**Summary of Major Literature Related to COVID-19 (Nov 17-Dec 7)**

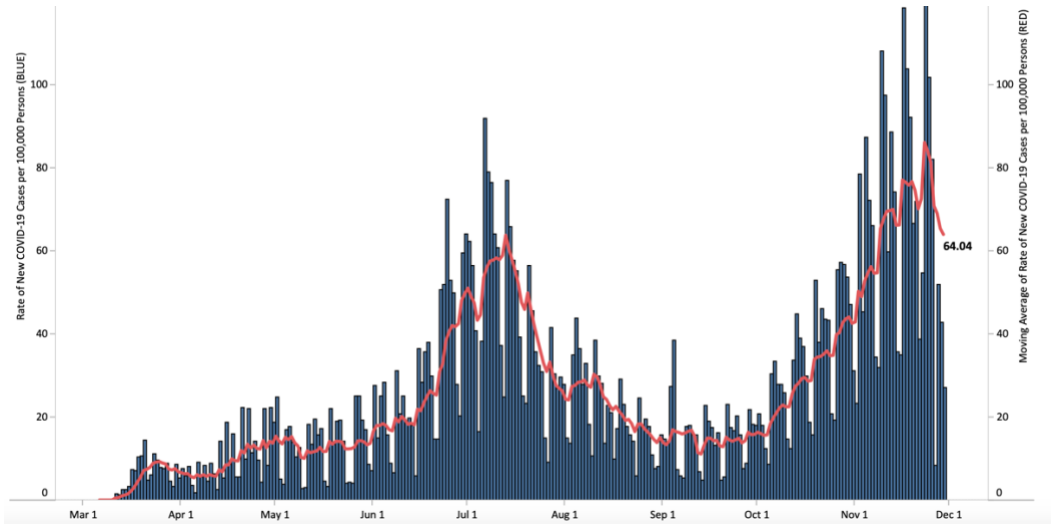
Led by Loren Lipworth (Epidemiology) and Holly Algood (Infectious Diseases), with contribution from XO Shu, D Yu, A Ahonkhai, DOM

***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 December 7, in TN

- Total cases = 408,730
- Active cases = 40,903
- Current hospitalizations = 2,529
- Total deaths = 5,009
- Top counties:
  - Shelby = 51,550
  - Davidson = 50,275
- In Davidson county, Active cases = 3,303
  ICU availability = 9%

Test % positive 7-d = 14%

- Demographics:

| Groups | No. of Cases | No. of Deaths |
|---|---|---|
| By sex | | |
| Female | 214,925 | 2,280 |
| Male | 190,569 | 2,727 |
| By race/ethnicity | | |
| White | 234,609 | 3,604 |
| Black | 57,622 | 1,032 |
| Hispanic | 33,444 | 183 |
| Asian | 3,389 | 34 |
| Other | 39,456 | 176 |
| By age | | |
| 0–10 | 20,367 | 4 |
| 11–20 | 53,725 | 2 |
| 21–30 | 77,496 | 31 |
| 31–40 | 64,188 | 63 |
| 41–50 | 61,083 | 166 |
| 51–60 | 55,686 | 457 |
| 61–70 | 39,448 | 932 |
| 71–80 | 23,604 | 1,510 |
| 80+ | 12,584 | 1,844 |

## EPIDEMIOLOGY

1. **COVID-19 Severity Is Tripled in the Diabetes Community: A Prospective Analysis of the Pandemic's Impact in Type 1 and Type 2 Diabetes.** Gregory et al. (**VUMC paper**). Diabetes Care. 2 Dec 2020.

- A prospective cohort analysis of 6138, 40, and 273, COVID 19 patients without diabetes, with type 1, and with type 2 diabetes, respectively, based on VUMC electronic health record data
- Clinical information was gathered by electronic health record query, chart review, and patient contact
- COVID-19 patients with type 1 diabetes had 3.9-fold increased odds of hospitalization and 3.4-fold increased odds of having severe illness comparing to non-diabetic COVID 19 patients after adjusting for age and other confounders. These estimates are similar to those for COVID-19 patients with type 2 diabetes

- Probability of hospitalization for patients with type 1 diabetes ranged between 15% and 22% for patients <40 years of age, after adjustment for BMI, which is substantially higher than the 5% for non-diabetic COVID-19 patients
- Among patients with type 1 diabetes, glycosylated hemoglobin (HbA1c), hypertension, race, recent diabetic ketoacidosis, health insurance status, and less diabetes technology use were significantly associated with illness severity
- None of the type 1 patients was deceased, diagnosed with myocarditis, acute cardiac injury, or arrythmia
- Limitations: Based on a single academic health system, thus results may not be generalizable to all COVID-19 patients with diabetes; relatively small sample size
- Implication: Protection of type 1 and type 2 diabetes patients from infection with SARS-CoV-2 is urgently needed; VUMC Researchers urge priority vaccination for individuals with diabetes

2. **Delirium in Older Patients With COVID-19 Presenting to the Emergency Department.** Kennedy et al. JAMA Netw Open. 19 Nov 2020**.**

- Multicenter cohort study of 817 older adults (mean age 77.7y) presenting to US Emergency Departments (ED) with diagnosed active COVID-19 illness since March 13
    - 47% male; 62% white, 27% Black, 7% Hispanic
- Delirium was identified through a reliable and widely used medical record review approach, with sensitivity 74%, specificity 83%, and high interrater reliability (κ = 1.0)
- 226 patients (28%) had delirium at presentation, and delirium was the sixth most common of all presenting symptoms and signs
- Among patients with delirium, 16% had delirium as a primary symptom and 37% had no typical COVID-19 symptoms such as fever or shortness of breath
- Factors significantly associated with delirium were: age > 75y, living in a nursing home or other long term care facility, prior use of psychoactive medication, stroke, and Parkinson disease
- Delirium was associated with intensive care unit admission (aRR 1.67; 95% CI, 1.30-2.15), discharge to a rehabilitation facility (aRR 1.55, 95% CI, 1.07-2.26), and death (aRR 1.24; 95% CI, 1.00-1.55)
- Limitation: 30% of patients had a prior diagnosis of cognitive impairment/dementia and 13% had a history of stroke, placing them at high risk for delirium
- Implications: High frequency of delirium as a primary or sole symptom among older patients in the ED suggests that delirium should be considered for inclusion in CDC guidance on COVID-19 symptom profiles; delirium may be an important marker to identify patients at high risk for poor outcomes

**Pandemic effects on healthcare**

3. **Trends in Outpatient Care Delivery and Telemedicine During the COVID-19 Pandemic in the US.** Patel et al. JAMA Intern Med. 16 Nov 2020**.**

- Examination of telemedicine and in-person outpatient visits from Jan 1 - June 16, 2020 among a national sample of 16.7 million individuals with commercial or Medicare Advantage insurance
- During the study period, the rates for telemedicine visits increased from 0.8 to 17.8 visits per 1000 enrollees (2013% change); in-person visits dropped from 102.7 to 76.3 (−30.0% change); total visits (telemedicine and in-person visits combined) decreased from 103.5 to 94.1 (−9.1% change)
    - Weekly rate of telemedicine visits peaked the week of April 15, before declining by the week of June 10
- By the last four weeks of the study, there was wide geographic variation in the percent of total visits delivered by telemedicine (ranging from 8.4% in South Dakota to 47.6% in Massachusetts)
    - Tennessee: −23.6% change in total visits with 10.4% of all visits as telemedicine

- Implications: Growth in telemedicine offset only ~2/3 of the decline in in-person visit volume, raising concerns about chronic illness management or deferred acute care
- Limitations: Commercially insured population may limit generalizability; could not separate discretionary care that could be postponed without harm; racial/ethnic, socioeconomic or other inequities in deferred care were not addressed

4. **Overdose-Related Cardiac Arrests Observed by Emergency Medical Services During the US COVID-19 Epidemic.** Friedman et al. JAMA Psychiatry. 3 Dec 2020.

- Retrospective observational study based on emergency medical services (EMS) data, representing over 80% of EMS calls nationally; examined trends in overdose-related cardiac arrests during the COVID-19 pandemic
    - Calculated weekly overdose-related cardiac arrests and overdose-related EMS activations for 2020 compared to weekly average of 2018 and 2019 (baseline trend)
    - Adjusted for overall increase in call volume
- Total of 25.9 million EMS activations in 2020, 50% from female patients and 50% from patients age ≥61y
- Overdose-related cardiac arrests rose during April, reaching 74.1/100 000 EMS activations (123.4% above baseline) by May 4, and subsequently decreased but remained elevated, reaching 48.7/100 000 (53.7% above baseline) by July 27
- Trends aligned temporally with drops in mobility due to stay at home orders
- Limitations: All overdose-related calls remained stable throughout the pandemic, but no data are presented on cardiac arrest trends relative to other causes for EMS calls; no data on specific substance use or on methods for classifying calls as overdose-related; no distinction between fatal and non-fatal cardiac arrests
- Implications: Social isolation may have played a role in the overall 50% increase in overdose-related cardiac arrests between January and August 2020, but additional data

**Viral kinetics/infectiousness**

5. **SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis.** Cevik et al. Lancet. 19 Nov 2020.

- Systematic review and meta-analysis of the viral dynamics of SARS-CoV-2, as well as SARS-CoV and MERS-CoV, including viral kinetics and duration of shedding
    - Included 79 studies (5340 individuals) on SARS-CoV-2, 58 of which were conducted in China
- Duration of SARS-CoV-2 RNA shedding:
    - Mean 17.0 days (95% CI 15.5–18.6; 43 studies, 3229 individuals) in upper respiratory tract, 14.6 days (9.3–20.0; seven studies, 260 individuals) in lower respiratory tract, 17.2 days (14.4–20.1; 13 studies, 586 individuals) in stool, and 16.6 days (3.6–29.7; two studies, 108 individuals) in serum samples
    - Maximum shedding duration was 83 days in the upper respiratory tract, 59 days in the lower respiratory tract, 126 days in stool, and 60 days in serum
    - Pooled mean SARS-CoV-2 shedding duration was positively associated with age (slope 0.304 [95% CI 0.115–0·.93]; p=0.0016) but not sex
    - No study detected live virus beyond day 9 of illness, despite persistently high viral loads
- Viral load:
    - SARS-CoV-2 viral load in the upper respiratory tract (inferred from cycle value thresholds) peaked in the first week of illness (vs. SARS-CoV and MERS-CoV which peaked later), followed by a consistent decline

- Viral loads at start of infection appear to be similar among asymptomatic and symptomatic patients; most studies demonstrated faster viral clearance in asymptomatic individuals (also seen in MERS-CoV)

- Limitation: Data on shedding of infectious virus in asymptomatic individuals are limited and do not allow estimation of transmission potential; Most patients studied received treatments that may have modified viral dynamics; considerable study heterogeneity
- Implications:
  - Duration of viable SARS-CoV-2 virus is short-lived, despite prolonged RNA shedding; thus, early case-finding and isolation is critical for limiting spread and repeat testing might not be indicated
  - Asymptomatic individuals may have a shorter infectious period than symptomatic patients but similar potential transmissibility at the onset of infection
- **See also: Transmission heterogeneities, kinetics, and controllability of SARS-CoV-2.** Sun et al. Science. 24 Nov 2020.

**TREATMENT**

6. **Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results.** WHO Solidarity Trial Consortium. NEJM. 2 Dec 2020.

- Results of open-label mortality trials of four repurposed antiviral drugs - remdesivir (N=2750), hydroxychloroquine (N=954), lopinavir (N=1411), and interferon beta-1a (N=2063) - in patients hospitalized with COVID-19 in 405 hospitals in 30 countries
  - Primary analyses examined in-hospital mortality in the four pairwise comparisons of each trial drug and its control (drug available but patient assigned to the same care without that drug); no placebos were used
  - Hydroxychloroquine, lopinavir, and interferon regimens were discontinued for futility on June 19, July 4, and October 16, 2020, respectively
- 9120 patients (81%) were <70 years of age, 6985 (62%) were male, 2768 (25%) had diabetes, 916 (8%) were already receiving ventilation, and 7002 (62%) underwent randomization on day 0 or 1 of hospitalization
- 1253 deaths were reported (median day of death, day 8)
  - Kaplan–Meier 28-day mortality was 11.8% (39.0% if the patient was already receiving ventilation at randomization and 9.5% otherwise)
- Results:
  - Remdesivir: 301/2743 deaths vs 303/2708 in its controls (rate ratio, 0.95; 95% CI, 0.81 to 1.11)
  - Hydroxychloroquine: 104/947 deaths vs 84/906 in controls (rate ratio, 1.19; 95% CI, 0.89 to 1.59)
  - Lopinavir: 148/1399 deaths vs 146/1372 in controls (rate ratio, 1.00; 95% CI, 0.79 to 1.25)
  - Interferon: 243/2050 deaths vs 216/2050 receiving its control (rate ratio, 1.16; 95% CI, 0.96 to 1.39)
- Weighted average of stratified results of Solidarity trial and other trials for mortality yielded rate ratios for remdesivir, hydroxychloroquine and lopinavir of 0.91 (95% CI 0.79-1.05), 1.09 (95% CI 0.98-1.21), and 1.01 (95% CI 0.91-1.13), respectively
  - No drug reduced the need for ventilation or hospital duration (no point estimates presented)
- Implications:
  - There is a need for better treatments

- None of the four drugs significantly reduced in-hospital death among hospitalized COVID-19 patients, overall or in any subgroup of age at entry or respiratory support at entry, or reduced initiation of ventilation or hospitalization duration
- This is the only large trial of interferon

## ANTIBODY RESPONSE/IMMUNOLOGICAL MEMORY

7. **Dynamic changes in anti-SARS-CoV-2 antibodies during SARS-CoV-2 infection and recovery from COVID-19.** Li et al. Nature Communications. 27 Nov 2020.

- This is an analysis of laboratory findings of 1,850 patients (tested 1-10 times) for total antibody; 712 samples from 418 patients had laboratory results for spike, RBD, and nucleoprotein (N)-specific IgM and IgGs during infection and recovery (commercially available ELISA kits); ~40% of patients were sampled more than once at different time points in each assay
- S-, RBD-, and N-specific IgG is detectible one week later in patients with severe/critical COVID-19 compared to patients with mild/moderate disease, but levels of S- and RBD- specific IgG are higher in the severe/critical patients (7-10 weeks after onset)
  - 39.6% of patients were IgM positive, and 70.8% were IgG positive within the first week after symptom onset (based on total Ab, not Ag specific Ab assays)
  - Total SARS-CoV2 IgG could be detected in 95.3% of patients 5 weeks after symptom onset
- Total SARS-CoV2 Ab levels in non-survivors were significantly lower than those in survivors
- S-and RBD-specific Ab levels were 2x higher in patients who were $PCR^-$ than in $PCR^+$ patients
- Lower S-, RBD-, and N-specific IgG levels are significantly associated with lower lymphocyte % but also with higher PMN%
- Limitations: Some speculation in this manuscript that low Ab may result in reinfection (antidotes are in the results); No neutralization data on the Ab in this study; all patients from Wuhan, China
- Implications: Timing of the IgG response may be associated with disease progression and viral clearance

8. **Immunological memory to SARS-CoV-2 assessed for greater than six months after infection.** Dan et al. BioRxiv (Pre-print not yet peer-reviewed). 17 Nov 2020.

- A cohort of 185 subjects with COVID-19 (92% were never hospitalized); most subjects provide one blood sample defined at the days post symptom onset (PSO, 41 were >6mo PSO) and 38 subjects provided multiple samples between 2-4 mo PSO
- Multiple ELISAs were used to quantify Ab titer in serum (specific for spike IgG, spike RBD IgG, and nucleocapsid IgG, spike IgA and RBD IgA) and a functional assay for neutralization (SARS-CoV2 pseudovirus Ab assay)
  - SARS-CoV-2 spike IgG titers were nearly stable from d20-d240 PSO, when assessing all COVID-19 subjects by cross-sectional analysis (half-life t1/2 = 140d; but a wide confidence interval due to heterogeneity among subjects)
  - The % of subjects seropositive for spike IgG at 3wk-7wk PSO and at 6mo-8mo PSO (d>178) was 98% (54/55) and 90% (36/40), respectively
  - RBD IgG titer maintenance largely matched that of spike IgG; neutralization titers largely matched the results of RBD IgG titers
- Antigen (spike, RBD, and nucleocapsid) specific memory B cells ($IgD^-CD27^+$) were detected by flow cytometry
  - Cross-sectional analysis revealed that frequencies of SARS-CoV-2 spike-specific memory B cells increased over the first ~150d PSO; and with pairs, samples > at 6 months than at 1 month
  - ~10-30% of spike-specific memory B cells from convalescent donors were specific for the RBD

- A pattern was observed for all antigen-specific B cells over time - increasing IgG+ memory, short-lived IgM+ memory, and stable IgA+ memory (although IgA was a small fraction ~5%)

- SARS-CoV-2-specific CD4+ T cells (including T follicular helper cells) and CD8+ T cells declined with a half-life of 3-5 months
  - CD8+ memory T cells ($CD69^+CD137^+$) recognized peptides from spike (S), membrane (M), nucleocapsid (N), and ORF3a; at 3-7 wk PSO 61% of subjects had detectible circulating memory CD8+ T cells; at ≥6 months PSO 50% had detectible circulating memory CD8+ T cells
  - CD4+ memory T cells ($CD137^+OX40^+$) recognized peptides from S, M, N, and ORF3a, and nsp3; at 3-7 wk PSO 94% of subjects had detectible circulating memory CD4+ T cells; at ≥6 mo PSO 89% had detectible circulating memory CD4+ T cells
  - Virus specific T follicular helper cells (Tfh cells) were stable; nearly all subjects have detectible cTfh cells up to 6 mo PSO
- Males had higher spike IgG and nucleocapsid and RBD IgG; no differences were observed in memory B cell frequencies or T cells between males and females
- Limitations: Limited by sampling (many one-time donors); Levels of circulating SARS-CoV-2 neutralizing Ab required for protection is still unknown; IgA measures in the serum may not represent what is at the mucosal sites where IgA is more relevant
- Implications: Different components of SARS-CoV-2 immune memory response (antibodies, CD4+ cells and CD8+ T cells) each exhibit distinct kinetics; the heterogeneity in immune memory to SARS-CoV-2 was not primarily attributable to gender

## VACCINE STUDIES

**9. Durability of Responses after SARS-CoV-2 mRNA-1273 Vaccination.** Widge et al. NEJM. 3 Dec 2020**.**

- Most recent immune response data, 119 days after first vaccination among participants enrolled in the phase 1 Moderna vaccine trial; previous results demonstrated a strong immune response in all 34 participants at 57 days
- In all age groups, mRNA-1273 produced high levels of binding and neutralizing antibodies that declined slightly over time, as expected, but remained elevated in all participants 3 months after the second dose
- Compared to 41 control patients who had been naturally infected with SARS-CoV-2 (median of 34 days since diagnosis), the median binding and neutralizing geometric mean titers at day 119 were higher in the phase 1 trial participants
- Implication: mRNA-1273 has the potential to provide durable humoral immunity, but memory B cell response to mRNA-1273 is not yet known

**10. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial.** Zhang et al. Lancet. 17 Nov 2020**.**

- Trial of an inactivated SARS-CoV2 vaccine candidate (CoronaVac, Sinovac Life Sciences, Beijing) in China; phase 1 (144 participants) was a dose-escalating trial; phase 2 (600 participants) consisted of different cohorts receiving immunizations on 2 different schedules (0 and 14 day or 0 and 28 days) and two different doses [high (6 µg, N=120) v. low (3 µg, N=120) or placebo (N=60)]
- In the phase 2 trial, among all participants who were given at least one dose of the vaccine, the incidence of adverse reactions was:
  - for the days 0 and 14 cohort: 33% in the 3 µg group, 35% in the 6 µg group, and 22% in the placebo group

    - for the days 0 and 28 cohort: 19% in the 3 µg group, 19% in the 6 µg group, and 18% in the placebo group
- The 1° immunogenic outcome was development of neutralizing antibodies to live SARS-CoV-2, in the Phase 2 trial
    - Seroconversion (defined as change from seronegative at baseline to seropositive or a 4x increase if the participant was seropositive at baseline) was observed in 92% of participants in the low-dose (3 µg) group, 98% in the high-dose (6 µg) group, and 3% in the placebo group at day 14 after the days 0 and 14 schedule
    - At day 28 (after the days 0 and 28 schedule), seroconversion was seen in 97% in the 3 µg group, 100% in the 6 µg group, and 0% in the placebo group
    - Reciprocal Ab titers (both neutralizing and RBD-specific) are often significantly higher in 6ug group than in 3ug group, especially at the later time points
- Limitations: No diversity in participants (all Han nationality, all healthy adults <59 yo). There was change in manufacturing of the vaccine to optimize the cell culture and authors state this change resulted in higher intact spike protein content of the vaccine batch for the phase 2 trial (without supportive data); interpreting the Phase 1 results difficult in light of change in manufacturing and they were largely left out of this summary for that reason. Seroconversion as defined is not a measure of immunity or efficacy.
- Implications: Authors interpret these findings as rationale for moving forward with the 3 µg dose, likely in order to achieve more rapid population vaccination with comparable seroconversion results to 6 µg; the 0 and 28 d scheduling results in fewer adverse events and increased seroconversion.

**11.** **Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002): a single-blind, randomised, controlled, phase 2/3 trial.** Ramasany et al. Lancet. 18 Nov 2020.

- Report of the phase 2 component of a single-blind, randomized, controlled, phase 2/3 trial (COV002), healthy adults (560 participants enrolled at the point of this analysis); immunogenicity reported in subgroups 18–55 years, 56–69 years, and ≥70 years; two-dosing regimens (low and standard) were used, as well as, single dose and prime-boost regimens.
    - This is an AstraZeneca/Oxford University vaccine candidate also known as AZD1222; a chimpanzee adenovirus-vectored vaccine candidate expressing the SARS-CoV-2 spike protein. Control vaccine group received the MenACWY vaccine (the meningococcal conjugate vaccine licensed to help protect against serogroups A, C. W, Y)
- Humoral responses at baseline and after each vaccination were assessed using ELISA, a multiplex immunoassay, and a live SARS-CoV-2 microneutralization assay
    - Median anti-spike SARS-CoV-2 IgG responses 28 days after the boost dose were similar across the three age cohorts
    - Neutralizing antibody titers were presented by 14 days after the boost dose in 99% of boosted participants; by 42 days after boost neutralizing antibody titers were similar across age groups
- Cellular responses were assessed using an ex-vivo IFN-γ ELIspot with PBMCs in response to spike peptide library; IFN responses peaked at 14 days and did not increase after booster
- The coprimary outcomes of the trial were efficacy, as measured by the number of cases of symptomatic, virologically confirmed COVID-19 (both are not discussed in this paper) and safety.
    - Adverse events were similar but more common in the 18-55 yo than the >56 yo and >70 yo groups; mostly mild- moderate; most common fatigue, fever, malaise and muscle aches
    - Some serious adverse events (13) were reported during the study period but not deemed to be related to vaccination

- Limitations: Further assessment of the efficacy of this vaccine is warranted in all age groups and individuals with comorbidities; T cell response analysis limited to IFNγ response
- Implications: ChAdOx1 nCoV-19 (AZD1222) appears to be better tolerated in older adults than in younger adults and has similar immunogenicity across all age groups after a boost dose. *early efficacy data was released by AstraZeneca on this vaccine: https://www.astrazeneca.com/media-centre/press-releases/2020/azd1222hlr.html