Summary of Major Literature Related to COVID-19 (Dec 8-21)

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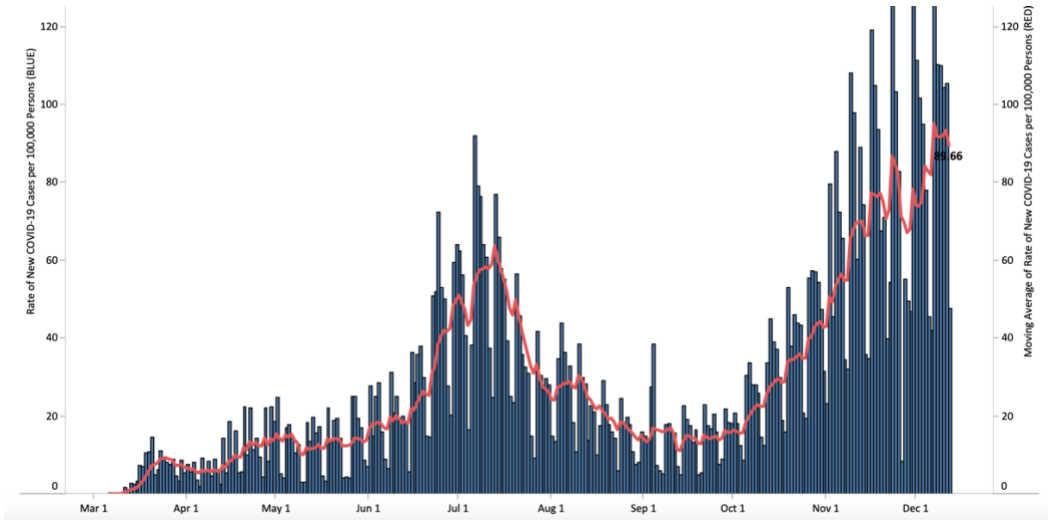
***This is informational and not intended to create variance from VUMC policies/guidance.**

STATISTICS – Daily new cases per 100,000 population

Tennessee

Davidson county

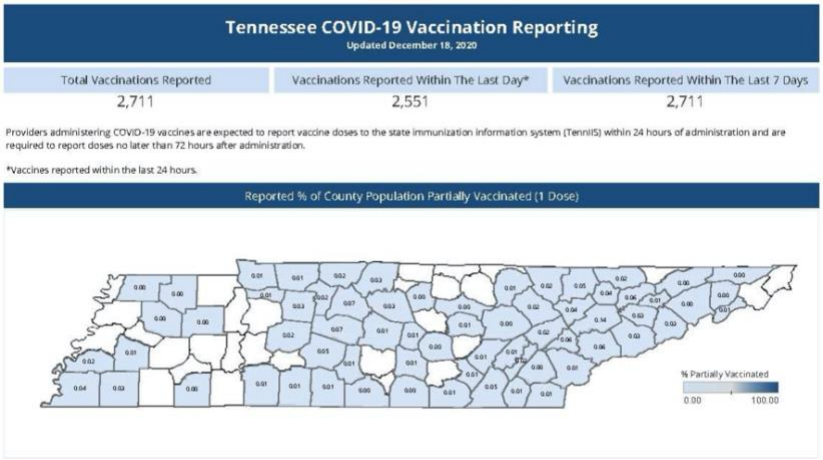


As of December 21, in TN

- Total cases = 519,687
- Active cases = 78,639
- Current hospitalizations = 2,789
- Total deaths = 6,071
- Top counties:
  - Shelby = 60,630
  - Davidson = 61,556
- In Davidson county, Active cases = 7,068
  ICU availability = 7%
  Test % positive 7-d = 16.6%
- Demographics:

Groups	No. of Cases	No. of Deaths
By sex		
Female	269,250	2,763
Male	236,584	3,251
By race/ethnicity		
White	296,186	4,401
Black	67,213	1,148
Hispanic	37,334	201
Asian	4,189	35
Other	47,118	213
By age		
0–10	26,600	4
11–20	67,741	4
21–30	96,316	37
31–40	81,156	66
41–50	77,846	190
51–60	71,671	525
61–70	51,039	1,104
71–80	30,550	1,835
80+	16,172	2,304

TN COVID-19 VACCINATION REPORTING DASHBOARD



EPIDEMIOLOGY

1. **Factors Associated with Positive SARS-CoV-2 Test Results in Outpatient Health Facilities and Emergency Departments Among Children and Adolescents Aged <18 Years — Mississippi, September–November 2020.** Hobbs et al. MMWR. 15 Dec 2020.

- Case-control study comparing children and adolescents <18y with positive outpatient SARS-CoV-2 PCR test results (cases, N=154) to those with negative test results (controls, N=243) in Mississippi
    - Controls frequency matched by age group, sex, and testing date interval
    - 21% were aged 0-3 years, 54% were female, 55% were non-Hispanic Black, and 37% were non-Hispanic White
    - Parents were interviewed an average of 32 days after testing
- Overall (n=397), in-person school or childcare attendance ≤14 days before the SARS-CoV-2 test was not associated with a positive SARS-CoV-2 test result (aOR = 0.8, 95% CI = 0.5–1.3)
- Among 236 children aged ≥2 years who attended childcare or school during the 2 weeks before the SARS-CoV-2 test, parents of 64% of case-patients and 76% of control participants reported that their child and all staff members wore masks inside the facility (aOR = 0.4, 95% CI = 0.2–0.8)
- In the 2 weeks preceding SARS-CoV-2 testing, case-patients were more likely to have attended gatherings with persons outside their household, including social functions (aOR = 2.4, 95% CI = 1.1–5.5) or activities with other children (aOR = 3.3, 95% CI = 1.3–8.4), or have had visitors in the home (aOR = 1.9, 95% CI = 1.2–2.9) than were control participants
- Limitations: Single academic medical center; low (45%) response rate; potential for residual confounding as estimates only adjusted for age, sex and race; study period Sept 1- Nov 5, before current surges in community transmission
- Implications: Avoiding gatherings outside of school and wearing masks inside school are important strategies for risk mitigation in children

2. **Analyses of Risk, Racial Disparity, and Outcomes Among US Patients With Cancer and COVID-19 Infection.** Wang et al. JAMA Oncology. 10 Dec 2020.

- Case-control analysis of electronic health records from 73.4 million patients from 360 hospitals in the US through August 14, 2020
    - Over 2.5 million had a prior diagnosis of at least 1 of the 13 common cancers; of these, 273,140 had recent cancer (diagnosed within the last year)
    - Among 16,570 patients diagnosed with COVID-19, 1200 had a prior cancer diagnosis and 690 had a recent cancer diagnosis of at least 1 of the 13 common cancers
- Compared to individuals without cancer, those with a cancer diagnosis (aOR, 1.46 [95% CI, 1.42-1.50]) and particularly a recent cancer diagnosis (aOR, 7.14 [95% CI, 6.91-7.39]) were at significantly increased odds for COVID-19 infection, after accounting for comorbidities, cancer treatments, transplant procedures, and nursing home stay
    - Significant associations were observed for each cancer examined, with the strongest associations for recently diagnosed leukemia (aOR, 12.16 [95% CI, 11.03-13.40]), non–Hodgkin lymphoma (aOR, 8.54 [95% CI, 7.80-9.36]), and lung cancer (aOR, 7.66 [95% CI, 7.07-8.29])
- Among patients with recent cancer diagnosis, African Americans had a significantly higher risk for COVID-19 infection than White patients; this racial disparity was largest for breast cancer (aOR, 5.44 [95% CI, 4.69-6.31]) and prostate cancer (aOR, 5.10 [95% CI, 4.34-5.98])
- Patients with recent cancer and COVID-19 had significantly worse outcomes (hospitalization, 47.76%; death, 14.93%) than patients with COVID-19 without cancer (hospitalization, 24.26%; death, 5.26%) ($P < .001$) and patients with cancer without COVID-19 (hospitalization, 12.39%; death, 4.03%) ($P < .001$)

- Implications: Patients with *active cancer* are the most vulnerable to COVID-19 among the population with any cancer, and Black patients with cancer may have higher risk than white patients with cancer
- Limitations: Potential confounding by socioeconomic and lifestyle factors and access to healthcare in this EHR database limits causal conclusions

3. **Household Transmission of SARS-CoV-2. A Systematic Review and Meta-analysis.** Madewell et al. JAMA Network Open. 14 Dec 2020.

- Meta-analysis of 54 studies with 77,758 participants
- Estimated household and family secondary attack rate was 16.6% (95% CI, 14.0%-19.3%)
    - higher than secondary attack rates for SARS-CoV (7.5%) and MERS-CoV (4.7%)
- Household secondary attack rates were higher:
    - to adult contacts (28.3%; 95% CI, 20.2%-37.1%) than to child contacts (16.8%; 95% CI, 12.3%-21.7%)
    - to spouses (37.8%; 95% CI, 25.8%-50.5%) than to other family contacts (17.8%; 95% CI, 11.7%-24.8%)
    - in households with 1 contact (41.5%; 95% CI, 31.7%-51.7%) than in households with 3 or more contacts (22.8%; 95% CI, 13.6%-33.5%).
- Limitations: Substantial heterogeneity across studies, due in part to varied testing and monitoring strategies across studies, selection bias and confounders. Few studies included asymptomatic cases so estimation of secondary attack rates for asymptomatic/pre-symptomatic cases is unreliable due to incomplete ascertainment of these cases. Levels of community transmission may affect results
- Implication: Households are a high-risk setting for SARS-CoV-2 transmission as it may be difficult to isolate from infected household members

VACCINE STUDIES

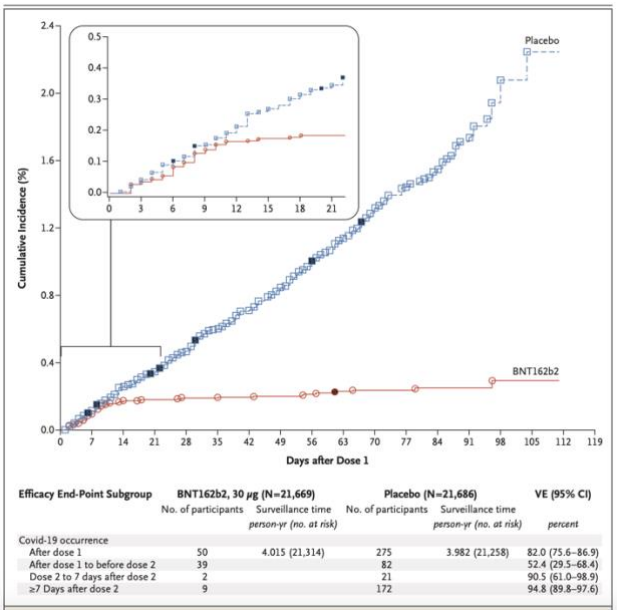
Dec 11: FDA grants Emergency Use Authorization (EUA) for Pfizer-BioNTech COVID-19 Vaccine (BNT162b2)
Dec 18: FDA grants EUA for Moderna COVID-19 Vaccine

Eleven months after the SARS-CoV-2 genetic sequence was released by the Chinese Center for Disease Control and Prevention and disseminated globally by the GISAID

4. **Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine.** Polack et al. NEJM. 10 Dec 2020.

- Report from the ongoing placebo-controlled, observer-blinded trial of BNT162b2 vaccine candidate (**Pfizer-BioNTech**, 30 µg per dose). Individuals 16 years of age or older were randomized to receive two doses, 21 days apart, of vaccine or placebo
    - 21,720 received BNT162b2, 21,728 received placebo at 152 sites worldwide
    - Median age at vaccination = 52 years (range 16-91)
    - Primary end points were efficacy of the vaccine against confirmed COVID-19 with onset at least 7 days after the second dose, and safety over two months; secondary endpoint was efficacy against severe COVID-19
- Primary endpoint: Among 36,523 participants who had no evidence of existing or prior SARS-CoV-2 infection, 8 cases of COVID-19 were observed at least 7 days after the second dose in the treatment arm vs. 162 cases among those assigned to placebo
    - 95.0% vaccine efficacy in preventing COVID-19 (95% CI, 90.3 to 97.6)
    - Efficacy was similar across subgroups defined by age, sex, race, ethnicity, baseline BMI, and presence of coexisting conditions including hypertension
- Secondary endpoint: Among 10 cases of severe COVID-19 with onset after the first dose, 9 occurred in placebo recipients and 1 in a BNT162b2 recipient

- Early protection by the vaccine started as soon as 12 days after the first dose, when cumulative incidence for vaccine and placebo groups begin to diverge (see Figure)
    - During the interval between the first and second dose, vaccine efficacy was 52% (95% CI, 29.5 to 68.4), with lower bound CI below FDA efficacy threshold of 30%
- Safety: Mild to moderate pain was the most commonly reported local reaction; fatigue (51-59%) and headache (39-52%) were the most commonly reported systemic events
    - Severe systemic events were reported in less than 2% of vaccine recipients after either dose, except for fatigue (in 3.8%) and headache (in 2.0%) after the second dose
    - Fever was reported after the second dose by 16% of younger (16-55y) vaccine recipients and by 11% of older (>55y) recipients
    - Both local pain and systemic events were reported more frequently after the second dose, and among younger participants than older participants



Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669) No. of participants	BNT162b2, 30 μg (N=21,669) Surveillance time person-yr (no. at risk)	Placebo (N=21,686) No. of participants	Placebo (N=21,686) Surveillance time person-yr (no. at risk)	VE (95% CI) percent
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)

- Limitations: 83% of participants were white; low statistical power in subgroups
- Implications: The trial met primary efficacy endpoints, and a two-dose regimen of BNT162b2 was found to be safe and 95% effective against COVID-19; favorable safety profile observed during phase 1 was confirmed during phase 2/3

5. **Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK.** Voysey et al (Oxford COVID Vaccine Trial Group). Lancet. 08 Dec 2020.

- Primary efficacy results from a pooled analysis of ongoing blinded, randomized, controlled trials in the UK and Brazil, that randomized 11,636 participants aged 18 years and older to ChAdOx1 nCoV-19 vaccine (**Oxford Univ/AstraZeneca AZD1222**) or control (meningococcal group A, C, W, and Y conjugate vaccine or saline)
    - Participants in the ChAdOx1 nCoV-19 group received two standard doses containing 5×10^{10} viral particles (SD/SD cohort); a subset in the UK trial inadvertently received a half dose as their first dose (low dose) followed by a standard dose as their second dose (LD/SD cohort)
- Primary vaccine efficacy endpoint was virologically confirmed, symptomatic COVID-19 occurring >14 days after second dose:
    - In SD/SD cohorts overall, efficacy was 62.1% (95% CI 41.0–75.7); 27 (0.6%) of 4440 in the ChAdOx1 nCoV-19 group *vs* 71 (1.6%) of 4455 in the control group
    - In LD/SD cohort overall, efficacy was 90.0% (67.4–97.0); 3 (0.2%) of 1367 *vs* 30 (2.2%) of 1374
- Secondary efficacy analysis of cases occurring more than 21 days after the first standard dose in participants who received only standard doses
    - vaccine efficacy was 64.1% (95% CI 50.5–73.9)
- No COVID-19-related hospital admissions occurred in ChAdOx1 nCoV-19 recipients, whereas ten (two of which were severe) occurred in the control groups
- Safety analyses included all randomized participants who received at least one dose of any vaccine in any study (20,000 participants in UK, Brazil and South Africa)

- Median 3.4 months of safety follow-up, IQR 1·3–4·8)
- Favorable safety profile: 84 severe events in the ChAdOx1 nCoV-19 group and 91 in the control group

- Limitations:
  - Only 12% of those assessed for efficacy were >55y, limiting efficacy inferences for older individuals at highest risk for COVID-19
  - Notable differences across the trials in participant age, dosing and time interval between vaccine doses (e.g., age >55y were not included in LD/SD cohort; >12 weeks between doses in the UK and <6 weeks between doses in Brazil)
  - Vaccine efficacy in older age groups could not be assessed in this interim analysis due to insufficient data
- Implications:
  - Induction of immune responses against spike protein using a viral vectored vaccine may provide protection against COVID-19, but further examination of doses and timing of doses is needed
  - If high efficacy of a low dose for priming is confirmed, it could provide substantially more vaccine for distribution without compromising protection; but observed differences in efficacy by dose were not consistent with previous immunogenicity results for this vaccine
- **See also**: **Oxford-Astrazeneca COVID-19 vaccine efficacy** (Comment). Knoll and Wonodi. Lancet. 08 Dec 2020.
  - "This is the first report of efficacy against COVID-19 for a non-profit vaccine aiming for global supply, equity, and commitment to low-income and middle-income countries (LMICs), and as such its publication is very welcomed"

ANTIBODY RESPONSE

6. **IgA dominates the early neutralizing antibody response to SARS-CoV-2**. Sterlin et al. Science Transl Med. 07 Dec 2020.

- This study measured the frequency of antibody-secreting cells and the presence of SARS-CoV-2 specific neutralizing antibodies in serum (159 COVID-19 patients), saliva and bronchoalveolar lavages (BAL) fluid in 10 patients
- Peripheral blood studies indicate that IgA plasmablasts ($Ki67^{+}CD19^{low}CD27^{high}CD38^{high}$ cells) were detected shortly after the onset of symptoms (1-9 d after onset of symptoms), peaked 10-15 days, decreased day 16 to 25; 40% expressed CCR10 suggesting ability to migrate to the lung
- The virus-specific antibody [nucleocapsid (NC) and receptor binding domain (RBD) specific] responses included IgG, IgM and IgA
  - Early virus-specific IgG, IgM and IgA titers were not significantly different in severe v. non-severe patients
  - IgA neutralization is linked to RBD binding (not NC binding) and had more efficient neutralizing potential than IgG; IgA levels were 5x lower than IgG levels in serum
- Anti-RBD and anti-NC IgA (in serum) decreased after one month post onset of symptoms
- IgG concentrations were consistently higher than IgA in the BAL samples (in all but one patient)
- Anti-RBD IgA were consistently more abundant in saliva than in serum; IgA concentrations are higher than IgG in saliva (collected at 49-73d post symptoms) and 8 of 10 IgA samples neutralized in the pseudotype assay
- Limitations: Low sample size limited statistical power of certain time trend analyses (i.e., "IgA might be detected earlier than IgG", BAL and saliva testing only on n=10); neutralization assays were all done with monomeric IgA (and dimeric IgA is predominant at mucosal sites)

7. **Enhanced SARS-CoV-2 neutralization by dimeric IgA**. Wang et al. Science Transl Med. 17 Dec 2020

- This study characterizes the IgA (secretory antibody) in response to SARS-CoV-2 infection in 149 convalescent individuals (studied on average 40 days after infection).
- IgA responses in plasma generally correlated with IgG responses; levels of anti-RGD IgA were more modest than IgG but higher than IgM.
    - Females had lower concentrations of RBD-specific IgA than males
    - hospitalized individuals showed higher anti-RBD IgA titers than those with milder symptoms
    - cases had higher anti-RBD IgA titers than contacts
    - individuals who suffered gastrointestinal symptoms showed significantly higher plasma anti-RBD IgA but not IgG titers comparing to those without
- Neutralization activity of plasma IgA and IgG was compared in 99 individuals
    - One-fourth of individuals had more potent IgA than IgG; IgA potency did not correlate with symptom severity or hospitalization
    - Neutralizing activities of purified IgG and IgA were not correlated with age, duration of symptoms, or sex; potency was significantly higher in individuals with gastrointestinal symptoms
- SAR-CoV-2 specific IgA dimers (which would be found at high concentrations in mucosal secretions) were on average 15x more potent than IgA monomers (from the plasma) against the same target.
- Limitations: This study focused on only RBD specific antibodies; no measure of IgA in mucosal secretions (dimer studies were done by expressing the Ab recombinantly)

Implications of both studies: The majority of research on SARS-CoV-2 antibodies to date has focused on the IgG subtype. Both studies find that IgA is more potent than IgG in neutralizing SARS-CoV-2; one study points to the important role of IgA antibodies during the early phase of COVID-19 illness. COVID vaccine development should consider stimulating IgA antibody production