Summary of Major Literature Related to COVID-19 (September 10, 2021)

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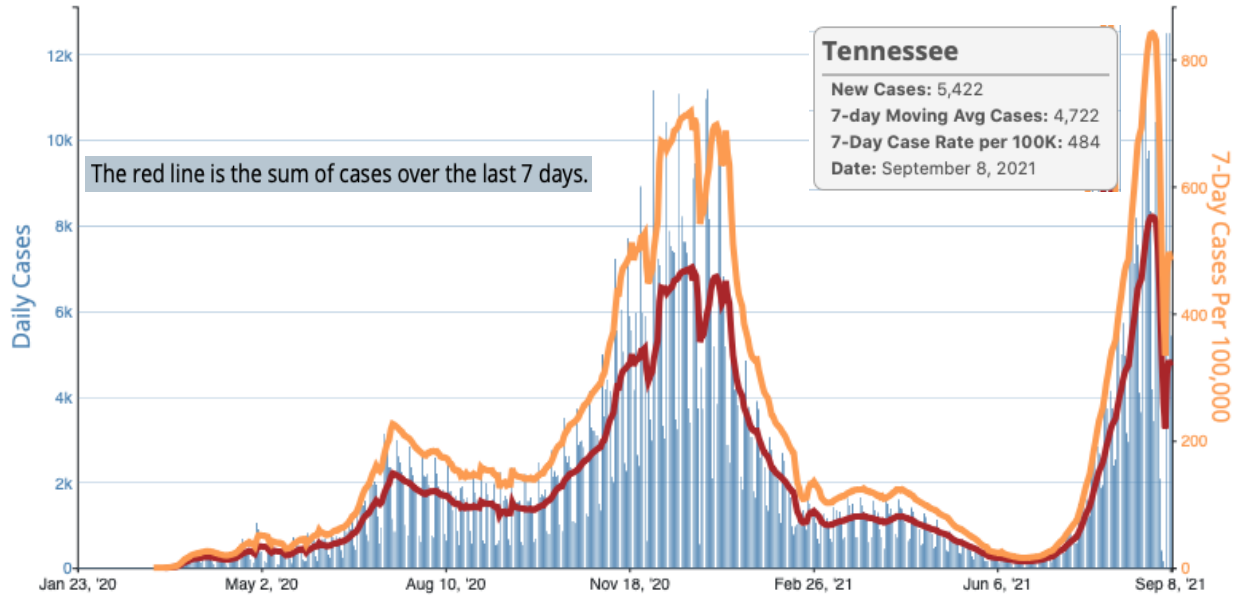
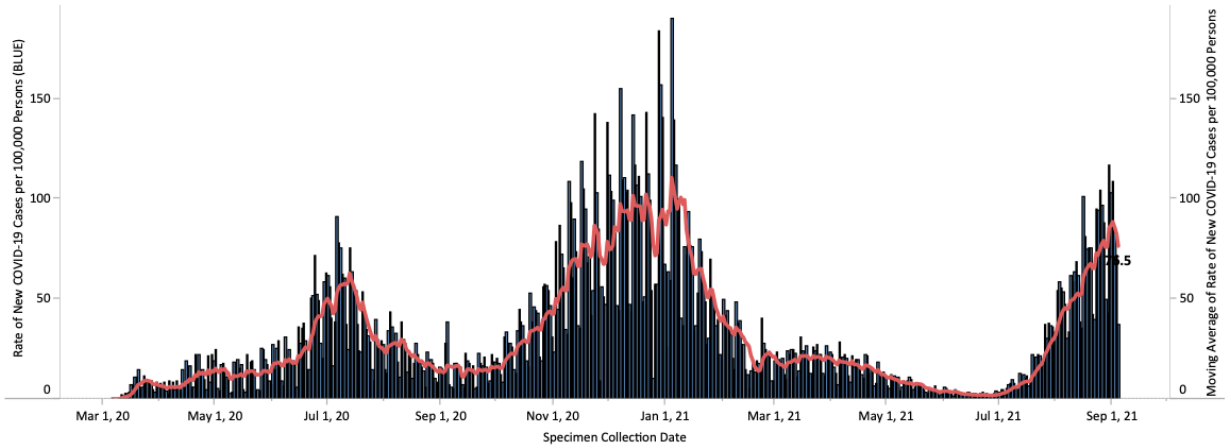
***This is informational and not intended to create variance from VUMC policies/guidance**

Tennessee

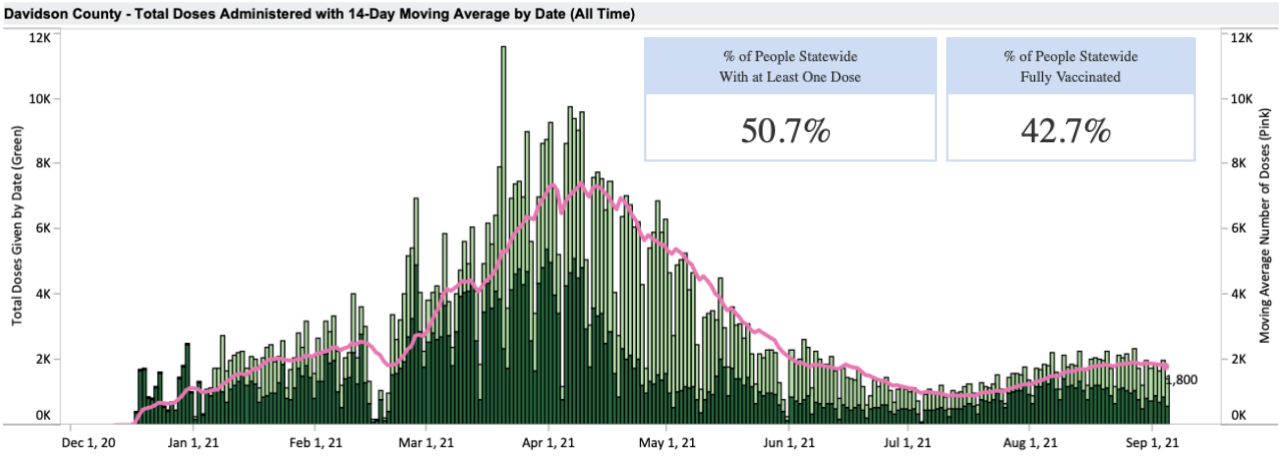
Daily Trends in Number of Cases and 7-Day Cumulative Incidence Rate of COVID-19 Cases in Tennessee Reported to CDC, per 100,000 population.



Davidson county



Davidson County Vaccination Curve



EPIDEMIOLOGY

Post-vaccination illness

1. **Hospitalisation among vaccine breakthrough COVID-19 infections.** Juthani et al. Lancet Infect Dis. 7 Sept 2021.

- Data on 969 patients admitted to Yale New Haven Health System hospitals with a positive SARS-CoV-2 PCR test between March 23 and July 1, 2021
- 797 (82.2%) were unvaccinated, and 103 (10.6%) had not completed a full vaccine course
- 54 (5.5%) were fully vaccinated (14 days after completed course) and were deemed to have a "breakthrough" infection
    - 46% (25/54) were asymptomatic (admitted for non-COVID-19 diagnosis and had incidental positive SARS-COV-2 PCR test)
    - 26% (14/54) had severe or critical illness, of whom 3 died
- Among the 14 with severe illness:
    - Median age 80.5y (IQR 76.5-85.0)
    - Preexisting comorbidities included: overweight (n=9), CVD (n=12), lung disease (n=7), malignancy (n=4), type 2 diabetes (n=7), and use of immunosuppressive agent (n=4)
    - 13 of the 14 had received Pfizer-BioNTech vaccine
- Limitations: Potential selection bias of patients admitted to Yale New Haven hospitals in terms of vaccine type or other factors; unable to disentangle effects of variants, time since vaccination, age, and comorbidities on
- Implications: Vaccines confer strong protection against COVID-19 hospitalization; additional data are needed to identify factors associated with inadequate vaccine response in those with "breakthrough" infections

Pregnancy

2. **Maternal COVID-19, vaccination safety in pregnancy, and evidence of protective immunity. Pham, Aronoff, Thompson (VUMC).** J Allergy Clin Immunol. September 2021.

- Review of evidence related to effects of SARS-CoV-2 infection, vaccination safety, and protective immunity in pregnancy
- Maternal COVID-19
    - Disease profile in pregnant women, including clinical and radiological findings and laboratory parameters, resembles that in the nonpregnant population
    - Substantial increases in morbidity and mortality compared with non-pregnant women
    - Compared to mothers with asymptomatic COVID-19 infection, women with severe or critical COVID-19 are at increased risk for cesarean birth, hypertensive disorders of pregnancy, preterm birth, venous thromboembolism, neonatal ICU admission, lower birth weight
    - Comorbidities (obesity, diabetes, CVD) and advanced maternal age are independent risk factors for adverse outcomes
- Risk of vertical transmission of SARS-COV-2 virus is ~3.2%
- Vaccine safety
    - >128,306 pregnant women have received the mRNA vaccines and registered with CDC V-safe
    - Vaccine side effects are similar between pregnant and nonpregnant women
    - No evidence of increased risk for adverse pregnancy outcomes including miscarriage, preterm birth, small for gestational age, and neonatal death compared with data before COVID-19 pandemic

    - Vaccine-induced antibody titers are similar in pregnant and lactating women and nonpregnant women, were higher than those generated by SARS-CoV-2 infection during pregnancy, and were found in umbilical cord and breast milk samples
    - Cohort study from Israel reported robust maternal-induced humoral response to the vaccine that transfers to the fetus
- Data are reassuring that pregnant women have similar safety profiles and response to the COVID-19 vaccine as nonpregnant women

VACCINES

Safety

3. **Spontaneous Abortion Following COVID-19 Vaccination During Pregnancy.** Kharbanda et al. JAMA. 8 Sept 2021.

- Case-control surveillance study (15 Dec 2020-28 June 2021) of COVID-19 vaccination during pregnancy, using the Vaccine Safety Datalink which included data from 8 health systems and represents ~3% of US population
    - Used EHR, claims, and regional or state information systems
    - Compared odds of receiving a COVID-19 vaccine in the past 28 days for women with spontaneous abortion vs women with ongoing pregnancy
- 13,160 spontaneous abortions and 92,286 ongoing pregnancies were identified
    - During pregnancy and before 20 weeks' gestation, 7.8% and 6.0% of women received 1 or more doses of Pfizer-BioNTech or Moderna vaccine, respectively, and 0.5% received Janssen vaccine
- A COVID vaccine was received within 28 days prior to index date among 8.0% of ongoing pregnancy periods vs. 8.6% of spontaneous abortions
    - Spontaneous abortions did not have an increased odds of exposure to a COVID-19 vaccination in the prior 28 days compared with ongoing pregnancies (adjusted odds ratio, 1.02; 95% CI, 0.96-1.08)
- Limitations: Vaccines may have been undercounted; potential confounding by factors such as prior pregnancy history
- Implications: Data support vaccine recommendation for pregnant women

Transmission

4. **Effect of Vaccination on Transmission of SARS-CoV-2.** Shah et al. NEJM. 8 Sept 2021.

- National registry-linked study of household transmission from 8 Dec 2020 through 3 March 2021, using data from 194,362 household members (mean age 31y) of 144,525 health care workers (mean age 44y) in Scotland
    - 78.4% of HCW had received at least one dose of either the Pfizer-BioNTech or the Oxford-Astrazeneca vaccine, 25.1% had received two doses
- Infection of household members:
    - Rate of infection in household members was 5.93/100 person-years starting 14 days after first dose and 2.98 after second dose, compared to 9.40 in unvaccinated period before first dose
    - Adjusted HR for household member to become infected was 0.70 (95% CI 0.63-0.78) beginning 14 days after first dose and 0.46 (95% CI 0.30-0.70) after second dose, compared to unvaccinated period before first dose
- Similar protection against COVID-19 hospitalization of household members starting 14 days after first vaccine among HCW
- Limitations: Could not account for differences in testing behavior of household contacts before and after HCW vaccination; pre-Delta variant

- Implication: Study provides empirical evidence that vaccination of HCWs reduces transmission within their households

Animal models

5. **Adaptive immune determinants of viral clearance and protection in mouse models of SARS-CoV-2.** Israelow et al. Science Immunology. 2 Sept 2021.

- This study employs in vivo model where the mouse respiratory tract is transduced adeno-associated virus expressing human ACE2 (AAV-hACE2) to create a permissive environment for the virus.
- Rag1-/- mice (devoid of mature B and T cells) and μMT mice (deficient in B cells) administered AA-hACE2 were infected with SARS-CoV2 WA1 strain
    - $Rag1^{-/-}$ mice were unable to clear virus by 14d (wild type (WT) C57Bl/6 mice clear virus by 7d)
    - μMT mice cleared virus earlier than Rag1-/- mice but 50% of μMT still had detectible infectious virus by 7d (and 17x the viral RNA load at 14D).
    - Sera or T cells from previously infected WT mice to recipient AAV-hACE2 $Rag1^{-/-}$ mice reduced viral RNA and titers; convalescent sera resulted in complete reduction in viral load (7d)
- AAV-hACE2 WT or μMT mice were treated with αCD4, αCD8, or αCD4/αCD8 depleting Ab and infected
    - depletion of CD8+ T cells or CD4+ T cells alone inhibited viral clearance; depletion of both had a confounding impact on viral clearance (~30x more viral RNA compared to WT mice; ~60% with detectible infectious virus); T cell depletion significantly reduced level of S-specific Ab produced
    - when T cell depletions were performed in the μMT background, the CD8 depletion had greatest impact on viral clearance
- Transgenic mice that express human ACE2 under the epithelial keratin 18 promoter (K18 hACE2 mice) were used to assess correlates of protection (no weight loss and survival) after Pfizer-BioNtech BNT162b2 immunization (1.0 0.3μg- 1μg) and challenge with WA1 strain SARS-CoV2 (>30d later)
    - a significant positive Spearman's correlation coefficient of 0.7936 was observed between preinfection S1 IgG area under the curve and weight loss at 6 DPI
    - significant positive correlation between neutralization titer (IC50) and protection from weight loss was found; ~1:30 IC50 as the required neutralization titer for 50% probability of survival
- SARS-CoV2 S-specific CD8+ T cells were found in circulation of immunized (single dose) or infected mice, but only convalescent mice had SARS-CoV2 specific T cells in the lung (with tissue resident memory markers)
- (prior to challenge) Prime/boost vaccinated mice (K18 hACE2) developed higher S1 Ab titer and higher neutralization levels against WA1 (VSV pseudo virus assay) than convalescent mice; reduction in neutralization titer against variant B.1.351
    - Prime/boost vaccinated mice and convalescent mice were resistant to disease (whether challenge was with WA1 or B.1.351), showing no physical signs of disease or weight loss (naïve mice demonstrated significant disease and morbidity); depletion of CD8+ T cells did not increase susceptibility
    - Small (not significant) increases in viral RNA in the setting of B.1.351 infection at 2 DPI or 7 DPI; viral titers were undetectable in vaccinated nor convalescent mice irrespective of challenge virus or CD8+ T cell depletion
- Limitations: CD8+ T cell contribution largely only assessed in the setting of strong humoral response
- Implications: Innate immune responses are insufficient to clear acute SARS-CoV-2 infection; vaccination and prior infection provide significant protection against infection and complete protection against disease by B.1.351 VOC, likely due to sufficient antibodies

IMMUNE RESPONSE

6. **Distinct systemic and mucosal immune responses during acute SARS-CoV-2 infection.** Smith et al. Nature Immunology. 2 Sept 2021.

- This study was designed to perform a comparative analysis of S-specific Ab, cytokines, viral load and bacterial communities in paired samples (nasopharyngeal swabs and plasma) in hospitalized patients with acute SARS-CoV-2 infection (with moderate, severe or critical disease)
    - plasma viral RNA load increased with increasing disease severity, nasopharyngeal viral RNA load was independent of the clinical presentation
    - In plasma IL-6, IL-10, CCL20, VEGF, FGF, PD-L1, TNF, IL-1β and IL-1RA increased with disease severity; IFN-α2 decreased with severity
    - In the nasopharynx CCL2, VEGF, FLT3-L, EGF, CXCL1, PDGF-AA, IL-7 and TGF-α increased with disease severity
- Higher viral RNA load in plasma was associated with inflammatory response (IL-6, TNF and CCL19) and several regulatory cytokines (IL-10 and IL-1RA), (weak association with) S-specific Ab and more severe COVID-19 disease
- Higher viral RNA load in the nasopharyngeal swabs positively correlated with increased Ab responses and negatively correlated with interferon responses [decreased IFN-α2, IFN-λ3, IFN-β and IFN-γ]; lower interferon responses correlated with presence of *Corynebacterium*
- Analysis of α-diversity (evenness and number of bacteria) showed a decrease in 16S rRNA sequences in patients with severe and critical COVID-19; β-diversity (richness) clearly decreased with disease severity; 16S rRNA profiles in patients with critical disease were different from other patients (based on Bray–Curtis distance matrix and principal-coordinate analysis)
- Inflammatory cytokines in the nasopharynx (CCL2 and VEGF) were elevated in severe COVID-19 and associated with pathogenic microorganisms (*Prevotella, Streptococcus, Peptostreptococcus* and *Clostridial* genera)
- Limitations: Comparisons are limited to paired samples from healthy and acutely hospitalized patients (8-12d before treatment intervention); cannot rule out that any dysbiosis identified was not present in individual before COVID-19 disease
- Implications: Immune responses (Ab and cytokines) compartmentalized during SARS-CoV-2 infection and are regulated in a tissue-dependent fashion; SARS-CoV-2 infection is associated with perturbations in nasopharyngeal bacterial communities of hospitalized patients

7. Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths. Bastard et al. Science Immunology. 19 Aug 2021.

- Addresses the prevalence of auto-Abs against type I IFNs in the general, uninfected, population, whether the prevalence increases with age, and whether there is an association with critical or fatal COVID-19 cases
- Auto-Abs against IFN-α2 and -ω were detected from circulating IgG using ELISA from critical COVID-19 patients (3,595), severe COVID-19 patients (623) or individuals with asymptomatic or mild upper respiratory tract SARS-CoV-2 infection (1,639)
    - high levels of anti-IFN-α2 and/or anti-IFN-ω auto-Abs in 6.9% of critical patients, 3.4% of patients with severe COVID-19, and only 0.6% of the asymptomatic or mild
    - another 12.7% of patients with critical COVID-19 had intermediate levels of anti-IFN-α2 and/or IFN-ω auto-Abs; another 8.6% of patients with severe COVID-19 and 11% of the asymptomatic or mild cohort had intermediate levels.
- Using a luciferase reporter assay to detect IFN responses in HEK cells, the ability of the plasma to neutralize recombinant IFN-α2 and -ω was measured
    - When using high levels of IFN (10 ng/mL IFN-α2 or IFN-ω in medium containing 1/10 plasma or

serum), 9.8% (307 of 3,136) of the critical patients tested and 3.53% (22 of 623) of the severe patients had auto-Abs neutralizing IFN-α2 and/or IFN-ω, versus only 0.37% (4 of 1,076) controls
    - When using more physiological levels of IFNs (100 pg/mL IFN-α2 and/or IFN-ω in plasma 1/10), 13.6% of all critical patients tested (N=489 of 3,595), 6.5% (N=34 of 522) of the severe patients, and 1% of the controls (N=17 of 1,639) had circulating auto-Abs that neutralized type I IFN
- An in vitro assay was used to determine if auto-Abs can neutralize the protective effect that IFN-α2 (~400 pg/mL) can have blocking SARS-CoV-2 replication in Huh-7.5 cells
    - 1/100 dilutions of plasma from 4 out of 5 critical COVID-19 patients and 1 of 2 elderly individuals with auto-Abs neutralizing 100 pg/mL IFN-α2 neutralized the protective effect
- Screened 1,773 patients with critical COVID-19 pneumonia, and found that 1.3% (N=23) had neutralizing auto-Abs against IFN-β; presence of neutralizing auto-Abs against IFN-β was significantly associated with critical, but not severe, disease relative to the controls
- Proportion of patients with auto-Abs ranged from 9.6% of patients <40 yo, to > 21% of those >80 yo; in men > 80 yo, the proportion of critical COVID-19 patients carrying auto-Abs neutralizing 100 pg/mL IFN-α2 and/or IFN-ω increased to 23%
- 13.3% of the deceased patients (1124 deceased out of 3595 individuals) carried auto-Abs neutralizing 10 ng/mL IFN-α2 and/or IFN-ω
- 34,159 individuals aged 20 to 100 years (general population, equal sexes)
    - prevalence of auto-Abs neutralizing 10 ng/mL type I IFN was > 10x higher in individuals >70 yo (0.17% in individuals <70 yo, 0.9% in individuals 70- 75, 1.6% 75 - 80 and > 4% between 80 -85 yo); this prevalence increases when looking at ability to neutralize 100pg/mL
    - auto-Abs were highly significant risk factors in comparisons of patients with critical or severe COVID-19 with the general population
        - Auto-Abs neutralizing both IFN-α2 and IFN-ω at 10 ng/mL (OR=30, $P<1 \times 10^{-13}$),
        - Auto-Abs neutralizing IFN-α2 +/− IFN-ω at 10 ng/mL (OR=20, $P<10^{-13}$), and IFN-ω +/− IFN-α2 at 10 ng/mL (OR =15, $P<10^{-13}$)
        - Auto-Abs neutralizing both IFN-α2 and IFN-ω at 100 pg/mL were also highly significant risk factors (OR [95% CI]=12 [9-16], $P<10^{-13}$)
- Limitations: Addressing why auto-Abs increase with age is beyond the scope of this study
- Implications: Type I interferons inhibit viral replication as part of the immune response. This study demonstrates that there is an increase in the prevalence of auto-Abs neutralizing type I IFNs with age in elderly individuals; the ability of auto-Ab to neutralize IFN-α2 and IFN-ω is a significant risk factor for severe COVID-19 disease