Summary of Major Literature Related to COVID-19 (June 23-July 13)

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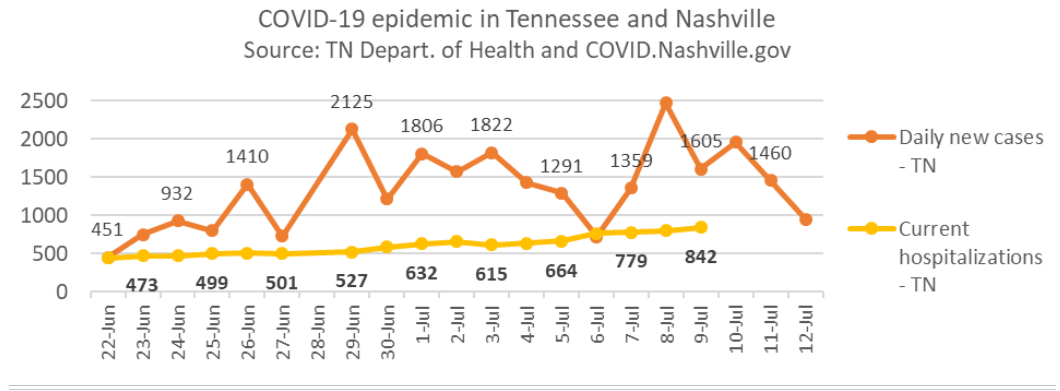
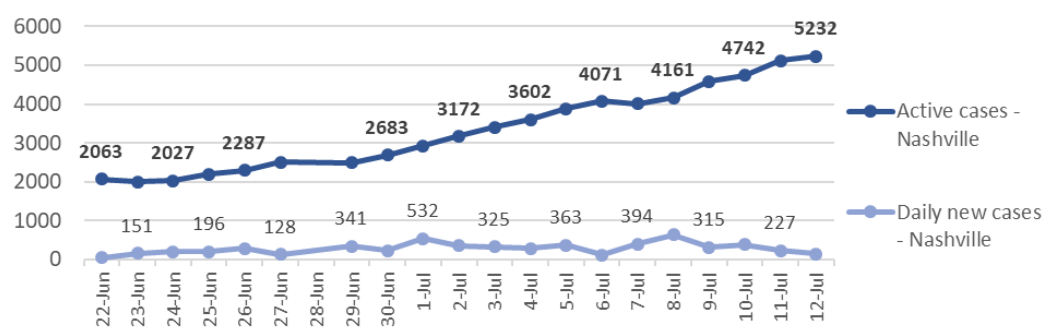
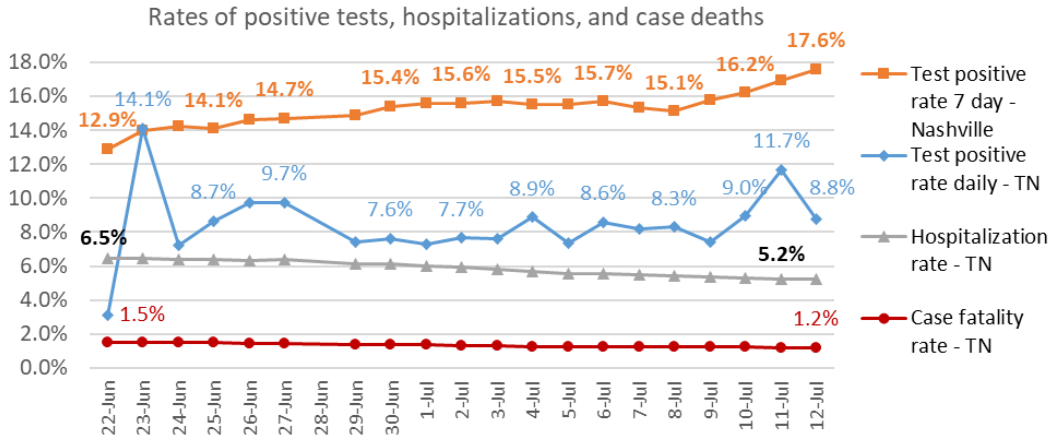
***This is informational and not intended to create variance from VUMC policies/guidance.**

STATISTICS – Tennessee and Nashville

July 3: Nashville reverted to modified Phase 2 of Roadmap for Reopening







As of July 12, in TN

- Total cases = 61,960
- Total hospitalizations = 3,250
- Total deaths = 741
- Active cases = 25,364
- Top counties:
  - Shelby = 13,594
  - Davidson = 13,309
- Steady increases in numbers of current hospitalizations in TN and active cases and testing % positive in Nashville
- Demographics:

Groups	Cases	%
By sex		
Female	29,033	46.9%
Male	31,935	51.5%
By race/ethnicity		
White	25,886	41.8%
Black	12,551	20.3%
Hispanic	13,846	22.3%
Asian	710	1.1%
Other	9,691	15.6%
By age		
0–10	2,821	4.6%
11–20	6,334	10.2%
21–30	14,731	23.8%
31–40	12,140	19.6%
41–50	9,980	16.1%
51–60	7,761	12.5%
61–70	4,461	7.2%
71–80	2,284	3.7%
80+	1,279	2.1%

EPIDEMIOLOGY

1. **OpenSAFELY: factors associated with COVID-19 death in 17 million patients.** Williamson et al. Nature. July 8.
   - One of the first large-scale population-based studies and included the largest population of Blacks and South Asians
   - 17 million English general practice patients' health records linked to Office for National Statistics death data (1.8 million non-white)

- 10,926 deaths due to COVID-19 or its complications
- Confirms higher risk of death associated with older age, male, obesity, Black ethnicity, South Asian ethnicity, severe asthma, recent cancer history, reduced kidney function, stroke/dementia, liver disease and other comorbidities
- Limitations: data derived solely from health records and could not account for economic or other factors which may drive some of the disparities or associations

2. **Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study.** Varatharaj et al. Lancet Psych. June 25.

- Study was based on physician reports via online web-portals established through network of the Association of British Neurologists (ABN), British Association of Stroke Physicians (BASP), and Royal College of Psychiatrists (RCPsych), and included acute neurological and psychiatric complications among confirmed COVID-19 cases in the UK through April 26
    - 153 cases; median age 71 years (IQR 58-79)
- 62% of patients presented with a cerebrovascular event, of whom 74% had an ischemic stroke and 12% an intracerebral hemorrhage
- 31% presented with altered mental status, comprising 23% with unspecified encephalopathy and 18% with encephalitis. The remaining 59% with altered mental status were new-onset psychosis, a neurocognitive (dementia-like) syndrome, and an affective disorder
- 49% of patients with altered mental status were younger than 60 years, whereas 18% of patients with cerebrovascular events were younger than 60 years
- Limitation: Small snapshot of COVID-19 patients with acute neurological or psychiatric complications; larger, prospective studies needed
- Implication: Altered mental status is a common presentation and occurrs often in young people

3. **Risk of Ischemic Stroke in Patients with Coronavirus Disease 2019 (COVID-19) vs Patients with Influenza.** Merkler et al. JAMA Neurology. July 2.

- A retrospective cohort study comparing risk of acute ischemic stroke between patients with COVID-19 and patients with influenza at 2 hospitals in NYC
- Among 1916 patients with emergency department visits or hospitalizations with COVID-19 from March 4 through May 2, 2020, 1.6% (95% CI, 1.1%-2.3%) had an acute ischemic stroke.
- Among patients with stroke:
    - median age was 69 years (IQR, 66-78 years)
    - median duration from COVID symptom onset to stroke diagnosis was 16 days (IQR, 5-28 days)
    - median NIH Stroke Scale score was 16 (IQR, 6-23)
    - inpatient mortality was 32%
- In comparison, 0.2% (95% CI, 0.0%-0.6%) of 1486 patients with influenza from January 1, 2016, through May 31, 2018 had an acute ischemic stroke.
- The odds of stroke were 7.6-fold higher (95% CI, 2.3-25.2) with COVID-19 than with influenza after adjustment for age, sex, and race
    - Odds ratios ranged from 4.0 to 9.3 across multiple sensitivity analyses that adjusted for vascular risk factors, viral symptomatology, and ICU admission
- Implication: COVID-19 substantially increases stroke risk

Seroprevalence

4. **Seroprevalence of SARS-CoV-2 Among Frontline Healthcare Personnel During the First Month of Caring for COVID-19 Patients — Nashville, Tennessee.** Stubblefield et al. Clin Infect Dis. July 7.

- Seroprevalence study of 249 VUMC health care workers (median age 33 years) with direct patient contact in COVID-19 hospital units for one month early in the pandemic
- 19 (7.6%) tested positive for SARS-CoV-2 antibodies using new CDC serology assay with sensitivity and specificity of 96% and 99%, respectively
    - 11 of the 19 reported symptoms of a prior viral illness
    - Seropositivity was more common among those who reported not universally wearing PPE for all encounters versus those who reported always wearing PPE (15.8% versus 4.3%) (p=0.07)
- Limitation: Convenience sample could introduce bias; small sample size precluded comparisons of clinical role and other participant characteristics
- Implications: Asymptomatic healthcare personnel with frequent exposure could be an important source of SARS-CoV-2 transmission and may justify enhanced surveillance; PPE reduces infection rate

5. **Prevalence of SARS-CoV-2 in Spain (ENE-COVID): a nationwide, population-based seroepidemiological study.** Pollan et al. Lancet. July 6**.**
   See also: Comment: SARS-CoV-2 seroprevalence in COVID-19 hotspots. Eckerle and Meyer.

- A nationwide population-based seroprevalence study involving 35,883 households and 61,075 participants in Spain between April 27 to May 11
- All received a point-of-care antibody test (rapid finger prick blood test) and 51,958 received additional testing with chemiluminescent microparticle immunoassay
- Prevalence of IgG antibodies was adjusted for sampling probability, age, sex and census tract income
- Seroprevalence varied from 5.0% (point-of-care) to 4.6% (immunoassay), 3.7% for both test positive to 6.2% for one test positive
- Seroprevalence was higher in urban areas around Madrid (hotspot of outbreak, >10%), in health care workers (10%), and in individuals with a confirmed case in their household (31-37%), workplace (10%), or among non-cohabitating family, friends, caregivers or cleaning staff (11-14%); no sex differences
- Seroprevalence was 17% in those who reported a history of symptoms compatible with COVID-19, 90% in those with a self-reported positive PCR more than 14 days before the test, and 2.0-2.5% for asymptomatic individuals
    - One in three infected individuals was asymptomatic
- Limitation: Seroprevalence studies like this provide information only about previous exposure, rather than immunity, as no neutralizing antibodies are measured
- Implications: Despite the high impact of COVID-19 in Spain, prevalence estimates remain low and are insufficient to provide herd immunity; rapid point-of-care test yielded comparable epidemiological information while having greater uptake, lower cost, and easier implementation

College reopening

6. **COVID-19 screening strategies that permit the safe re-opening of college campuses.** Paltiel et al. medRxiv preprint. July 7**.**

- Decision and cost-effectiveness analysis linked to a compartmental epidemic model (S-I-R type model) to evaluate campus screening. Budget impact analysis ($) of various regimens given results under modeled scenarios
- Baseline model used hypothetical cohort of 5000 college-age, uninfected students. Model analysis varied based on testing frequency (daily-weekly), test accuracy [sensitivity (70%-99%), specificity (98%-99.7%)], and cost ($10-$50/test). Infectious reproductive numbers **Rt** = {1.5, 2.5, 3.5} defined three epidemic scenarios
- 80-day abbreviated semester with exogenous shocks (infections and infectious/super spreader events) and implementation of an isolation dorm for positive test results. 2nd highly accurate and more expensive test performed within 24 hours of initial, positive test

- Outcomes: Across all scenarios, test frequency exerts more influence on outcomes than test sensitivity
    - Only under lowest risk condition could testing occur less frequently than daily or every 2 days
    - Rapid, inexpensive and frequently conducted screening even if only 70% sensitive would be cost-effective and produce a modest number of COVID-19 infections
    - Daily testing at lowest cost test was over $3M. Additional cost of $300-600 per student for testing alone
- Limitation: Super spreader event (parties) occurrence and behavioral interventions (limiting extent, effective reporting, isolation and tracing of such events) are assumed to be efficacious across the population of students; No modeling on impact to faculty; Is it realistic to conduct nasal swab test every 1-2 days in this population?
- Implications: While the optimal screening frequency hinges on the success of behavioral interventions to reduce the base severity of transmission (Rt), this could permit the safe return of students to campus at a moderate cost of ~$500 per student
    - saliva-based tests or tongue swabs with good diagnostic characteristics may become more widely available and would facilitate frequent testing

TRANSMISSION

Aerosol transmission

7. It is Time to Address Airborne Transmission of COVID-19. Morawska et al. Clin Infect Dis. July 6**.**

- On July 6, 239 scientists from 32 countries wrote an open letter to urge the World Health Organization and other bodies to recognize the potential for airborne transmission of COVID-19
- Authors stated that a growing body of evidence suggests that the virus spreads indoors through tiny aerosols
- The authors recommend taking additional measures to mitigate airborne transmission risk, including:
    - Providing sufficient and effective ventilation particularly in public buildings, workplace environments, schools, hospitals, and aged care homes
    - Supplementing general ventilation with airborne infection controls such as local exhaust, high efficiency air filtration, and germicidal ultraviolet lights
    - Avoiding overcrowding and confined indoor spaces
- **See also: Identifying airborne transmission as the dominant route for the spread of COVID-19**. Zhang et al. PNAS. June 30.
- Implications: Both droplets and aerosols may be responsible for transmission of COVID-19; thus, in addition to ventilation and filtration and avoiding overcrowded indoor settings, wearing face coverings and maintaining physical distancing continue to represent effective means of transmission prevention

Children

A high proportion of SARS-CoV-2 infections in children are mild or asymptomatic, but their contribution to transmission is unclear, and data on transmission of SARS-CoV-2 from school-aged children to adults are limited because most schools have been closed since March.

8. Viral RNA Load in Mildly Symptomatic and Asymptomatic Children with COVID-19, Seoul. Han et al. Emerg Infect Dis. June 4**.**

- Analysis of SARS-CoV-2 viral RNA load in clinical specimens from 12 children <18 years with confirmed COVID-19 in South Korea from March 8 - April 28, median age 6.5 years (range 27 days–16 years)
- Both mildly symptomatic (n=9) and asymptomatic (n=3) children had high levels of viral RNA in the nose and saliva early during infection, but these levels declined rapidly within 1-2 weeks
- Fecal RNA load remained high for more than 3 weeks after onset of symptoms

- Symptomatic children had higher initial RNA load in nasopharyngeal swab specimens than asymptomatic children; there were no significant differences in feces and in saliva and no correlation between RNA load and age
- Limitations: Small sample size; detection of SARS-CoV-2 RNA does not necessarily mean that infectious virus is present
- Implication: Feces is a promising source for detecting both current and recent SARS-CoV-2 infection

See also: Culture-Competent SARS-CoV-2 in Nasopharynx of Symptomatic Neonates, Children, and Adolescents. L'Huillier et al. Emerg Infect Dis. June 30.

- Among 23 children with COVID-19 in Switzerland (median age 12 years, IQR 3.8-14.5), nasopharyngeal viral RNA load at diagnosis was comparable to that of adults
    - Samples were collected a median of 2 (IQR 1–3) days after symptom onset
- SARS-CoV-2 was isolated from 12 children
    - Isolation of infectious virus was largely comparable with that of adults
    - Sex, age, duration of symptoms, clinical diagnosis, symptoms, and likelihood of admission did not differ between patients with and without isolation
- Implication: Symptomatic children of all ages shed infectious virus in early acute illness

TREATMENT

9. Effect of Colchicine vs Standard Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized With Coronavirus Disease 2019 - The GRECCO-19 Randomized Clinical Trial. Deftereos et al. JAMA Network Open. June 24**.**

- Open-label randomized clinical trial of low-dose colchicine (anti-inflammatory) with standard medical treatment in 105 patients (median age 64 years) hospitalized with COVID-19 in Greece
- Rate of the primary clinical end point (clinical deterioration, or change in clinical condition requiring invasive or noninvasive mechanical respiratory support or death) was higher in control group (14.0%) than in colchicine group (1.8%) (odds ratio, 0.11; 95% CI, 0.01-0.96)
- The cumulative event-free 10-day survival was higher in the colchicine group (97%) than in the control group (83%)
- No significant differences in hs cardiac troponin or C-reactive protein level were observed between the two groups at baseline or at peak values; however peak median D-dimer concentration was significantly lower in colchicine group
- Adverse events were similar in the 2 groups, except for more frequent diarrhea in colchicine group
- Limitations: small number of clinical events; open-label study

IMMUNOLOGY AND VACCINE DEVELOPMENT

See: Draft landscape of COVID-19 candidate vaccines. *World Health Organization. July 6.*

10. Phase 1/2 Study to Describe the Safety and Immunogenicity of a COVID-19 RNA Vaccine Candidate (BNT162b1) in Adults 18 to 55 Years of Age: Interim Report. Mulligan et al. medRxiv preprint. July 1**.**

- This *interim report* provides safety, tolerability, and immunogenicity data from an ongoing placebo-controlled, observer-blinded dose escalation study among healthy adults, receiving a lipid nanoparticle-formulated, nucleoside-modified, mRNA vaccine that encodes trimerized SARS-CoV-2 spike receptor binding domain (RBD)(vaccine is referred to as BNT162b1)
- Participants (ages 18-55) were randomized to receive 2 doses, separated by 21 days, of placebo, 10 µg, 30 µg, or 100 µg of BNT162b1 (12 participants per dose/ 9 received placebo). These data are from 14 days after the second dose.
- Local reactions and systemic events were dose-dependent, generally mild to moderate (including pain at injection site, fatigue, headache, chills and fever) and transient. Participants who received 100 µg for

their first dose did not receive a second 100 µg dose due to reactivity observed (50% fever, notable decreases in lymphocytes).

- RBD-binding IgG concentrations and SARS-CoV-2 neutralizing titers in sera increased dependent on dose by 21 days after dose 1; significantly increased again after a second dose with either 10 or 30 µg
    - Geometric mean neutralizing titers reached 1.8- to 2.8-fold that of a panel of COVID-19 convalescent human sera
- Limitations: As expected for an interim report, small sample size; T cell immunity was not addressed in the study (focused only on serology results); Durability of the antibody response needs to be assessed; The same study needs to be performed in age 55+ population and in high risk populations
- Implications: Apart from the high dose arm, the data indicate that this vaccine should be considered for further development

11. **Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19.** Sekine et al. bioRxiv. June 29**.**

- SARS-CoV-2-specific memory T cell responses were investigated across five distinct cohorts, including healthy individuals who donated blood either before or during the pandemic, family members who shared a household with convalescent individuals and were exposed at the time of symptomatic disease, and individuals in the convalescent phase after asymptomatic/mild or severe COVID-19.
- SARS-CoV-2-specific CD8+ and CD4+ T cells were identified in ~70% and 100% of COVID-19 convalescent patients, respectively, using CD8 tetramer staining and ELISpot assays (antigen specific, IFNg)
- Spike-specific CD4+ T cells were skewed toward a T follicular helper cell profile, whereas membrane-specific and nucleocapsid-specific CD4+ T cells were skewed toward a Th1 or a Th1/Th17 profile
- CD4+ T cell responses to spike, the main target of most vaccine efforts, were robust and correlated with the magnitude of the anti-SARS-CoV-2 IgG titers
- Memory T cell responses were detected at times in the absence or presence of circulating antibodies. SARS-CoV-2 reactive T cell responses were detected in ~40%–60% of unexposed individuals
- Implications:
    - Cross-reactive T cell recognition in unexposed individuals suggest circulating "common cold" coronaviruses may induce cross-reactive memory T cells
    - Serology may underestimate exposure/previous infection since T cell responses are more common than antibody responses
- Limitations: Sample sizes for groups are relatively small; no evidence that there is *protection* from SARS-CoV2 infection due to the cross-reactive T cell response

12. **A Potently Neutralizing Antibody Protects Mice against SARS-CoV-2 Infection.** Alsoussi et al. J Immunology. June 26**.**

- Using mouse immunization strategy [i.m. vaccination of receptor binding domain (RBD), d14 boost, D24 boost, d29 harvest lymph nodes and serum], RBD and S protein-specific and- neutralizing Ab responses were generated.
- After screening individual plasmablasts (PBs) for RBD-binding, sorting and cloning the variable genes into a human IgG1 expression vector, 26 out of 34 mAb screened, bound recombinant SARS-CoV-2 RBD expressed in mammalian cells
- 19 mAb were screened further based on their clonal lineage. Of those 19 which all bound SARS-CoV-2 S protein, only 5 bound SARS-CoV S protein and none bound MERS-CoV S protein. Using an in vitro VERO cell neutralization assay, 5 of the 19 neutralized SARS-CoV-2 and mAb **2B04** was most potent
- mAb 2B04, administered one day prior to challenge with SARS-CoV-2, protected hACE2-expressing mice from significant weight loss, reduced viral load, and decreased inflammatory infiltrate in the lung

compared to mice receiving isotype control Ab. (mH04 Ab treatment showed some intermediate impact on disease).

- Limitations: Mouse model of infection; protection experiment is prophylactic set up rather than therapeutic; does not address critical question whether a suboptimal dose or delayed therapeutic administration could enhance viral infection
- Implications: 2B04, a murine/human chimeric mAb, could be tested further for therapeutic potential in a natural infection model

VIRAL TROPISM - IN VITRO MODEL DEVELOPMENT

13. **A Human Pluripotent Stem Cell-based Platform to Study SARS-CoV-2 Tropism and Model Virus Infection in Human Cells and Organoids.** Yang et al. Cell Stem Cell. July 2.

- Human pluripotent stem cells (hPSCs)-derived cells/organoids were used to investigate cell and tissue tropisms using a spike-enabled pseudo-entry virus
- The spike-enabled pseudo-entry virus entered pancreatic endocrine cells, liver organoids, cardiomyocytes, and dopaminergic neurons (little to low levels of pseudo-entry virus was detected in hPSC-derived endothelial cells, microglia, macrophages, or cortical neurons)
- Human pancreatic beta cells and liver organoids are highly permissive to the SARS-CoV-2, as well as primary human islets and adult hepatocyte and cholangiocyte organoids
- hPSC-derived cells/organoids express similar chemokines when exposed to SARS-CoV-2 (USA-WA1/2020) as those seen in COVID-19 pulmonary autopsy tissues (*CCL2, CXCL5, and CXCL6*)
- Limitations: Vesicular stomatitis virus-based SARS-CoV-2 pseudo-entry virus only was used for several of these viral entry assays; analysis is limited to viral entry not viral replication or release from the host cells; more primary patient samples would be needed to confirm permissive tissues/cells in vivo
- Implications: hPSC-derived cells/organoids provide valuable models for understanding the cellular responses of human tissues to SARS-CoV-2 infection

14. **Critical Role of Type III Interferon in Controlling SARS-CoV-2 Infection in Human Intestinal Epithelial Cells.** Stanifer et al. Cell Report. June 19.

- Colon-derived cell lines (T84 and Caco-2 cells) and primary non-transformed colon organoids support SARS-CoV-2 (strain BavPat1) infection, replication, and production of infectious de novo virus particles
- Type III interferon (IFN) is elicited in infected cell lines; type III IFN receptor deficient cells are more permissible to SARS-CoV-2 infection and produce more de novo virus suggesting an intrinsic mechanism of viral control. Pretreatment of T84 or Caco-2 cells with either IFN-β1 and IFN-λ significantly impaired with SARS-CoV-2 infection
- Infection of organoids led to no type I IFN (IFN-β1) production but did lead to upregulation of type III IFN (IFN-λ). Pretreatment of colon organoids with either IFN-β1 and IFN-λ significantly interfered with SARS-CoV-2 infection and de novo synthesis of virus
- Limitations: While SARS-CoV-2 genomes have been detected in feces, origin of the replicating SARS-CoV-2 in the intestinal epithelium is not clear
- Implications: An enteric phase of SARS-CoV-2 is possible and could contribute to the immune response and/or viral replication