Summary of Major Literature Related to COVID-19 (November 1, 2021)

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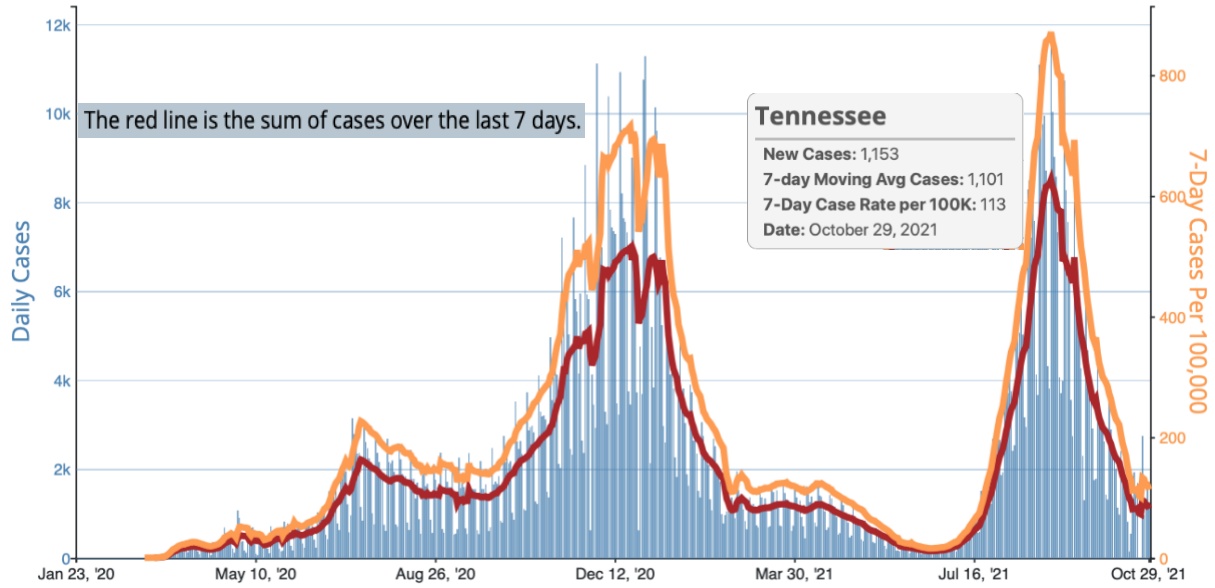
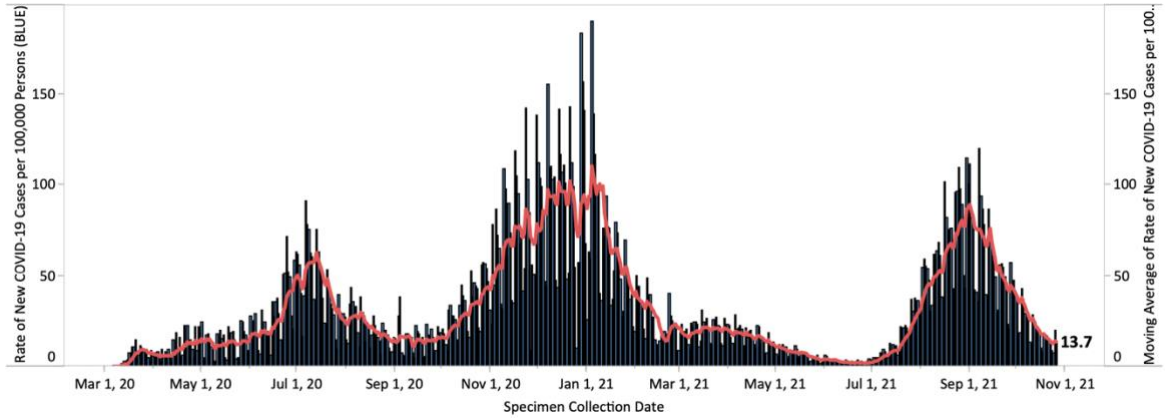
***This is informational and not intended to create variance from VUMC policies/guidance**

Tennessee

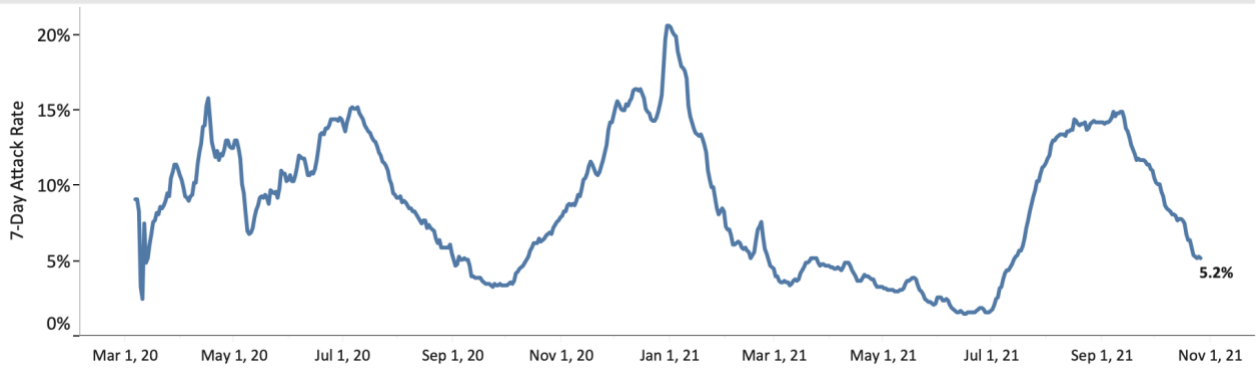
Daily Trends in Number of Cases and 7-Day Cumulative Incidence Rate of COVID-19 Cases in Tennessee Reported to CDC, per 100,000 population.



Davidson county



7-Day Percent Positive of COVID-19 Tests



TREATMENT

1. **Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial.** Reis et al. Lancet Global Health. 27 Oct 2021. (NCT04727424)

- Fluvoxamine is a commonly used SSRI antidepressant and σ–1 receptor (S1R) agonist hypothesized to impact COVID-19 through its anti-inflammatory activity
- This RCT assessed the efficacy of fluvoxamine (n=741; 100 mg twice daily for 10 days) vs. placebo (n=756) in preventing hospitalization among high-risk symptomatic adult COVID-10 patients in Brazil from 20 Jan – 5 Aug 2021
- Eligibility criteria included:
    - presenting to an outpatient care setting with an acute clinical condition consistent with COVID-19 and symptoms beginning within 7 days of the screening date, or positive rapid test for SARS-CoV-2 antigen done at the time of screening, or patient with positive SARS-CoV-2 diagnostic test within 7 days of symptom onset
    - having at least one known risk factor for progression to severe disease
- Median age 50y; 58% women; 95% self-identified as mixed race; average 3.8 days with symptoms before randomization
- Primary outcome: composite endpoint of hospitalization was defined as either retention in a COVID-19 emergency setting or transfer to tertiary hospital due to COVID-19 progression during up to 28 days of follow up
- 79 (11%) participants in fluvoxamine group had a primary outcome event compared with 119 (16%) in the placebo group (5% absolute risk reduction)
    - 87% of events were hospitalizations
    - Relative risk was 0.68 (95% Bayesian credible interval: 0.52 - 0.88)
    - Randomization was stopped on Aug 5 as the probability of superiority of 99.8% surpassed the prespecified superiority threshold
- Findings were more pronounced in the per-protocol analysis (patients with high adherence (>80%); RR 0.34, 95% BCI, 0.21 - 0.54)
- No statistically significant evidence of modification of treatment effect in pre-specified subgroups of age, sex, days since symptom onset, smoking status, or comorbidities
- No significant differences between groups for pre-specified secondary outcomes, although suggestive benefits of fluvoxamine were observed for several such as length of hospitalization
    - 17 deaths in fluvoxamine group and 25 in placebo group; OR 0.68 (95% CI 0.36-1.27)
    - In per-protocol population, there was one death in fluvoxamine group and 12 in placebo group; OR 0.09 (95% CI 0.01–0.47)
- No significant differences in number of treatment emergent adverse events in the two groups
- Limitations: variability in standard of care for treatment of early COVID-19; low rate of vaccination of the study population (6%) so further study is needed to examine effect in vaccinated populations
- Implications: Results provide compelling evidence of fluvoxamine's benefit in reducing morbidity among high-risk outpatients with early diagnosed COVID-19; these findings could have important implications for clinical management of outpatient COVID-19 given fluvoxamine's safety, tolerability, ease of use, low cost, and widespread availability

2. **Effect of Antithrombotic Therapy on Clinical Outcomes in Outpatients With Clinically Stable Symptomatic COVID-19. The ACTIV-4B Randomized Clinical Trial.** Connors et al. JAMA. 11 Oct 2021.

- ACTIV-4B Outpatient Thrombosis Prevention Trial of the potential benefit of anticoagulant or antiplatelet therapy among symptomatic but clinically stable outpatients aged 40-80y with COVID-19

- From Sept 2020-June 2021, random 1:1:1:1 allocation of 657 patients to aspirin 81 mg once daily, prophylactic-dose apixaban 2.5 mg twice daily, therapeutic-dose apixaban 5.0 mg twice daily or placebo twice daily for 45 days
- Adjudicated primary composite outcome: all-cause mortality, symptomatic venous or arterial thromboembolism, myocardial infarction, stroke, or hospitalization for cardiovascular or pulmonary cause
    - Trial was stopped early (after ~9% enrollment) because of unanticipated very low event rate
- 558 randomized patients initiated treatment
    - Median time from diagnosis to randomization=7 days (IQR, 3-10)
    - Median time from randomization to study treatment initiation=3 days (IQR, 2-5)
    - Median age 54y (IQR, 46-59), 59.1% women, 12.7% Black and 28.1% Hispanic patients
    - 18.3% had diabetes, 19.9% history of smoking, 35.3% hypertension, median BMI 30.1
- There were 3 adjudicated primary composite events
    - Risk was 0.0% (95% CI, 0.0% to 2.6%) in the aspirin group, 0.7% (0.1% to 4.1%) in the prophylactic apixaban group, 1.4% (0.4% to 5.0%) in the therapeutic apixaban group, and 0.0% (0.0% to 2.8%) in the placebo group
- Risk differences compared with placebo for bleeding events were 2.0% (95% CI, –2.7% to 6.8%), 4.5% (–0.7% to 10.2%), and 6.9% (1.4% to 12.9%) among participants who initiated therapy in the aspirin, prophylactic apixaban, and therapeutic apixaban groups, respectively, although none were major
- Limitations: Study was conducted prior to June 2021, limiting generalizability to period of Delta variant predominance and high vaccination rates; potential efficacy of more immediate intervention cannot be ruled out
- Implications: Among symptomatic clinically stable outpatients with COVID-19, treatment with aspirin or apixaban compared with placebo did not reduce the rate of a composite clinical outcome

3. **Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial.** RECOVERY Collaborative Group. Lancet Respir Med. 18 Oct 2021.

- Some anti-inflammatory regimens have been shown to improve clinical outcomes in patients with severe COVID-19; colchicine is safe and inexpensive and has a wide range of anti-inflammatory effects, including inhibition of the nucleotide binding domain (NOD)-like pyrin domain 3 (NLRP3) inflammasome which is activated in COVID-19
- This is the first large RCT of efficacy and safety of colchicine in hospitalized COVID-19 patients
    - 177 hospitals in the UK and 2 each in Indonesia and Nepal, Nov 2020-March 2021
    - Randomized to usual care (n=5,730) or usual care plus colchicine (n=5,610; 1 mg at randomization, followed by 500 μg 12h later, then 500 μg twice a day for 10 days total or until hospital discharge)
    - Mean age 63.4y, median time since symptom onset 9 days (IQR 6-12), 94% were receiving corticosteroids at randomization
- Primary outcome: There was no significant difference in the proportion of patients who died within 28-days between the two groups (1173 [21%] patients in the colchicine group *vs* 1190 [21%] patients in the usual care group; rate ratio 1·01 [95% CI 0·93–1·10]; p=0·77)
    - Similar results across all pre-specified subgroups (including age, sex, ethnicity, level of respiratory support, use of corticosteroids) and in exploratory analysis by baseline CRP
- Secondary outcomes: no differences between groups in median time to discharge from hospital alive (10 days in both groups), or probability of being discharged alive within 28 days, or composite outcome of progression to invasive mechanical ventilation or death

- Implications: This large, well-powered randomized trial with more than 2000 deaths found no evidence of a mortality benefit of colchicine among hospitalized COVID-19 patients

VACCINEs

Safety

4. **Adverse Effects after BNT162b2 Vaccine and SARS-CoV-2 Infection, According to Age and Sex.** Dagan et al. NEJM. 27 Oct 2021.

- Updated report of previously published study presenting subgroup data by age (10-year age groups) and sex on adverse events following Pfizer-BioNTech vaccination or natural SARS-CoV-2 infection
- Myocarditis
    - After vaccination, the risk was increased mostly among young male adolescents and adults (16-39 years), with 8.62 excess events per 100,000 persons (95% CI, 2.82 to 14.35)
    - After infection, the risk was increased in both age categories (16-39 and ≥40 years) and in both male and female adolescents and adults, with 11.54 excess events per 100,000 persons (95% CI, 2.48 to 22.55) in young male adolescents and adults
- Limitations: Due to small numbers of events and wide confidence intervals in certain subgroups, results should be interpreted with caution
- Implications: Small increased risk of myocarditis was observed after both vaccination and SARS-CoV-2 infection and was more pronounced after natural infection

Efficacy

5. **Laboratory-Confirmed COVID-19 Among Adults Hospitalized with COVID-19–Like Illness with Infection-Induced or mRNA Vaccine-Induced SARS-CoV-2 Immunity — Nine States, January–September 2021**. Bozio et al. MMWR. 29 Oct 2021.

- Among adults with COVID-19-like illness hospitalization at 187 hospitals in 9 states from Jan-Sept 2021, investigators compared the odds of having PCR-confirmed COVID-19 between unvaccinated patients with a previous SARS-CoV-2 infection and patients who were fully vaccinated with an mRNA vaccine and had no prior documented infection
    - Prior infection or vaccination occurred 90-179 days before hospitalization
    - Patients who did not receive SARS-CoV-2 testing ≥14 days before hospitalization were excluded
- 7,348 patients met eligibility criteria; 1,020 hospitalizations were among previously infected and unvaccinated persons, and 6,328 were among fully vaccinated and previously uninfected
- Odds of laboratory-confirmed COVID-19 among hospitalized patients were greater than five times higher among previously infected, unvaccinated patients than among fully vaccinated patients (aOR = 5.49; 95% CI = 2.75–10.99)
    - The effect was more pronounced among patients aged ≥65y (aOR=19.57) than for those aged 18-64y (aOR-2.57; p for interaction = 0.05)
    - Similar results were observed in secondary analyses that considered Delta variant predominance or considered different time intervals since previous infection or full vaccination
- Limitations: Limited data to assess relative protection of vaccination versus infection by product type, age or time since infection or vaccination; potential misclassification if vaccinated individuals are less likely to seek testing and may in fact have been infected; possible confounding by behavioral differences between groups
- Implications: All eligible individuals should be vaccinated, including those previously infected with SARS-CoV-2

IMMUNOLOGY

6. **Cytokine signature and COVID-19 prediction models in the two waves of pandemics.** Cabaro et al. Scientific Reports. 21 Oct 2020.

- This study was designed to determine if there are common patterns of cytokines between two waves of the pandemic (Italy) in individuals with mild or severe/critical forms of COVID-19 and whether machine learning approach could be useful to identify cytokines which might predict clinical disease
- First wave was defined as March-May 2020 with 65 individuals + 49 controls; Bio-Plex multiplex Human Cytokine and Growth factor kits were used to determine concentration of ~27 proteins
    - A significant increasing trend of IL-1β, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12(p70), IL-15, IL-17, FGF-b, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1α, PDGF, TNF-α, and VEGF was observed across the three groups (Controls ≤ Mild COVID-19 ≤ Severe COVID-19); groups defined by WHO clinical scores; severe patients were significantly older than mild or controls
    - Linear Discriminant Analysis (LDA) recognized the three groups based on cytokine patterns (accuracy 0.96, 95% CI: (0.91, 0.99)); IL-6, IL-8, IL-10 and IP-10 showed either diagnostic and/or prognostic classification performance, with an AUC > 0.95 in at least 2 out of the 3 groups (Control vs mild + severe COVID-19; mild vs control + severe COVID-19; severe vs control + mild COVID-19)
    - Classification and Regression Tree (CART) indicated that IL-6 discriminated controls and COVID-19 patients; combination of IL-6 and IL-8 defined disease severity (overall accuracy was 0.85; 95% CI: (0.77, 0.91))
- Second wave, Sept-Oct 2020, 36 patients + 15 controls; fewer cytokines were significantly different between clinical groups
    - Differences and increasing trends of IL-1β, IL-1ra, IL-2, IL-6, IL-8, IL-10, GM-CSF, IFN-γ, IP-10, were observed in the three groups (Controls ≤ Mild COVID-19 ≤ Severe COVID-19); only IL-1ra, IL-2, IL-6 IL-8 and IFN-γ concentrations were significantly higher in serum of mild and severe COVID-19 patients compared to controls
    - CART analysis was carried out using data of the 2nd wave as test sample. Test accuracy was 0.68; 95% CI: (0.54, 0.80), with a low sensitivity for the discrimination of severe COVID-19 and low specificity for mild COVID-19 patients
    - Challenge of this prediction model with data from the 2nd wave achieved an accuracy of 0.83; 95% CI: (0.68, 0.93), sensitivity of 0.88 and specificity of 0.73, indicating IL-6 as the best predictor of COVID-19
- Limitations: Treatment approaches changed between waves, and potential confounders were not controlled for in the analysis (i.e., steroid use); sample sizes were relatively small per group - especially in second wave
- Implications: Serum cytokine patterns may provide biomarkers useful for COVID-19 diagnosis or prognosis