Summary of Major Literature Related to COVID-19 (Sept 8-21)

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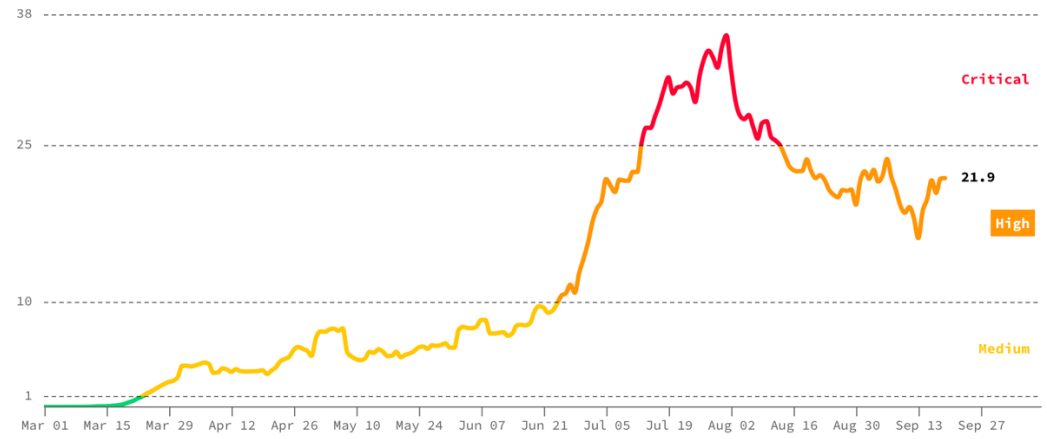
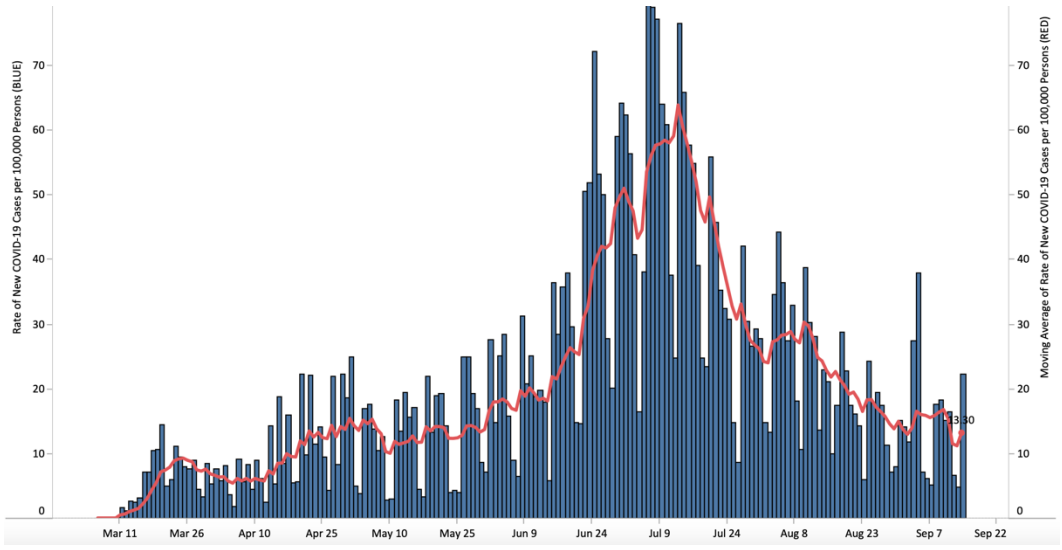
***This is informational and not intended to create variance from VUMC policies/guidance.**

STATISTICS – Daily new cases per 100,000 population

Tennessee



Davidson county



As of 09/20, in TN

- Total cases = 183,514
- Active cases = 15,452
- Current hospitalizations = 662
- Total deaths = 2,218
- Top counties:
  - Shelby = 30,062
  - Davidson = 28,002 (active cases = 932)
- Numbers of active cases in Davidson co. and TN both ↓ since Sept 7
- Demographics:

Groups	Cases	%
By sex		
Female	93,467	50.9%
Male	88,307	48.1%
By race/ethnicity		
White	97,973	53.4%
Black	33,861	18.5%
Hispanic	24,624	13.4%
Asian	1,686	0.9%
Other	25,370	13.8%
By age (average: 39 years)		
0–10	8,980	4.9%
11–20	24,212	13.2%
21–30	38,876	21.2%
31–40	31,007	16.9%
41–50	27,406	14.9%
51–60	23,468	12.8%
61–70	15,612	8.5%
71–80	8,840	4.8%
80+	4,828	2.6%

EPIDEMIOLOGY

Transmission setting/infectivity

1. **Duration of SARS-CoV-2 Infectivity: When is it Safe to Discontinue Isolation? Rhee et al. Clin Infect Dis. August 25.**

- Comprehensive review of current evidence related to duration of infectivity and transmission dynamics
- Median incubation period for SARS-CoV-2 is 5 days (IQR 2-7); approximately 98% of infected individuals who develop symptoms do so within 12 days of exposure
- Viral RNA levels are detectable in the respiratory tract 2-3 days before symptoms appear, peak at symptom onset, and decline over the following 7-8 days in most patients
  - Asymptomatic and pre-symptomatic people can transmit virus prior to symptom onset

- Infectivity decreases to essentially zero after about 10 days from symptom onset in mild-moderately ill patients and after about 15 days in critically ill and immunocompromised patients
    - Most studies have been unable to isolate replication-competent virus from patients beyond 15 days
    - Epidemiologic data also show low infection rate among people with contact with case patients >5 days after symptom onset
- Patients who test positive by PCR after negative PCR (up to 82 days) have not been found to have replication competent virus
    - Some test inconsistency may reflect results at the limits of a PCRs cycle threshold
- Implications:
    - SARS-CoV-2 is most contagious right before and immediately following symptom onset
    - Persistent RNA detection does not necessarily translate into contagiousness; thus, test-based clearance with at least two negative RT-PCR tests for COVID-19 patients is *no longer recommended*, as it can lead to unnecessarily prolonged isolation

2. **Community and Close Contact Exposures Associated with COVID-19 Among Symptomatic Adults ≥18 Years in 11 Outpatient Health Care Facilities — United States, July 2020.** Fisher et al. MMWR. Sept 11**. (VUMC paper)**

- Enrolled symptomatic adults (≥18 years) seeking outpatient SARS-CoV-2 testing at one of 11 Influenza Vaccine Effectiveness in the Critically Ill (IVY) Network sites during July 1–29, 2020. Potential participants were contacted 14-23 days after testing
    - Case-patients (n=154) had SARS-CoV-2 infection confirmed by RT-PCR
    - Control-participants (n=160) were negative for SARS-CoV-2 infection and matched by age, sex, study location to a case-patient
- Close contact with one or more persons with known COVID-19 was reported by 42% of case-patients compared with 14% of control-participants ($p<0.01$), and 51% of close contacts were family members.
- No significant differences were observed between case and controls in terms of: shopping, visiting others inside a home (≤10 persons), going to an office setting, going to a salon, gatherings with >10 persons in a home, going to a gym, using public transportation, going to a bar/ coffee shop, or attending church/religious gathering. In the 14 days before illness onset, 71% of case-patients and 74% of control-participants reported always using face coverings when in public
- Case-patients were more likely to have reported dining at a restaurant (adjusted OR 2.4, 95% CI 1.5–3.8) in the 2 weeks before illness onset than control-participants. After removing participants with a known COVID close contact, case-patients were more likely than control-participants to have reported dining at a restaurant (aOR 2.8, 95% CI 1.9–4.3) or going to a bar/coffee shop (aOR 3.9, 95% CI 1.5–10.1)
- Limitations. Recall bias, generalizability, misclassification of disease status
  Implications: Close contact with known COVID-19 case and going to locations with on-site eating and drinking options are major risk factors for infection

Delay of medical care

3. **Delay or Avoidance of Medical Care Because of COVID-19–Related Concerns — United States, June 2020.** Czeisler et al. MMWR 69(36);1250–1257. Sept 11**.**

- Web-based survey was administered during June 24–30 to a nationwide sample of US adults aged ≥18 years to assess delay or avoidance of urgent or emergency and routine medical care because of concerns about COVID-19
    - 55% response rate (5,412/9,896); 4,975 (92%) provided complete data

- Overall, 40.9% of US adults avoided medical care during the pandemic, including urgent or emergency care (12%) or routine care (31.5%)
- In multivariable analyses, adjusted prevalence of urgent or emergency care avoidance was significantly higher among unpaid caregivers for adults (versus non-caregivers); persons with two or more selected underlying medical conditions; persons with health insurance; Black and Hispanic versus White adults; aged 18–24 years versus 25–44 years; and persons with disabilities
- Limitations: Potential for selection or reporting bias; findings may not be generalizable, but are consistent with previously reported declines in hospital admissions or emergency department visits during pandemic; no information collected on reasons for avoiding medical care
- Implications: Widespread avoidance of medical care among those at increased risk for COVID-19 raises concerns about chronic disease management or early detection of new, potentially life-threatening conditions and about exacerbation of health disparities

Young adults/children

4. **Clinical Outcomes in Young US Adults Hospitalized With COVID-19.** Cunningham et al. JAMA Intern Med. Sept 9**.**

- Study of clinical profile and outcomes of 3222 young adults (age 18-34y) who required hospitalization for COVID-19 at 419 US hospitals
    - Mean (SD) age 28.3 (4.4) years; 1849 (57.6%) men; 1838 (57.0%) Black or Hispanic
    - 789 (24.5%) had morbid obesity, 588 (18.2%) diabetes, and 519 (16.1%) hypertension; 42% had one or more of these conditions
- During hospitalization, 684 patients (21%) required intensive care, 331 (10%) required mechanical ventilation, and 88 (2.7%) died
    - Proportion with mechanical ventilation or death rose to >20% and >5%, respectively, among those with multiple comorbidities
- Odds of death or mechanical ventilation were higher among men (aOR 1.53; 95% CI, 1.20-1.95) and among those with morbid obesity (aOR 2.30; 95% CI, 1.77-2.98 vs. no obesity) or hypertension (aOR 2.36; 95% CI, 1.79-3.12)
- Implications: Young adults who have multiple comorbidities and are hospitalized with COVID-19 experience risk of adverse outcomes comparable to those in healthy middle-aged (35-64y) adults with COVID-19
- Limitations: Inconsistent reporting of race/ethnicity across hospitals; reliance on ICD-10 diagnosis and billing codes may lead to some misclassification

5. **SARS-CoV-2–Associated Deaths Among Persons Aged <21 Years — United States, February 12–July 31, 2020.** Bixler et al. MMWR. Sept 15**.**

- 121 SARS-CoV-2–associated deaths were reported to CDC among persons aged <21 years from February 12–July 31:
    - 63% were male
    - 10% were aged <1 year, 20% aged 1–9 years, 70% aged 10–20 years (half of these among 18-20 year olds)
    - 45% were Hispanic, 29% were non-Hispanic Black, and 4% were non-Hispanic American Indian or Alaska Native (AI/AN)
    - 75% had an underlying medical condition and 45% had two or more underlying conditions; most common were chronic lung disease, including asthma (28%), obesity (27%), neurologic and developmental conditions (22%), and cardiovascular conditions (18%)

    - 65% died after admission to a hospital, and 32% died at home or in the emergency department (2.5% had unknown location of death); 25% of those who died had no underlying condition
    - 12% met the definition of multisystem inflammatory syndrome in children
- Implications:
    - Disproportionate representation of Hispanic, Black, and AI/AN children among COVID-19 deaths is likely due to higher risks for SARS-CoV-2 exposure, adverse social determinants of health, and inequities in health care access
    - Deaths at home or in ED suggest delay of necessary care during the pandemic
- Limitations: Potential for incomplete or nonuniform reporting across public health jurisdictions

Myocarditis in competitive athletes

6. **Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection.** Rajpal et al. JAMA Cardiol. Sept 11.

- Cardiac magnetic resonance (CMR) imaging in 26 competitive college athletes 11-53 days following confirmed positive test for COVID-19
    - Mean (SD) age 19.5 (1.5) years; 58% male
    - None required hospitalization; 27% reported mild symptoms, the rest were asymptomatic
- Ventricular volumes and function were within the normal range in all athletes
- Four athletes (15%; all male) had CMR findings consistent with myocarditis based on the presence of myocardial edema by elevated T2 signal and myocardial injury by presence of nonischemic LGE
    - 2 had mild symptoms (shortness of breath), 2 were asymptomatic
- 8 additional athletes (31%) exhibited LGE without T2 elevation suggestive of prior myocardial injury
- Implications: CMR imaging has the potential to identify infected athletes with a high-risk for adverse outcomes and may, importantly, risk stratify athletes for safe participation
    - Current guidelines suggest return to play after 14 day period of rest, but myocardial inflammation by CMR has been associated with poor cardiac outcomes and death
- Limitations: No baseline CMR imaging; long-term follow up and large studies including control populations are needed

HUMAN IMMUNE RESPONSE

Timing of immunity/antibody changes

7. **Change in Antibodies to SARS-CoV-2 Over 60 Days Among Health Care Personnel in Nashville, Tennessee.** Patel et al. JAMA. Sept 17. (**VUMC paper**, W. Self senior author)

- Evaluation of anti–SARS-CoV-2 antibodies at baseline and 60 days later in a convenience sample of 249 health care personnel at VUMC who had regular direct contact with adult COVID-19 patients
    - 65% female; 92% White; median age 33 years (range, 21-70 years)
    - 42.2% nurses, 34.5% physicians and advanced practice clinicians, 6.8% radiology technicians, and 16.5% other health care personnel
- Serum samples were tested for anti–SARS-CoV-2 antibodies using a validated ELISA against the prefusion-stabilized extracellular domain of the SARS-CoV-2 spike protein; these antibodies have correlated with neutralizing antibodies
- Seropositivity decreased from 7.6% (19/249) at baseline to 3.2% at 60 days
    - 42% (8/19) of those who tested positive for SARS-CoV-2 antibodies at baseline remained seropositive at 60 days
    - Of the 11 who became seronegative, 6 (55%) were asymptomatic prior to the baseline visit, compared to 25% (2/8) who remained seropositive

- Antibodies declined consistently, regardless of baseline signal-to-threshold ratio, among participants who remained seropositive at 60 days and also among those whose antibody levels decreased below the threshold
- Limitations: antibody kinetics could not be evaluated given lack of information of timing of infection; unknown whether observed decline in antibodies increases risk of reinfection and disease
- Implications: Cross-sectional seroprevalence studies may underestimate rates of prior infections because antibodies may only be transiently detectable following infection, particularly among those who did not have symptoms; window for donating convalescent plasma may be limited

8. **Rapid Decay of Anti–SARS-CoV-2 Antibodies in Persons with Mild Covid-19.** Ibarrondo et al. Correspondence to the Editor, NEJM. Sept 10**.**

- A longitudinal assessment of SARS-CoV2 receptor-binding domain (RBD) binding IgG in serum of 34 persons who had recovered from COVID-19 (31 had two measurements; 3 had 3 measurements)
    - Participants had mild disease although 2 did receive low-flow supplemental oxygen and a CCR5 antagonist (leronlimab)
    - 20 women, 14 men; mean age 43y (range 21-68)
- Blood samples were analyzed by enzyme-linked immunosorbent assay (ELISA) to detect anti–SARS-CoV-2 spike receptor-binding domain IgG
- The first and second measurements were obtained at a mean of 37 days and 86 days, respectively, after the onset of symptoms
- Using a linear regression model, the estimated mean change was calculated and translated to a half-life of approximately 36 days
- Limitations: Small number of participants; unable to extrapolate data past the first 90 days (i.e. decay of antibodies may decelerate)
- Implications: Antibody loss in this study was quicker than that reported for SARS-CoV-1; humoral immunity may not be long-lasting for those with mild disease, results are consistent with previously reported findings (Long Q-X, Nat Med 2020)

9. **Seasonal coronavirus protective immunity is short-lasting.** Edridge et al. Nature Medicine. Sept 14.

- Examined duration of protective immunity of four distinct species of seasonal human coronaviruses that cause respiratory tract infections - HCoV-NL63, HCoV-229E, HCoV-OC43 and HCoV-HKU1
- 10 healthy individuals were selected from the Amsterdam Cohort Studies on HIV-1 infection and AIDS, a cohort study with blood collection from adult males every 3-6 months since the 1980s
- Increases in antibodies to the carboxyl (C)-terminal region of the nucleocapsid protein (NCt), an immunodominant region of the structural coronavirus capsid protein, were measured for each seasonal coronavirus to detect how often infections occurred during follow-up
- A total of 101 events, ranging from 3 to 17 per individual, were classified as coronavirus reinfections
- The reinfection times ranged between 6 and 105 months; reinfection intervals of more than 6 months showed intermediate reductions in antibodies between infections
- Limitations: small study; strain variation was not identified and could play a role in susceptibility to reinfection
- Implications: Evidence that reinfections occur for all four seasonal human coronaviruses as early as 6 months but more frequently after one year, along with previous data showing decreases in neutralizing SARS-CoV-2 antibody levels after two months post-infection, may imply similar short-term protective immunity for SARS-CoV-2

Prediction of clinical outcome

10. **A neutrophil activation signature predicts critical illness and mortality in COVID-19.** Meizlish et al. medRxiv preprint (not yet peer-reviewed). Sept 2**.**

- Report of proteomic profiling of blood of hospitalized patients with COVID-19 and clinical data from a health system database (Yale) of over 3,300 patients
    - used a machine learning algorithm to define biomarkers that best discriminate between critically ill patients and those with milder disease
- In the longitudinal analysis, elevated neutrophil biomarkers (RETN, LCN2, HGF and MMP8) at the time of hospital admission identified ICU-transfers and predicted increased in-hospital mortality; correlates with absolute neutrophil counts
- While markers of macrophage activation were also elevated in ICU-transfers, these markers (IL6, IL10, TNF and CXCL9) were also significantly higher in non-ICU COVID19 patients compared to controls
- Based on data from first blood draws of over 3,300 patients, in-hospital mortality was significantly higher among patients with elevated initial immature granulocytes and neutrophil absolute count; initial absolute monocyte count was *NOT* associated with increased mortality
- Neutrophil to lymphocyte ratio (NLR), which has been reported as a prognostic indicator in COVID-19, was not significantly different between non-ICU and ICU-transfer patients on the first day of hospitalization
- D-dimer, another well-established marker of disease severity in COVID-19, was significantly different between patients who did and did not survive their hospitalization
- Implications: Both neutrophil activation and monocyte/macrophage activation precede the onset of critical illness; neutrophil degranulation may be a more specific feature of severe COVID-19

Children

11. **The Immunology of Multisystem Inflammatory Syndrome (MIS-C) in Children with COVID-19.** Consiglio et al. Cell (In press). Sept 6**.**

- Analysis of blood immune cells, cytokines and autoantibodies in healthy children, children with Kawasaki disease enrolled prior to COVID-19, children infected with SARS-CoV-2 and children presenting with MIS-C
    - Enrollment included 41 SARS-CoV-2^{+} children (CoV2+, all mild disease), 13 children with MIS-C; compared to 28 children presenting with Kawasaki disease before May 2019, and 19 healthy controls
- Children presenting with MIS-C were significantly older than the children with Kawasaki disease (8.6 vs. 2 yrs); MIS-C children had more severe lymphopenia, lower platelet counts, higher levels of CRP, increased ferritin levels compared to both Kawasaki disease patients and CoV2+ children
- Based on an analysis of 120 plasma proteins, inflammatory response in MIS-C differs from the cytokine storm of severe acute COVID-19 where IL-7 and IL-8 levels were high
    - Filtered out 60 proteins with >30% of measurements below threshold for detection
- MIS-C and Kawasaki disease resulted in lower T cell frequencies compared to healthy children; MIS-C and CoV2+ patients had increased central and effector memory T cells and fewer naïve and follicular helper T cells compared to Kawasaki patients; IL-17A and biomarkers associated with arterial damage (ESDN) were higher in Kawasaki disease than in MIS-C
- Using VirScan (a method for testing IgG binding of >90K epitopes from >200 viruses), children had IgG antibodies to RSV, rhinovirus, and herpesvirus family; IgG antibodies to human coronavirus HKU1 and βCoV1 were commonly observed in the cohort; MIS-C patients were the only ones lacking antibodies to either of these common coronaviruses

- Multiple MIS-C autoantibodies were overrepresented (relative to other groups) including members of the casein kinase family, antibodies to MAP2K2 that could be involved in the pathogenesis of MIS-C; autoantibodies to EDIL3 (a glycoprotein in arteriole cell walls) were overrepresented in Kawasaki
- Limitations: Largely a descriptive study; clear need to understand these hyperinflammatory mechanisms including candidate autoantibodies
- Implications: While there are some similarities in the inflammatory response in children with Kawasaki disease and those with MIS-C as a result of CoV2 infection, there are also marked differences

THERAPEUTIC DEVELOPMENT

12. De novo design of picomolar SARS-CoV-2 miniprotein inhibitors. Cao et al. Science. Sept 9**.**

- Design of two novel three helix bundle proteins that compete for the Ace2 binding site on SARS-CoV-2 Spike protein
    - SARS-CoV-2 Spike-Ace2 interaction allows SARS-CoV-2 infection of cells
- Two strategies to develop small protein inhibitors:
    - One uses the interacting helix from Ace2 and stabilizes its conformation with two additional helixes, making a stable three helix bundle
    - The second strategy uses an entirely novel three helix bundle
- Both strategies use ROSETTA computational methods to either stabilize a three helix bundle that presents the binding elements from Ace2 (method 1), or to stabilize a completely novel protein and a somewhat novel binding mode
- ROSETTA is a "knowledge-based" computational approach. It uses a large (billions) library or short peptide sequence derived from structures in the pdb. This is a powerful computational approach that assembles these peptides and searches for favorable sequences to meet a given design target. In this instance the authors searched for and identified stable 3 helix bundles that bound SARS-CoV-2 Spike
- Ace2 derived binders were identified using ROSETTA. The top 18,000 sequences were expressed in a yeast display system (surface expression of 1 construct per organism); for the de-novo 3 helix bundle, a similar strategy was used and 100,000 sequences were expressed in yeast.
    - From these yeast libraries binders were identified and subsequently optimized by directed evolution (error prone PCR)
- The identified proteins bound extremely potently (nM-pM), were very thermostable, easy to make, and bound SARS-CoV-2 Spike in the expected manner (as determined by cryo-EM)
- Implications: This approach may compete with antibody development. The authors note that similar mini proteins are poorly antigenic. As a Biologic drug, such proteins have short half-lives and would likely need to be reformulated as Fc fusion proteins.
    - As a new aerosol therapeutic or prophylactic, this could be a new and promising approach. There are very similar strategies being developed with nanobodies (https://www.ucsf.edu/news/2020/08/418241/aeronabs-promise-powerful-inhalable-protection-against-covid-19).