Summary of Major Literature Related to COVID-19 (September 3, 2021)

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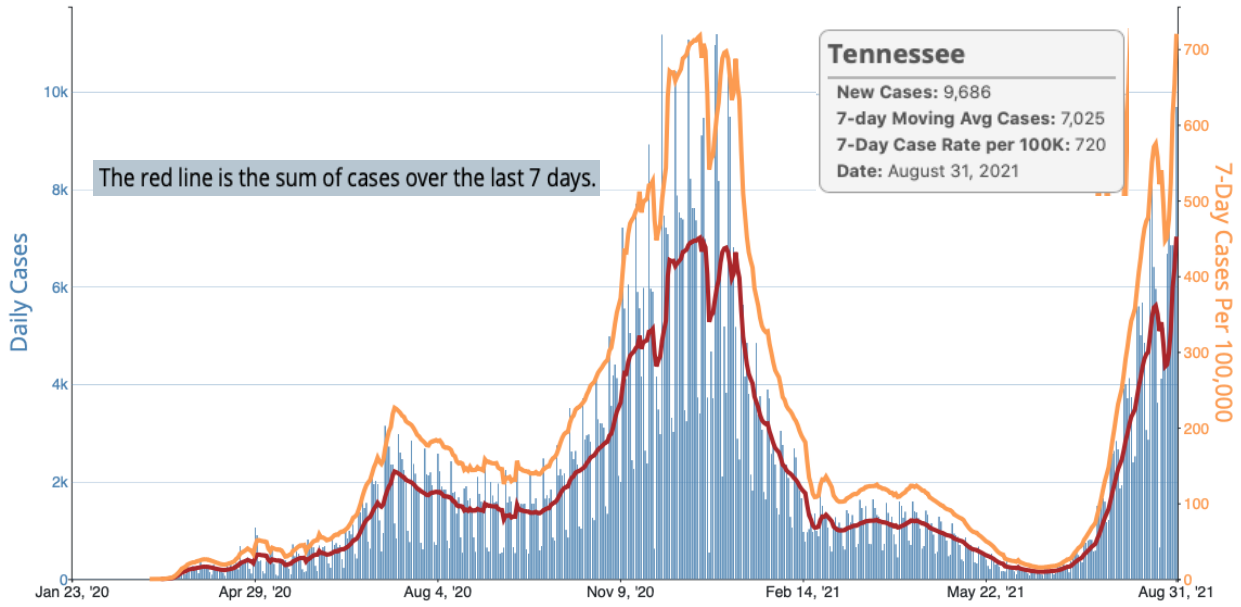
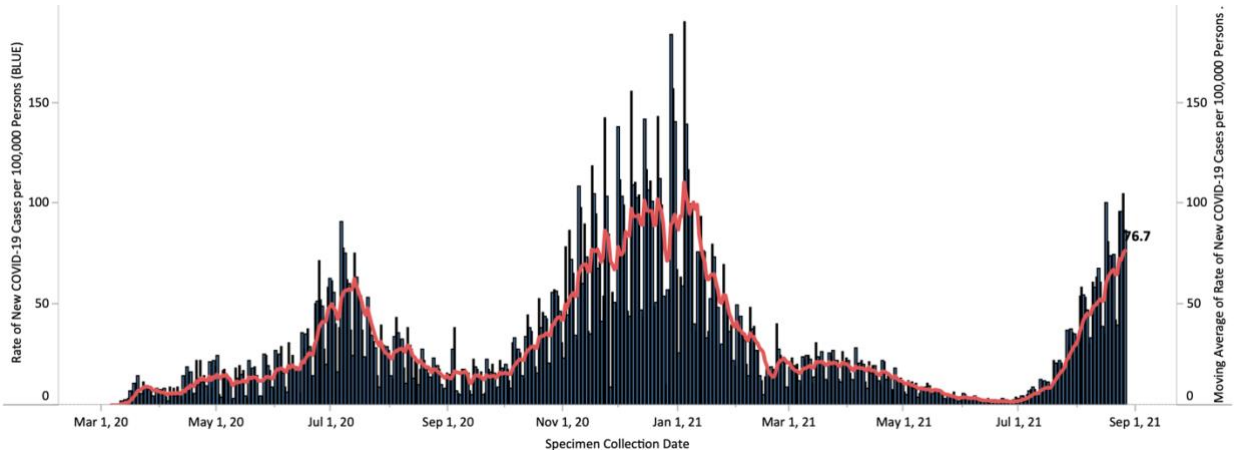
***This is informational and not intended to create variance from VUMC policies/guidance**

Tennessee

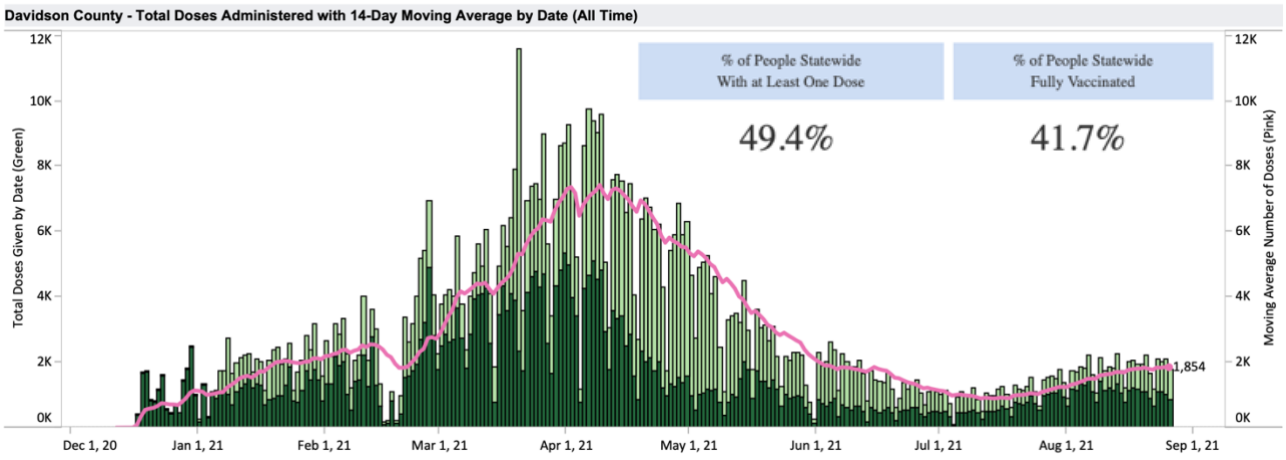
Daily Trends in Number of Cases and 7-Day Cumulative Incidence Rate of COVID-19 Cases in Tennessee Reported to CDC, per 100,000 population.



Davidson county



Davidson County Vaccination Curve



TREATMENT

Baricitinib in hospitalized patients

1. **Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial.** Marconi et al. Lancet. 1 Sept 2021.

- Phase 3, double-blind, multicenter (101 centers in 12 countries) RCT to study efficacy and safety of baricitinib (an oral selective Janus kinase 1\2 inhibitor) in combination with SOC for the treatment of hospitalized adults with COVID-19
    - 1525 participants, >18yo, at least one elevated inflammatory marker
    - SOC included systematic corticosteroids such as dexamethasone (79.3%) and remdesivir (18.9%) at baseline
    - hospitalized adults with COVID-19 then were randomized 1:1 to receive either 4mg baricitinib or placebo for 14d
- Composite primary endpoint: proportion who progressed to high-flow oxygen, ventilation or death by day 28 (NIAID-OS score 6-8)
    - 7.8% of participants receiving baricitinib and 30.5% receiving placebo progressed to meet the primary endpoint (odds ratio 0.85 [95% CI 0.67 to 1.08], p=0.18)
- Secondary endpoints:
    - 28-day all-cause mortality: 8% (n=62 deaths) for baricitinib and 13% (n=100 deaths) for placebo (hazard ratio [HR] 0.57 [95% CI 0.41–0.78]; nominal p=0.0018), a 38.2% relative reduction in mortality
    - 60-day all-cause mortality (exploratory) was 10% for baricitinib and 15% for placebo (HR 0.62 [95% CI 0.47–0.83]; p=0.0050)
- Safety: Frequencies of serious adverse events, serious infections and venous thromboembolic events were similar between groups receiving baricitinib or placebo
- Limitations: Primary outcome (progression on the basis of NIAID-OS) reflects treatment decisions and might be influenced by the heterogeneity of clinical practice across different geographical regions; as the primary endpoint did not achieve statistical significance, none of the key secondary endpoints were considered to have achieved statistical significance after adjusting for multiple comparisons, yet death (the secondary endpoint) is objective
- Implications: Baricitinib plus SOC should be considered to reduce overall deaths among hospitalized adults with COVID-19 in the context of the global burden of mortality
- This study is registered with ClinicalTrials.gov, NCT04421027.

EPIDEMIOLOGY

Myocarditis

2. **Association Between COVID-19 and Myocarditis Using Hospital-Based Administrative Data — United States, March 2020–January 2021.** Boehmer et al. MMWR. 31 August 2021.

- Data from a large hospital administrative database were used to examine myocarditis risk among 1,452,773 individuals who had their first inpatient or outpatient encounter with a COVID-19 diagnosis from March 2020–January 2021
    - Patients with a COVID vaccination during that time period were excluded
    - Comparison group was over 34 million individuals without COVID-19 but with at least one inpatient or hospital-based outpatient encounter with discharge during the same period
    - Myocarditis was defined as at least one inpatient encounter, at least two outpatient encounters, or at least one outpatient encounter with a relevant specialist with a myocarditis ICD-10-CM code during March 2020–February 2021

- Myocarditis was diagnosed in 0.146% of patients with COVID-19, compared to 0.009% of those without COVID-19
    - After adjusting for patient and hospital characteristics, aRR=15.7 (95% CI = 14.1–17.2)
- Among patients with COVID-19, the risk for myocarditis was higher among males (0.187%) than among females (0.109%) and was highest among adults aged ≥75 years (0.238%), 65–74 years (0.186%), and 50–64 years (0.155%) and among children aged <16 years (0.133%)
- Limitations: Potential misclassification of COVID-19 and/or myocarditis; potential surveillance/diagnostic bias for myocarditis among those with COVID-19
- Implications: Consistent with prior evidence, COVID-19 is a strong risk factor for myocarditis, but myocarditis is a rare occurrence in both those with and without COVID-19

Transmission

3. **Factors Associated With Household Transmission of SARS-CoV-2. An Updated Systematic Review and Meta-analysis.** Madewell et al. JAMA Netw Open. 27 August 2021.

- Updated systematic review and meta-analysis of 87 studies published through June 2021, representing 1,249,163 household contacts from 30 countries
    - Included studies that reported data for at least 2 of the following factors: number of household contacts with infection, total number of household contacts, and secondary attack rates (SAR) among household contacts
    - Also examined SAR by contact ethnicity (in the US), contact comorbidity, index case fever, index case cough, variant (if reported in ≥3 studies), and index case identification time period
- Overall household SAR was 18.9% (95% CI, 16.2-22.0%)
- Household SAR increased over time, from 13.4% for studies conducted in Jan-Feb 2020 to 31.1% for studies conducted for July 2020-May 2021
- Household SAR was significantly higher for:
    - adult contacts (29.9%; 95% CI, 24.0%-36.6%) than child contacts (17.5%; 95% CI, 12.6%-23.7%; $P < .001$)
    - spousal contacts (39.8%; 95% CI, 30.0%-50.5%) than other household contacts (18.3%; 95% CI, 12.1%-26.7%; $P = .001$)
    - contacts with comorbidities (50.0%; 95% CI, 41.4%-58.6%) than contacts without comorbidities (22.0%; 95% CI, 13.4%-33.9%; $P = .04$)
    - symptomatic index cases (20.2%; 95% CI, 13.9%-28.3%) than in asymptomatic (3.0%; 95% CI, 1.7%-5.4%) or presymptomatic (8.1%; 95% CI, 7.3%-9.1%; $P < .001$)
- Limitations: Potential for publication and time-trend biases; high heterogeneity across studies; no data specifically for delta variant
- Implications: Household remains an important site for SARS-CoV-2 transmission

IMMUNE RESPONSE

After natural infection

4. **Durability of Spike Immunoglobin G Antibodies to SARS-CoV-2 Among Health Care Workers With Prior Infection.** Egbert et al. JAMA Netw Open. 30 August 2021.

- Convenience sample of 94 HCWs with PCR-confirmed SARS-CoV-2 infection followed by at least 1 positive anti–SARS-CoV-2 IgG measurement prior to vaccination, nested in a prospective cohort of 3015 HCWs in Johns Hopkins Health System enrolled beginning in June 2020
    - 96% non-Hispanic/Latino, 74% White, median age 37.5y
- Serum specimens were tested using an ELISA that targets the S1 subunit of the SARS-CoV-2 spike protein and measures optical density ratios; used internally derived cutoff ratio of >1.23

- 52 of 59 (88%), 30 of 40 (75%), 25 of 33 (76%) HCWs who tested less than 100, 100 to 200, and more than 200 days post-PCR were IgG positive, respectively; IgG antibodies were positive in 72% (8 of 11) of those tested more than 250 days post-infection
- Estimated rate of IgG decay was 7% per month (95% CI, 3%-10%)
- Limitations: Convenience sample represented only 3.1% of cohort, limiting generalizability; remains uncertain to what extent these antibodies correlate with neutralizing antibodies or confer protection against reinfection or variants
- Implications: Spike antibodies to SARS-CoV-2 are durable up to 10 months after natural infection, longer than previously reported and beyond the 90 days reported by CDC as the window for reduced reinfection risk

5. **Profiling CD8+ T Cell Epitopes of COVID-19 Convalescents Reveals Reduced Cellular Immune Responses to SARS-CoV-2 Variants**. Zhang et al. Cell Reports. Online 27 August 2021

- 52 CD8+ T cell epitopes were identified from PBMCS from COVID-19 patients of four major HLA-A alleles (A*02:01, A*02:07, A*11:01 & A*24:02)
    - several CD8+ T cell epitopes were highly conserved among human coronaviruses; 7 epitopes (of those) were validated to induce IFNγ responses in CD8+ T cells in both healthy donors and convalescents. 3 tetramers (reagents) were made and bind to CD8+ T cells in both populations
- 4 epitopes were also validated in vaccinated donors (CoronaVac)- these 4 epitopes were studied further because they represent the locations of several mutations in the V.O.C.; variant-associated mutations in the four epitopes still activated IFNγ CD8+ T cells from vaccinated donors, but the response was significantly reduced
- Through analysis of crystal structures of two epitopes with respective HLAs (HLA-A∗02:01/HLA-A∗24:02), amino acids K417 and L452 of SARS-CoV-2 Spike are identified as being critical for mediating recognition by these HLA-I
- Limitations: only measured a defined response of a particular HLA molecule to a few short peptides (synthetic) of the virus (under-represents complexity); does not address impact on disease progression
- Implications: provides evidence of a reduced cellular responses of specific HLA-I subtypes to the epitope peptides containing the identified mutations in the variant viruses

After vaccination

6. **Comparison of SARS-CoV-2 Antibody Response Following Vaccination with BNT162b2 and mRNA-1273.** Steensels et al. JAMA Netw Open. 30 August 2021.

- Study of 1647 HCW in Belgium who received two doses of mRNA vaccines; serological testing was done to measure total immunoglobulin levels to the RBD of the spike protein prior to vaccination and 6-10 weeks after the second dose
    - 688 received mRNA-1273 (Moderna): mean age 43.2y, 76.7% women, 21.8% previously infected with SARS-CoV-2
    - 959 received BNT162b2 (Pfizer-BioNTech): mean age 44.7y, 84.9% women, 13.2% previously infected
- Higher antibody levels were observed in those vaccinated with 2 doses of Moderna compared with Pfizer-BioNTech vaccine (geometric mean titer [GMT], 3836 U/mL [95% CI, 3586-4104] vs 1444 U/mL [95% CI, 1350-1544]; $P < .001$)
    - In a multivariable model adjusted for age, sex, previous SARS-CoV-2 infection, and time between vaccination and serologic testing, Moderna vaccine was associated with higher log-transformed antibody titer compared to Pfizer-BioNTech (regression coefficient 0.359; 95% CI, 0.326-0.392)

    - The difference in antibody levels between vaccines was observed across age categories and among both previously infected as well as uninfected individuals
- Limitations: Uncertain to what extent humoral response after vaccination may translate to protection against COVID-19; lack of data on cellular immunity or neutralizing antibodies, but correlation of humoral response with neutralizing antibodies has been previously demonstrated; only examined RBD antibodies; overlap in antibody titer distribution between vaccines calls for cautious interpretation
- Implications: Higher humoral immunogenicity of Moderna vaccine might be explained by higher mRNA content and longer interval between doses compared to Pfizer-BioNTech
- **See also: Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection.** Khoury et al. Nature Medicine. 17 May 2021