Summary of Major Literature Related to COVID-19 (October 8, 2021)

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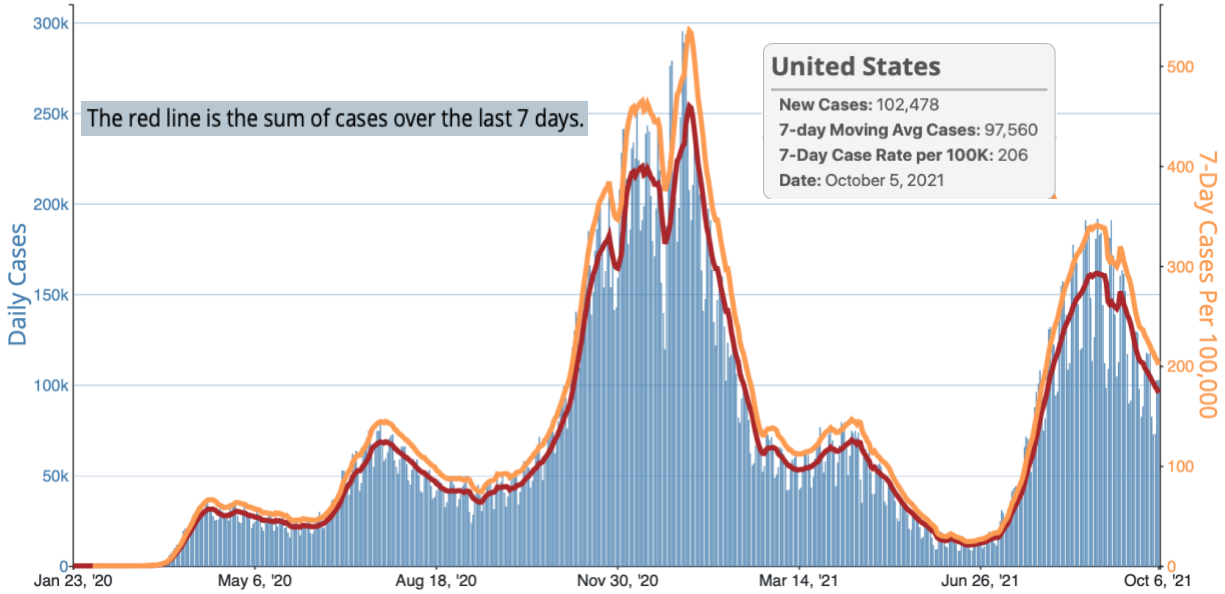
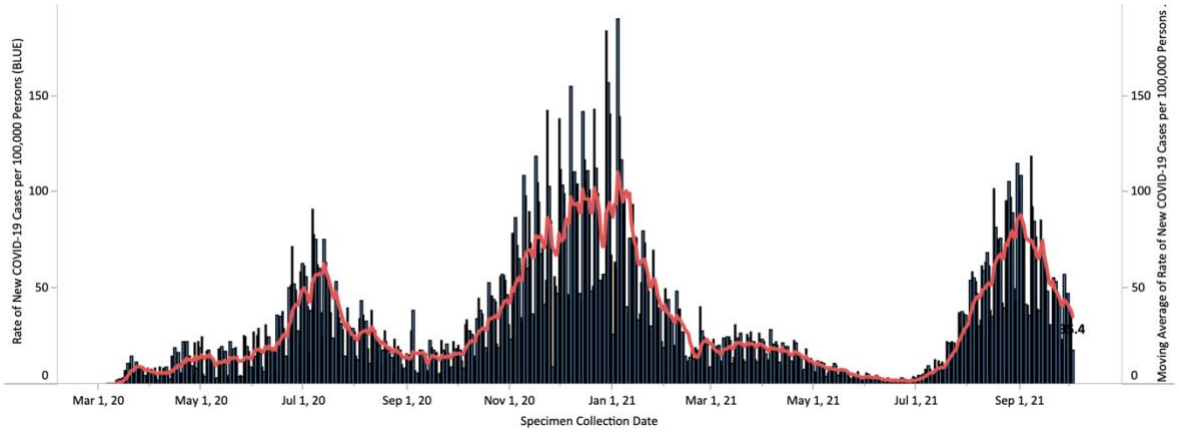
***This is informational and not intended to create variance from VUMC policies/guidance**

Tennessee

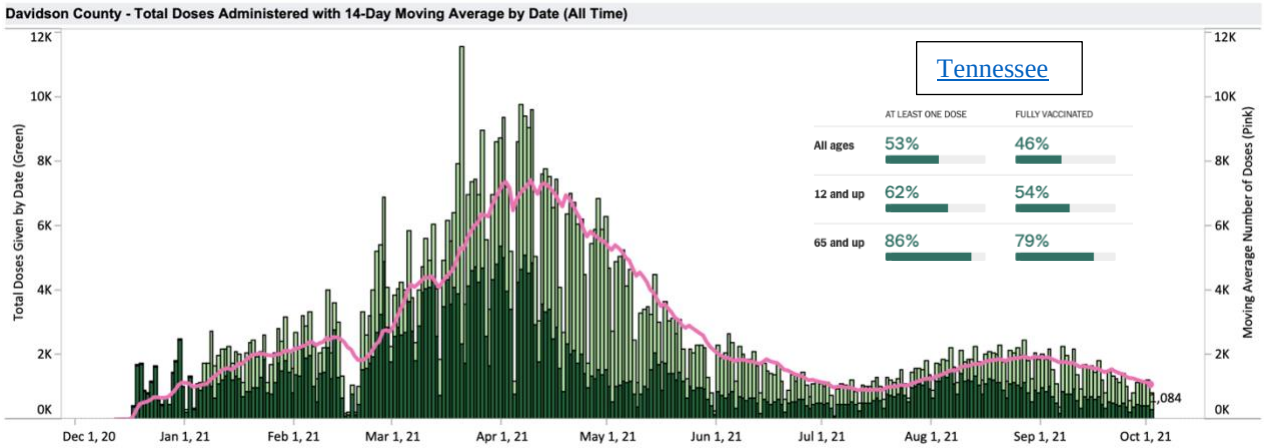
Daily Trends in Number of Cases and 7-Day Cumulative Incidence Rate of COVID-19 Cases in The United States Reported to CDC, per 100,000 population.



Davidson county



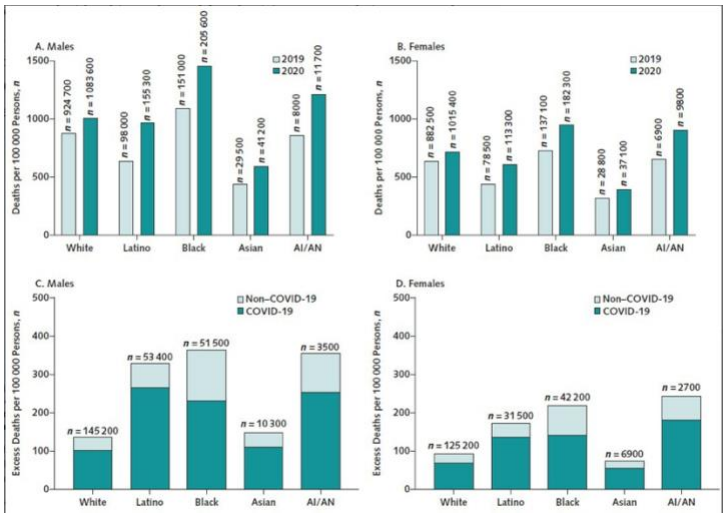
Davidson County Vaccination Curve



EPIDEMIOLOGY

Disparities

1. **Racial and Ethnic Disparities in Excess Deaths During the COVID-19 Pandemic, March to December 2020.** Shiels et al. Ann Intern Med. 5 Oct 2021.



- Previous studies have shown that certain racial/ethnic minority groups have been disproportionately affected by severe COVID-19 outcomes, including hospitalizations and death
- This surveillance study examined all excess deaths (not only those directly related to COVID-19) in the US from March to December 2020, by race/ethnicity and age
- 2.88 million deaths occurred during the study period
    - Between 2019 and 2020, all-cause mortality (per 100,000 persons) increased *and* racial disparities in mortality widened for both men and women (see Figure, top 2 panels)
- There were 477,200 excess deaths in 2020 compared to number expected based on 2019 data (accounting for population size and age), 351,400 (74%) of which were attributed to COVID
    - Age-standardized excess deaths per 100 000 persons (see Figure, bottom 2 panels) *and* non-COVID-19 excess deaths per 100,000 were 2 to 4 times higher among Black, AI/AN, and Latino males and females compared to White males and females
    - These included deaths due to diabetes, heart disease, cerebrovascular disease, Alzheimer's disease
    - The disparities were evident across age groups
- Limitations: Provisional CDC death certificate data may not be complete; potential for misclassification of race on death certificates
- Implications: Disparities in non-COVID-19 excess deaths (which account for 25% of the estimated excess deaths in 2020) are even more pronounced than those for COVID-19 deaths and have widened racial/ethnic disparities in all-cause mortality from 2019-2020

Post-acute COVID-19 syndrome (Long-COVID)

2. **Differential olfactory outcomes in COVID-19: A large healthcare system population study.** Chapurin et al (**VUMC authors**). Int Forum Allergy Rhinol. 21 July 2021.

- Cross-sectional survey of olfactory and taste dysfunction among 1,003 patients who tested positive for SARS-CoV-2 PCR in a large healthcare system from Feb-Nov 2020
    - Assessed patient-reported demographics, comorbidities, subjective assessment of smell and taste function pre- and post-infection, and symptom duration, and administered the validated SNOT-22 questionnaire (clinically validated instrument to measure sinonasal quality-of-life)
    - Median age 43y, 63% female; 94% reported having at least one symptom during their COVID-19 infection
    - >90% reported normal pre-infection taste and smell
- 73% of participants reported taste or smell loss or dysfunction post-COVID-19 diagnosis
    - Mean duration of smell loss was 19.7 days; initial severity of smell loss correlated with duration of symptoms

    - Among those who reported smell loss/dysfunction, 13.4% reported duration of smell loss >4 weeks, while 10.7% reported prolonged duration of smell loss >6 weeks
    - Male gender, prior taste disturbances, and sore throat, GI symptoms and absence of fever on COVID-19 presentation were predictors of moderate to severe smell loss
- SNOT-22 scores were inversely associated with time since COVID-19 diagnosis and positively associated with duration of patient-reported symptoms
- May be a useful test in measuring and following post CVOID overall and smell/taste disease burden
- Limitations: low response rate (21%); did not report median time between diagnosis and survey
- Implications: A proportion of COVID-19 patients experience prolonged or persistent olfactory dysfunction; the validated SNOT22 scale commonly used in rhinology may be a useful measure to track smell/taste disease burden and quality of life during recovery

VACCINE SAFETY

Myocarditis

Implications: A number of studies were published this week providing data from Israel and the US on risk of acute myocarditis following mRNA vaccination. They are briefly summarized below. The study designs and methods of ascertainment of myocarditis differed but collectively, these data in real-world cohorts demonstrate that **acute myocarditis is a rare event after vaccination**. Some signals of increased risk in young men, particularly after the second dose, warrant further study. However, these findings should be viewed in context along with numerous previously summarized studies demonstrating the high rate of myocarditis (as well as other serious adverse events) following COVID-19 infection:
increased risk of myocarditis following COVID-19 infection (~150 per 100,000 persons);
very high risk of myocarditis from primary COVID-19 infection in young males (~450 per million); and
lower increased risk of myocarditis after vaccination compared to after COVID-19 infection (risk difference for vaccinated vs. unvaccinated = 2.7 per 100,000; risk difference for SARS-CoV-2 infection vs. no infection = 11.0 per 100,000).
Limitations of the studies summarized below include: observational design; cannot rule out possible bias in surveillance or work up for chest pain after vaccination; no data on long-term prognosis

3. **Acute Myocarditis Following COVID-19 mRNA Vaccination in Adults Aged 18 Years or Older.** Simone et al. JAMA Intern Med. 4 Oct 2021.

- Examination of incidence rates and clinical outcomes of acute myocarditis among adults ≥18y following mRNA vaccination in Kaiser Permanente Southern California health system, Dec 2020-July 2021
- Cases were identified by clinician reports to KPSC or by hospital discharge diagnosis of myocarditis within 10 days of vaccination, and were adjudicated by 2 cardiologists
- 2,392,924 individuals received at least one dose of mRNA vaccine (94% completed 2 doses)
    - 54% women; 31.2% White, 6.7% Black, 37.8% Hispanic, 14.3% Asian; median age 49y, 35.7% younger than 40y
- Among vaccinated, 2 cases of myocarditis were identified after first dose (incidence 0.8/million) and 13 cases after second dose (incidence 5.8/million)
    - Compared to unvaccinated individuals (n=75 myocarditis cases), the incidence rate ratio was 0.38 (95% CI 0.05-1.40) for first dose and 2.7 (95% CI 1.4-4.8) for second dose
- 15 cases in vaccinated group:
    - 8 received Pfizer-BioNTech, 7 received Moderna
    - All male; median age 25y (IQR 20-32)
    - None had prior cardiac disease

- 14 (94%) reported chest pain between 1-5 days post-vaccination; all symptoms resolved, with no patients requiring ICU admission

4. **Myocarditis after Covid-19 Vaccination in a Large Health Care Organization.** Witberg et al. NEJM. 6 Oct 2021. [Same database as the earlier study by **Barda et al.,** but different case ascertainment method and different population age distribution]

- Retrospective EHR cohort study among 2,558,421 members aged 16y+ in an Israeli healthcare system who received at least one dose of the Pfizer-BioNTech vaccine (94% received two doses)
- New cases of myocarditis within 42 days after first vaccine dose were identified using diagnosis codes and then followed by adjudication through manual review of the patient's EHR, including presentation, clinical course and outcome
- 54 cases met the study criteria for a diagnosis of myocarditis
  - Median age 27y (IQR 21 to 35); 94% male
  - Presenting symptoms was chest pain in 82% of cases; most cases were mild or moderate in severity
  - 83% had no comorbidities
  - 37 (69%) received the diagnosis after the second dose
- Overall estimated incidence was 2.13 cases per 100,000 (95% CI, 1.56 to 2.70) persons who had received at least one dose of vaccine was
  - incidence of 4.12 per 100,000 (95% CI, 2.99 to 5.26) among male patients and 0.23 per 100,000 (95% CI, 0 to 0.49) among female patients
  - highest incidence (10.69 cases per 100,000; 95% CI, 6.93 to 14.46) was reported in male patients between the ages of 16-29y

5. **Myocarditis after BNT162b2 mRNA Vaccine against Covid-19 in Israel.** Mevorach et al. NEJM. 6 Oct 2021.

- Active/passive surveillance for myocarditis among over 9 million Israeli residents from 20 Dec 2020 to 31 May 2021 by the Israeli Ministry of Health using diagnostic criteria and classification of Brighton Collaboration
- Compared myocarditis incidence up to 21 days after first and up to 30 days after second vaccine doses
- 283 affirmed cases with symptoms of myocarditis were identified, 136 of which were deemed definite or probable and occurred in temporal proximity to BNT162b2 vaccine
  - 95% were judged to be clinically mild
  - 19 cases occurred after first dose, 117 occurred after second dose (appeared to cluster during first few days after second dose)
- Risk after second dose was 3.83 per 100,000 persons for males and 0.46 per 100,000 for females
  - Highest risks were observed for young males (15.07 per 100,000 for aged 16-19y and 10.86 per 100,000 for aged 20-24y
  - The risk difference between first and second doses was 1.76 per 100,000 persons (95% CI, 1.33 to 2.19); the largest difference was again among male recipients aged 16-19y (difference, 13.73 per 100,000; 95% CI, 8.11 to 19.46).

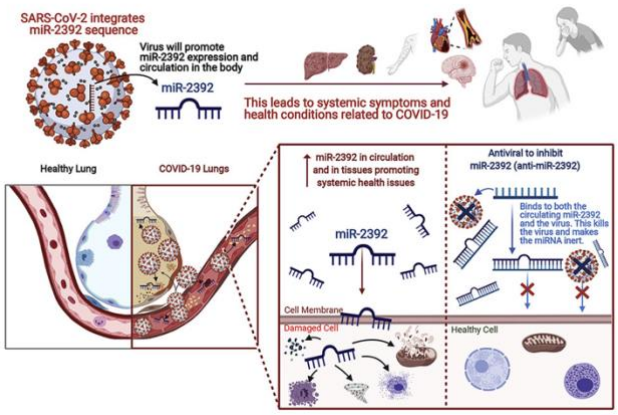
HOST RESPONSE

6. **The N-terminal domain of SARS-CoV-2 nsp1 plays key roles in suppression of cellular gene expression and preservation of viral gene expression.** Mendez et al. Cell Reports. 29 Sept 2021

- This study defines the contributions of 3 domains of nucleocapsid protein 1 (nsp1) to its function, namely inhibition of host mRNA translation and promotion of mRNA decay (also known as "host shutoff")
- Measuring translation repression and RNA cleavage activity in vitro and in cells, nsp1 of SARS-CoV-2 suppressed translation and induced mRNA cleavage
- Using a series of deletion mutants in translation and mRNA turnover assays, the data indicate that the N-terminal and central domains of Nsp1 are required for host shutoff
- Nsp1 N-terminus stabilizes Nsp1 binding to the 40S ribosomal subunit and this interaction is needed to induce mRNA cleavage; deletion mutants which lose functional activity also lose affinity for the ribosome and have reduced ribosomal protein interactions (IP)
- Mutation of Nsp1 N-terminal residues abrogates escape of SARS-CoV-2 5' leader mRNA sequence (which when intact protects the viral transcripts from nsp1's cleavage activity)
- Limitations: Experiments conducted on nsp1 expressed in uninfected cells (and not the most relevant cell types for SARS-CoV2 infection); relies on reporter mRNAs that function as a proxy for cellular or viral transcripts
- Implications: Improves our understanding of the role of nsp1 in pathogenesis as a regulator of host gene transcription; leads to the question of whether small molecule drugs that phenocopy mutations could serve as therapies or prophylactics for viral infection

7. **Role of miR-2392 in Driving SARS-CoV-2 Infection.** McDonald et al. Cell Reports. 29 Sept 2021.

- Investigates the role of a circulating miRNA, miR-2392, in post-transcriptional gene regulation during SARS-CoV-2 host infection



- Examining publicly available Bronchial Alveolar Lavage Fluid (BALF) RNAseq data combined with Ingenuity Pathway Analysis, miR-2392 was predicted to be upregulated in COVID-19 patients
  - Upregulation of miR-2392 in the BALF RNA-seq dataset impacted many downstream targets and pathways related to negative health outcomes
  - Downstream targets/pathways which were upregulated in association with increased miR-2392 included mitochondrial suppression, ROS activation, glycolytic pathways
  - Evaluation of mtDNA genes using MitoCarta identified 14 genes harboring miR-2392 seed sequences that were significantly dysregulated in the nasal and heart samples of COVID19 patients
- Analysis of the ubiquitinome of a SARS-CoV-2 human-derived cell culture model suggests that miR-2392 overexpression impacts genes involved with mitochondria and inflammation
- Reactome SARS-CoV-2 pathways were significantly activated in cells with miR-2392 overexpression compared to the controls; Significant Hallmark pathways show upregulation of hypoxia, glycolysis, and cell cycle pathways in cells with miR-2392 overexpression
- miR-2392 is present in the blood and urine of patients positive for COVID-19 (droplet digital PCR), but not present in patients negative for COVID-19
  - miR-2392 levels were higher when patients had more severe disease (i.e., intubated or ICU)
  - Low levels of miR-2392 appeared in the nasopharyngeal location with no significant differences occurring between seasonal coronavirus samples and SARS-CoV2^{+} samples

- The Nanoligomer platform was used to develop an antisense-based therapeutic against human miR-2392 and the therapeutic was tested in vitro in human cells and in the hamster model
    - Treatment of A549 cells infected with SARS-CoV2 with the Nanoligomer exhibited increased cell viability with an average of 85% viral inhibition (at 10 µM)
    - Infected hamsters were treated with either the anti-miR-2392 nanoligomers IP, IN or given PBS as control – either 24 hr before infection or 24 hr before and after infection; the IN administrations significantly reduced PFU/swab on day 1 relative to PBS, but there was no significant difference in histological score
- Limitations: Analysis limited to samples/tissues available; hamster model had a small sample size and timing of treatment before infection is not 'therapeutic' and may be too soon if miR-2392 is not upregulated until after infection
- Implications: miR-2392 could be a biomarker for COVID-19; expression of miR-2392 has the potential to contribute to suppression of mitochondrial gene expression, increasing inflammation, glycolysis, and hypoxia

ANIMAL STUDIES

Vaccines

8. **Intradermal-delivered DNA vaccine induces durable immunity mediating a reduction in viral load in a rhesus macaque SARS-CoV-2 challenge model**, Patel et al. Cell Reports Medicine 27 Sept 2021

- the immunogenicity and anamnestic protective efficacy of an intradermal (i.d.)-delivered SARS-CoV-2 spike DNA vaccine (INO-4800, encoding synthetic spike) was assessed in rhesus macaques (NHP)
- The vaccine candidate (2 intradermal administrations of INO-4800 at weeks 0 and 4)-induced humoral and cellular immunity
    - all animals seroconverted after prime immunization; serum IgG titers were detected against full-length spike, the S1, S2 and RBD regions; cross-reactive Ab were detected against SARS-CoV1 spike (not MERS-CoV spike)
    - neutralizing antibody responses were present against both the SARS-CoV-2 D614 virus as well as the G614 strain were detected
    - sera from 80% of immunized NHPs had reduced Spike-ACE2 binding [using a receptor-blocking assay (which correlated with pseudovirus neutralization titers)]
    - SARS-CoV-2 S antigen reactive T cell responses against all 5 peptide pools were induced in 4/5 immunized-NHP (responses peaked at week 6)
- SARS-CoV-2 challenge (intranasal and intratracheal), > 3 months (17 week), immunized NHP exhibited a recall response and a significant reduction in viral load (SARS-CoV-2 sgmRNA) in BAL compared to unimmunized
    - expansion of neutralizing antibody responses by d7 increasing through d14
    - expansion of T cell responses (IFNγ ELISpot) increased after challenge (but statistical tests were not presented)
- Limitations: No histological assessment of the lung tissue was performed; more recent VOC were not assessed (author state this will be in subsequent manuscript); lack of clinical symptoms in the NHP model did not allow for correlations between disease and reductions in viral RNA load
- Implications: Immune responses and protection induced by simple ID delivery of INO-4800 are promising in the NHP model; INO-4800 is in clinical trial, ClinicalTrials.gov Identifier: NCT04642638

Therapeutic

9. **The combined treatment of Molnupiravir and Favipiravir results in a potentiation of antiviral efficacy in a SARS-CoV-2 hamster infection model.** Abdelnabi et al. EBioMedicine. 23 September 2021.

- Reports on the combined antiviral effect of both drugs in a SARS-CoV-2 Syrian hamster infection model (Beta CoV2) where infected hamsters were treated twice daily for 4 days [vehicle (i.e. the control group) or Favipiravir (300 mg/kg, BID) or Molnupiravir (150 mg/kg, BID) or the combination of Favipiravir and Molnupiravir (at 300+150 mg/kg (BID), respectively)]
- suboptimal doses of either drug result in ~1.2 log10 reduction in infectious virus titers (plaque assay in vero cells) in the lungs
- Starting treatment just before infection - lungs of animals treated with both compounds see reduced infectious virus by ~5 log10
    - RNA copies correlated with infectious virus measures
    - there was no detectable infectious virus in the lungs of 6 out of 10 hamsters in the combined treatment group
    - significant improvement in the lung pathology scores (histology) was observed in the combined treatment group compared to control or Favi treatment alone
- Starting treatment at day 1- reduction of titers in the lungs of 2.4 log10 was measured; improvement in lung score was observed in only 2 out of 6 treated hamsters
- Treatment of infected animals nearly completely prevented transmission to co-housed untreated sentinels (assessed at day 4 p.i.)
- Both drugs result in an increased mutation frequency of the remaining viral RNA recovered from the lungs of treated animals
- Limitations: All animals were the same age, roughly the same weight and all female; Favi was administered IP while Moln was administered oral
- Implications: This study provides evidence that a combined all-oral treatment of Molnupiravir and Favipiravir should be explored for the treatment of SARS-CoV-2 infections; early treatment impacts efficacy; the hamster model does provide opportunity to investigate transmission

Also see: MOVe-OUT trial (MK-4482-002) (NCT04575597) and Recent news release from Merck on Phase 3 clinical trial