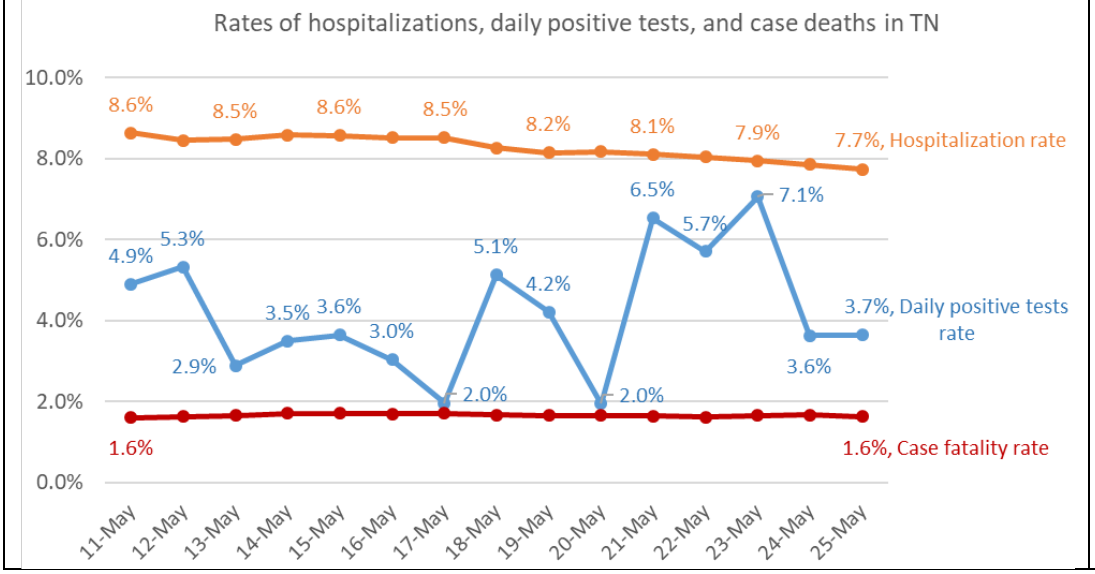
***This is informational and not intended to create variance from VUMC policies/guidance.**

STATISTICS - Tennessee and Nashville: Nashville entered Phase 2 of Roadmap for Reopening on May 25





As of 2 pm May 25,

- Total cases = 20,607
- Total tests = 396,219
- Top three counties:
  - Davidson = 4,632
  - Shelby = 4,451
  - Rutherford = 1,029
- Demographics:

Groups	Cases	%
By sex		
Female	8,567	41.6%
Male	11,256	54.6%
By race/ethnicity		
White	8,135	39.5%
Black	4,203	20.4%
Hispanic	3,706	18.0%
Asian	390	1.9%
Other	2,066	10.0%
Pending	2,107	10.2%
By age		
0–10	635	3.1%
11–20	1,534	7.4%
21–30	4,174	20.3%
31–40	4,098	19.9%
41–50	3,534	17.1%
51–60	2,980	14.5%
61–70	1,769	8.6%
71–80	858	4.2%
80+	565	2.7%

EPIDEMIOLOGY

1. **Viral and host factors related to the clinical outcome of COVID-19.** Zhang et al. Nature. May 20**.**

- Analysis of clinical, molecular and immunological data from 326 confirmed cases of COVID-19 in Shanghai, including asymptomatic, mild, severe and critical cases
- Genomic sequences of SARS-CoV-2 assembled from 112 samples (sputum, oropharyngeal swabs) together with sequences in the Global Initiative on Sharing All Influenza Data (GISAID) indicated:
  - limited variation in viral genome
  - two major lineages with differential exposure history during the early phase of the outbreak in Wuhan but with similar pathogenic effects and clinical outcomes

- Adverse clinical outcome was associated with as age, lymphocytopenia (especially loss of $CD3^+$ T lymphocytes) and its associated cytokine storm (high levels of IL-6 and IL-8)
- Implications: The determinants of COVID-19 disease severity stem mostly from host factors whereas viral genome is largely stable and does not significantly affect clinical outcomes

2. **Preliminary Estimate of Excess Mortality During the COVID-19 Outbreak — New York City, March 11–May 2, 2020.** New York City Department of Health and Mental Hygiene (DOHMH) COVID-19 Response Team. MMWR 2020:69:603-605. May 15.

- Seasonal periodic regression model was developed to provide an estimate of all-cause excess deaths (number of deaths above expected seasonal baseline levels, regardless of reported cause of death) in NYC from March 11-May 2
- This method provides a nonspecific measure of the severity/impact of the pandemic by accounting for factors temporally associated with SARS-CoV-2 that impact mortality
- DOHMH developed an electronic vital statistics reporting system to allow for rapid reporting and surveillance of deaths, including confirmed COVID-19 associated deaths (positive laboratory-confirmed) and probable COVID-19 deaths (COVID-19, SARS-CoV-2, or equivalent listed on death certificate, but no laboratory-confirmation)
- A total of 32,107 deaths were reported to DOHMH; of these deaths, 24,172 (95% confidence interval = 22,980–25,364) were estimated to be excess deaths, including:
    - 13,831 (57%) confirmed COVID-19–associated deaths
    - 5,048 (21%) probable COVID-19–associated deaths
    - 5,293 (22%) excess deaths that were not identified as COVID-19–associated deaths

3. **Risk factors for SARS-CoV-2 among patients in the Oxford Royal College of General Practitioners Research and Surveillance Centre primary care network: a cross-sectional study**. De Lusignan et al. Lancet. May 15.

- Data from Oxford Royal College of General Practitioners (RCGP) Research and Surveillance Center primary care network
- Of 3,802 patients tested from Jan 28 to April 4, 587 (15.4%) were SARS-CoV-2 positive (by RT-PCR of nasopharyngeal swabs)
- In adjusted models, factors associated with increased risk were male sex (aOR 1.55), black race (aOR 4.75 vs white), population density (aOR 4.59 urban vs rural living), living in most deprived areas (aOR 2.03 vs least deprived), obesity (aOR 1.41 vs normal weight) and chronic kidney disease (aOR 1.91)
- Active smoking was associated with a 50% reduced risk of testing positive vs. non-smoking
- Notably household size and malignancy or immunocompromised status were not independent predictors of test positivity
- Implications: Risk factors for testing positive (risk) for SARS-CoV-2 in primary care resemble those of general population

4. **SARS-CoV-2 Rates in BCG-Vaccinated and Unvaccinated Young Adults.** Hamiel et al. JAMA. May 22. **See also: Considering BCG vaccination to reduce the impact of COVID-19**. Curtis et al. Lancet. April 30.

- Bacille Calmette-Guérin (BCG) vaccine has beneficial nonspecific effects on immune system
    - SARS-CoV-2 is a single-stranded positive-sense RNA virus and the BCG vaccine has been shown to reduce the severity of infections by other viruses with similar structure
    - Two RCTs are assessing whether BCG vaccine reduces the incidence and severity of COVID-19 in HCW (NCT04327206 and NCT04328441)
- Routine BCG vaccine was given to newborns in Israel between 1955-1982 with 90% coverage, but not after 1982

- Study compared the proportion of positive COVID-19 tests between similar aged individuals born between 1979-1981, 35-37 yrs, (vaccinated) and 1983-1985, 39-41 yrs, (unvaccinated)
- 11.7% (361/3064) were positive for COVID-19 among the BCG-vaccinated group compared to 10.4% (299/2869) among the unvaccinated group
    - 1 case of severe disease in each group and no deaths reported; thus, cannot estimate association between BCG vaccine status and severity of disease
- Limitations: Comorbidity differences in two birth cohorts were not accounted for; low risk age groups for COVID-19; the study included immigrants with unknown vaccination history (<5% in each group)
- Implication: Study does not support that BCG vaccination in childhood will protect against COVID-19 in adulthood

Impact of COVID-19 pandemic on health care

5. **Effects of the COVID-19 Pandemic on Routine Pediatric Vaccine Ordering and Administration — United States, 2020.** Santoli et al. MMWR 2020:69:591-593**.** May 15.

- On March 24, CDC posted guidelines emphasizing the importance of routine childcare and immunizations (especially for ≤ 24 months)
- Two data sources were used to determine the effect of the pandemic on US pediatric vaccinations:
- Both data sources showed a decline in recommended non-influenza and measles-containing vaccines the week after a national emergency was declared (March 13, 2020)
    - Decline of approximately 2.5 million doses from last year, which included a decline in orders for about 250 000 doses of vaccines providing protection against measles
    - Decrease was less prominent among children aged ≤24 months than among older children
- Later increases (late March) for measles-containing vaccines in younger children may reflect strategies implemented by health care organizations to promote childhood vaccinations during the pandemic
- Implications: Declines in routine pediatric vaccines might increase the risk of outbreaks of vaccine-preventable diseases; continued effort needed to achieve rapid catch-up vaccination

Immunity

6. **The disease-induced herd immunity level for COVID-19 is substantially lower than the classical herd immunity level.** Britton et al. arXiv preprint. May 6**.**

- Using modifications to epidemic models, which took social activity and age cohorts into consideration, a new model was created to determine the disease-induced herd immunity for COVID-19
    - Disease-induced herd immunity reflects that immunity developed in the context of social distancing and other preventive measures
    - Classical herd immunity (Hc=1-1/Ro) does not take these additional factors into account, is estimated at 50-75% for COVID-19
- Using a timeline beginning in mid-Feb with the Ro at 2.5 and persons who become infected presumed latent for 3 days followed by infectious for 4 days, the model illustrates whether herd immunity will be reached long term with and without preventative measures
- Authors concluded that the disease-induced herd immunity level may be substantially lower than the classical herd immunity level and, using the new model, will be reached at 43%
- Differences in social activity levels impacted disease-induced herd immunity more heavily than mixing across age groups
- Limitations: Does not address what effect school closure and strong recommendations to work from home would have on the disease-induced herd immunity level; assumes non-homogenous mixing between/among age strata and different contact levels within strata (and does not account for population density/other structural heterogeneity)

- Implications: If preventative measures are lifted before disease-induced herd immunity level, then a resurgence is expected based on these models

7. **Individual variation in susceptibility or exposure to SARS-CoV-2 lowers the herd immunity threshold.** Gomes et al. medRxiv preprint. May 12**.**

- By fitting epidemiological models that allow for heterogeneity to SARS-CoV-2 outbreaks to consider variation in *susceptibility or exposure* to infection, the estimate that the herd immunity threshold (HIT) is 60-70% may be substantially reduced
- In this model the HIT declines sharply when coefficients of variation increase from 0 to 2 and remains below 20% for more variable populations
- Limitation: Since the coefficient of variation predicts the HIT and it is unknown how variable humans are in their susceptibility to infection, exposure to SARSCoV-2, and infectiousness, it is difficult to extrapolate the data
- Implications: The larger the inter-individual variation in susceptibility/infectiousness, the more optimistic the public health prognostics and the milder the required health policies

TRANSMISSION

8. **The airborne lifetime of small speech droplets and their potential importance in SARS-CoV-2 transmission.** Stadnytskyi et al. PNAS. May 13.

- Loud speech can emit thousands of oral fluid droplets per second which can harbor a variety of respiratory pathogens, including SARS-CoV-2
- At an average viral load of 7×10^6 per milliliter, it was estimated that 1 min of loud speaking can generate at least 1,000 virion-containing droplet nuclei that remain airborne for more than 8 minutes
- These droplets could be inhaled by others and, according to independent action hypothesis (i.e., each virion has an equal, nonzero probability of causing an infection) trigger a new SARS-CoV-2 infection
- Implication: These results support the Centers for Disease Control and Prevention's recommendation to wear a mask in public

CLINICAL MANAGEMENT/TREATMENT

9. **Respiratory Parameters in Patients With COVID-19 After Using Noninvasive Ventilation in the Prone Position Outside the Intensive Care Unit.** Sartini et al. JAMA. May 15.
Use of Prone Positioning in Nonintubated Patients With COVID-19 and Hypoxemic Acute Respiratory Failure. Elharrar et al. JAMA. May 15.
Is the Prone Position Helpful During Spontaneous Breathing in Patients With COVID-19? Telias et al. JAMA. May 15.

- Prone position during non-invasive ventilation (NIV) can improve oxygenation and can potentially result in less injurious ventilation
- Two small case series described the use of the prone position in non-intubated COVID-19 patients during spontaneous and assisted breathing outside the ICU
- A case series of 24 patients with acute hypoxemic respiratory failure and infiltrates on chest CT scans; prone positioning was started without changing the system for oxygen supply or fraction of inspired oxygen (Fio_2)
    - 6 of 15 patients who tolerated prone position showed a mean (SD) increase in Pao_2 of more than 20% from baseline (74 [16] to 95 [28] mm Hg; $P = .006$) but 3 patients returned to baseline Pao_2 after supination
- A 1-day cross-sectional before-after study of 15 patients with mild and moderate ARDS in Italy; estimated mean (SD) Pao_2:Fio_2 was 157; patients received NIV with sessions of prone positioning after poor response to continuous positive airway pressure

- Compared with before receiving NIV, oxygenation and respiratory rate improved during NIV while prone (estimated Pao_2:FiO_2, 100 [IQR, 60-112] to 122 [IQR, 118-122] and respiratory rate 28 breaths/min [IQR, 27-30] to 24 [21-25] breaths/min), and remained improved 1 hour after NIV session in prone position in 12 patients
- At 14 days, 1 patient was intubated and another died

- Implications: Providing NIV in the prone position to non-ICU patients with COVID-19 and ARDS is feasible and may decrease respiratory rate and increase oxygenation
- Limitations: small sample size, no control group, possible selection bias; findings require confirmation in clinical trials, including to examine clinical outcomes and to determine if intubation can be avoided or delayed

10. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. Mehra et al. Lancet. May 22.

- Multinational registry analysis of the use of hydroxychloroquine or chloroquine with or without a macrolide among >96,000 hospitalized confirmed COVID-19 patients (mean age 54 years)
- Four treatment groups (chloroquine alone, chloroquine with a macrolide, hydroxychloroquine alone, or hydroxychloroquine with a macrolide), and a control group who received none of these treatments
  - Treatment initiated within 48 hours of diagnosis and not while on mechanical ventilation
  - Excluded patients receiving remdesivir
- Compared with the control group, and controlling for multiple confounders including underlying cardiovascular disease and its risk factors, diabetes, underlying lung disease, smoking, immunosuppressed condition, and baseline disease severity:
  - Each of the four treatment groups had 33% to 44% increased risk of in-hospital death
  - Each of the four treatment groups had 2.4- to 5.1-fold increased risk of de-novo ventricular arrhythmia during hospitalization
- There was no significant difference in severity of illness between treatment and control arms measured by qSOFA and % of patients with SpO2<94%
- Implications: Large real-world analysis suggests no benefit, and potential harm, of chloroquine and hydroxychloroquine in hospitalized patients with COVID-19
- Limitations: Observational study; did not measure QT interval

IMMUNOLOGY/VACCINE DEVELOPMENT

11. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomized, first-in-human trial. Zhu et al. Lancet. May 22.

- Phase I safety trial was performed on 108 individuals given 3 different doses of the non-replicating adenovirus type-5 (Ad5) vectored vaccine containing the SARS-CoV2 spike protein. Vaccine by Beijing Institute of Biotechnology (Beijing, China) and CanSino Biologics (Tianjin, China).
- By 7 days post vaccination at least one mild to moderate side effect was reported in >75% of vaccine recipients; most common injection site adverse reaction was pain, reported in 54% vaccine recipients
- Severe fever, fatigue, dyspnea, muscle pain, and joint pain reported by some in high dose group
- Rapid spike specific T-cell responses (IFNγ producing cells) were significantly higher at day 14 in the high dose group than the low dose group, but not significant compared with the middle dose group
- Specific humoral responses against SARS-CoV2 peaked at day 28 post-vaccination based on ELISA (Spike receptor binding domain specificity) and neutralization assays with significantly higher antibody titers in the high dose group
- Limitations: Cannot predict the protection of the Ad-5 vectored COVID-19 vaccine based on the vaccine-elicited immune responses because correlates of protection for a COVID-19 vaccine unknown

- Implications: There is potential for further investigation of the Ad5 vectored COVID-19 vaccine for prevention of COVID-19; low dose and middle dose are to be further assessed in a phase 2 clinical trial

12. Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. Pinto et al. Nature. May 18.

- Identified several antibodies produced by memory B cells from an individual infected with SARS-CoV in 2003 which target the spike protein (S) of SARS-CoV-2.
- Focused studies on one antibody, S309, and demonstrated its ability to neutralize SARS-CoV-2 and SARS-CoV pseudoviruses and the authentic SARS-CoV-2 by binding S receptor-binding domain
- Cryo-electron microscopy studies and binding assays demonstrate that the S309 antibody recognizes a conserved binding site on the coronavirus that is conserved across many sarbocoviruses
- Combining administration of S309 with other antibodies from this study enhanced neutralization in vitro
- Limitation: No testing on neutralization/protection in a living organism.
- Implications: S309- and/or S309-containing antibody cocktails should be considered for prophylaxis in high risk individuals or as a post-exposure therapy

13. Potent neutralizing antibodies against SARS-CoV-2 identified by high-throughput single-cell sequencing of convalescent patients' B cells. Cao et al. Cell. May 18.

- SARS-CoV-2 neutralizing antibodies by high-throughput single-cell RNA and VDJ sequencing of antigen-enriched B cells from 60 convalescent patients.
- From screening over 8.5 thousand IgG1 clonotypes, 14 exhibited neutralizing ability in vitro and one had potent activity against pseudotyped and authentic SARS-CoV-2 (BD-368-2).
- BD-368-2 binds to an epitope of the SARS-CoV-2 Spike protein overlapping with the ACE2 binding site.
- BD-368-2 was tested in a hACE2-transgenic mouse model and demonstrated that it could reduce viral load and weight loss.
- Limitations: "Therapeutic" model delivered the antibody treatment 2 hr after viral inoculum. Mouse model is limited, and the pathological outcome of infection is measured only as weight loss up to 5 days post infection.
- Implications: Human neutralizing antibodies could be efficiently discovered by high-throughput single B-cell sequencing

14. Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. Liao et al. Nature Medicine. May 12.

- Single-cell RNA sequencing (scRNA-seq) on bronchoalveolar lavage fluid (BALF) from 3 patients with moderate COVID-19 infections, 6 patients with severe/critical COVID-19 infections, 3 healthy controls and publicly available data
- BALF of patients with severe/critical COVID-19 contained higher proportions of macrophages and neutrophils and lower proportions of myeloid dendritic cells, plasmacytoid dendritic cells and T cells than those with moderate infection
    - Suggests that a highly proinflammatory macrophage microenvironment is present in the lungs of patients with severe COVID-19, which is consistent with previous knowledge of macrophage populations during steady-state, inflammation and recovery
- CD8+ T cells in BALFs from patients with severe/critical infection were less expanded, more proliferative and more phenotypically heterogeneous, whereas a larger proportion of CD8+ T cell effectors with tissue-resident and highly expanded features were present in BALFs from patients with moderate infection

- Patients with severe/critical infection had higher levels of inflammatory cytokines compared to patients with moderate COVID-19 infections
    - Suggests lung macrophages in patients with severe COVID-19 infection may contribute to local inflammation by recruiting inflammatory monocytic cells and neutrophils though CCR1 and CXCR2, whereas macrophages in patients with moderate COVID-19 infection produce more T cell-attracting chemokines through engaging CXCR3 and CXCR6
- Limitations: limited and heterogeneous patients, lack of longitudinal samples pre/post infection, B cell response could not be analyzed due to low cell numbers, and potential confounders could not be assessed

MENTAL HEALTH

15. United Nations Policy Brief: COVID-19 and the Need for Action on Mental Health. May 13, 2020**.**

- Psychological distress is widespread, especially among healthcare workers, first responders, older adults, children, women, people with pre-existing health conditions, and people caught in fragile humanitarian and conflict settings.
- Recommended actions:
    - Apply a whole-of-society approach via including mental health considerations in national response plans, e.g. supporting learning environments for children at home, responding proactively to reduce domestic violence and acute impoverishment, and crafting all communications to be sensitive of their impact on people's mental health
    - Ensure widespread availability of emergency mental health support via supporting community actions that strengthen social cohesion and reduce loneliness, e.g. helping isolated older adults stay connected, investing in tele-mental health, ensuring in-person care for severe mental health conditions and ensuring that people with psychosocial disabilities have access to COVID-19 care
    - Support recovery from COVID by building mental health services for the future via mental health reforms, e.g. shifting care away from institutions to community services, making sure that mental health is part of universal health coverage, and building human resources to deliver mental health care

16. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. Rogers et al. Lancet Psychiatry. May 18.

- Systematic review of psychiatric and neuropsychiatric acute and long-term consequences of infection with SARS-CoV, MERS-CoV, or SARS-CoV-2 (65 studies)
- Consequences are common, long-term, and varied:
    - Acute: Any (63%), insomnia (42%), anxiety (36%), depressed mood (33%) and more
    - Post-illness: sleep disorder (100%), frequent recall of traumatic memories (30%), emotional lability (24%), impaired concentration (20%), euphoria (11%)
    - Psychiatric disorders and neuropsychiatric consequences appear uncommon
- Etiology likely multifactorial: direct effects of infection, cerebrovascular disease, physiological compromise, immune response, medical interventions, social isolation, stigma, concern for infecting others
- Limitations: possible selection bias; only 1 study with systematic neuropsychological assessments, study quality is not high; no pre-infection assessment; variations in follow-up time
- Given large number of individuals will be infected, mental health impacts could be substantial in SARS-CoV-2 pandemic