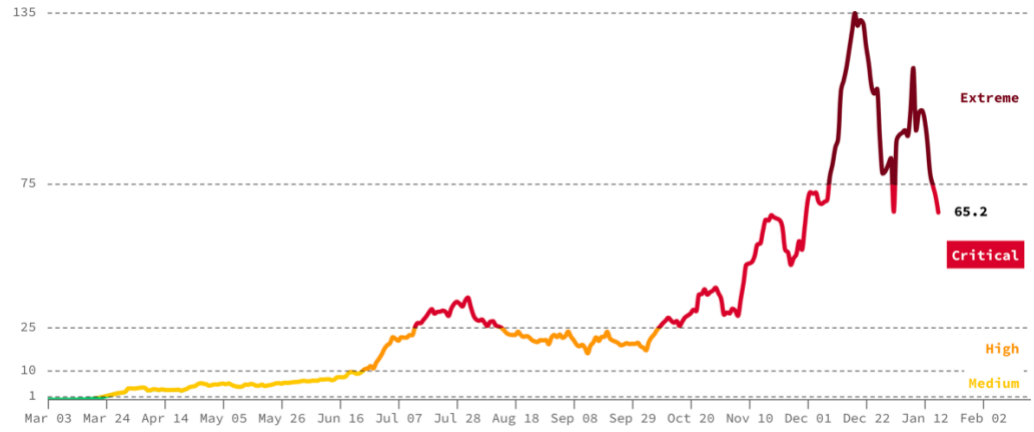
Summary of Major Literature Related to COVID-19 (Jan 5-19)

Led by Loren Lipworth (Epidemiology) and Holly Algood (Infectious Diseases),
with contribution from S Sudenga, D Yu, DOM

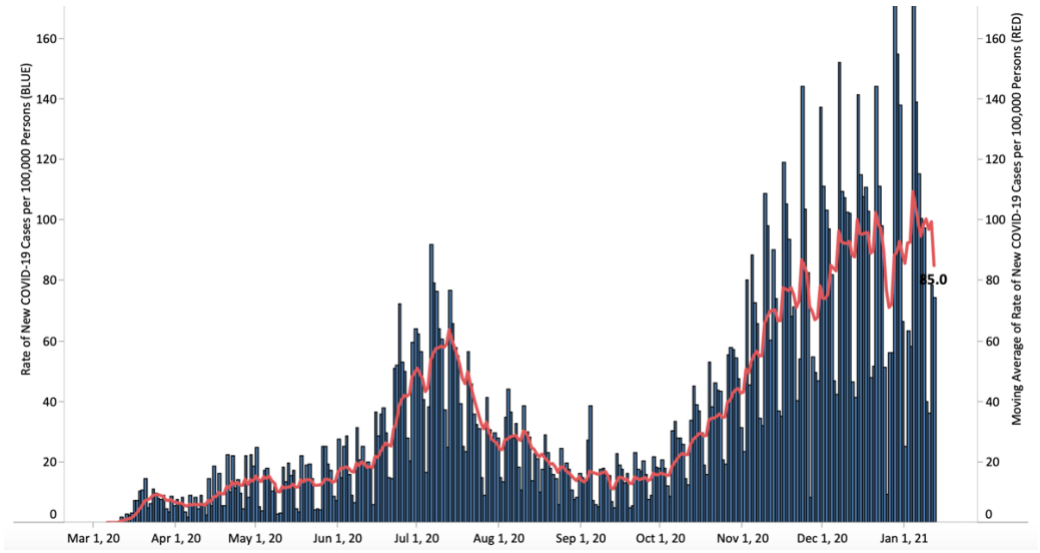
***This is informational and not intended to create variance from VUMC policies/guidance.**

STATISTICS – Daily new cases per 100,000 population

Tennessee



Davidson county



As of Jan 18, 2021, in TN:

- Total cases = 687,751
- Active cases = 64,601
- Total deaths = 8,430
- Beds availability = 15%
- ICU availability = 8%
- Test positivity 7-d = 16%

In Davidson county:

- Total cases = 80,415
- Active cases = 6,591
- Total deaths = 537
- Beds availability = 13%
- **ICU availability = 6%**
- Test positivity 7-d = 14%

Demographics:

Groups	No. of Cases	No. of Deaths
By sex		
Female	365,233	3,871
Male	317,193	4,553
By race/ethnicity		
White	408,682	6,200
Black	86,113	1,501
Hispanic	43,783	248
Asian	5,763	41
Other	58,224	298
By age		
0–10	35,401	4
11–20	86,463	3
21–30	125,540	39
31–40	107,013	83
41–50	102,724	274
51–60	96,526	714
61–70	69,441	1,539
71–80	41,676	2,558
80+	21,973	3,216

TN COVID-19 Vaccination Reporting

19 Jan 2021

Total Vaccinations Reported	Vaccinations Reported on 1/18/2021	Vaccinations Reported Since 1/11/2021
370,895	6,333	95,696

Providers administering COVID-19 vaccines are expected to report vaccine doses to the state immunization information system (TennIIS) within 24 hours of administration and are required to report doses no later than 72 hours after administration.

Number of People with 1 Dose Only vs 2 Doses: 53,210 | 263,888

Age Group

Age Group	People Vaccinated	% of People Vaccinated
16-20 years	1,994	0.63%
21-30 years	33,389	10.52%
31-40 years	44,073	13.89%
41-50 years	46,302	14.59%
51-60 years	49,030	15.45%
61-70 years	35,171	11.08%
71-80 years	62,685	19.76%
81+ years	44,612	14.06%
Pending	37	0.01%
Total	317,293	100.00%

Patient Race

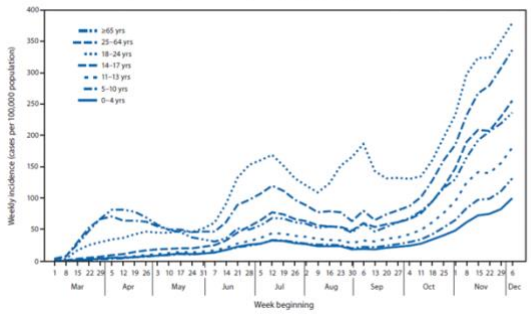
Patient Race	People Vaccinated	% of People Vaccinated
Asian	1,396	0.44%
Black or African American	11,304	3.56%
White	113,908	35.90%
Other/Multiracial	63,212	19.92%
Unknown	127,473	40.18%
Total	317,293	100.00%

EPIDEMIOLOGY

1. **COVID-19 Trends Among Persons Aged 0–24 Years — United States, March 1–December 12, 2020.** Leidman et al. MMWR. 13 Jan 2020**.**

- Trends in PCR-confirmed COVID-19 incidence and testing volume and percent positivity were examined among US children, adolescents, and young adults, including pre-school age children and college students (aged 0–24 years) from March 1- December 12, 2020
- Overall, 2,871,828 confirmed cases of COVID-19 were reported in this age group
    - 57.4% among young adults 18-24y, 16.3% among adolescents 14-17y, and 7.9%, 10.9% and 7.4% among those 11-13y, 5-10y and 0-4y, respectively
    - Among cases with complete information on race/ethnicity (52%), 50.2% were non-Hispanic White, 27.4% were Hispanic/Latino (Hispanic), and 11.7% were non-Hispanic Black
- Reported weekly incidence of COVID-19 (daily moving 7-day average per 100,000 persons) and percentage of positive test results increased during the study period, with spikes in early summer, followed by a decline and then steep increase in October through December (Figure)

FIGURE 1. COVID-19 weekly incidence,*† by age group — United States, March 1–December 12, 2020§



    - Weekly incidence and percentage of positive test results was higher in each successively increasing age group
    - Incidence among young adults 18–24y peaked in mid-July and early September and preceded increases among other age groups
    - Trends for ages 0-17y generally paralleled those in adults including during the fall when some schools reopened for in-person education
- Limitations: COVID-19 incidence may be underestimated due to frequent asymptomatic infection and lower testing volume in this age group; higher rate of positive test results compared to adults may be due to prioritization of those with symptoms
- Implications: Schools should implement strict mitigation strategies including universal mask wearing to reduce school and community transmission and enable safe in-person learning; young adults might contribute more to community transmission than do younger children

2. **6-month consequences of COVID-19 in patients discharged from hospital: a cohort study.** Huang et al. Lancet. 08 Jan 2020**.**

- Study objective was to describe the long-term consequences of COVID-19 in patients after hospital discharge and identify the potential risk factors, including disease severity, associated with these consequences
- Ambi-directional cohort study of patients with confirmed COVID-19 who had been discharged from Jin Yin-tan Hospital (Wuhan, China) between Jan 7-May 29, 2020
    - Follow-up metrics used: 1) face-to-face interview with modified British Medical Research Council (mMRC), dyspnoea scale, the EuroQol five-dimension five-level (EQ-5D-5L) questionnaire, the EuroQol Visual Analogue Scale (EQ-VAS), 2) pulmonary function test, 3) follow up CT, 4) venous blood samples for antibodies, 5) Estimated glomerular filtration rate
- Study population (N=1,733):
    - Median age was 57 (47–65) years, 52% men
    - The most common comorbidity was hypertension (29%), then diabetes (12%), and cardiovascular disease (7%)

    - 1172 (68%) participants required oxygen therapy during their hospital stay, and 122 (7%) required HFNC, non-IMV, or IMV. 76 participants (4%) were admitted to the ICU
    - The median duration of hospital stay was 14 (10–19) days and time exclusively in the ICU was 14 (6.5–25.5) days
- Follow-up study done from June 16-Sept 3, 2020
    - 76% of patients reported at least one symptom at follow-up and a higher percentage was observed in women
    - Patients with higher COVID disease severity score were more likely to report symptoms
    - Most common symptoms were fatigue or muscle weakness (63%) and sleep difficulties (26%)
    - More severely ill patients had increased risk of pulmonary diffusion abnormality, fatigue or muscle weakness, and anxiety or depression
    - Seropositivity and titers of neutralizing antibodies were significantly lower than at acute phase
- Limitations: Potential selection bias, as 1) many of the sickest or oldest patients would have been excluded from enrollment, 2) those with mild COVID-19 symptoms were not enrolled. Pre-COVID-19 pulmonary function, 6-min walking distance and anxiety/depression were unknown
- Implications: Six months after symptom onset, fatigue or muscle weakness and sleep difficulties were the main symptoms of patients who had recovered from COVID-19. Risk of anxiety or depression as an important psychological complication and impaired pulmonary diffusion capacities among patients with more severe illness require further study

Transmission

3. **SARS-CoV-2 Transmission From People Without COVID-19 Symptoms.** Johansson et al. JAMA Netw Open. 07 Jan 2021.

- Decision analytic model assessed the relative amount of transmission from presymptomatic, never symptomatic, and symptomatic individuals across a broad range of scenarios in which the infectious period and the proportion of transmission from people who never develop symptoms were varied according to published best estimates
    - All estimates set the incubation period at a median of 5 days and the infectious period duration at 10 days
- Baseline assumptions: peak infectiousness occurred at day 5, and 30% of individuals with infection never develop symptoms and are 75% as infectious as those who do develop symptoms
    - In this model, 59% of all transmission came from asymptomatic transmission: 35% from presymptomatic individuals and 24% from individuals who are never symptomatic
- If at least 30% of transmission was assumed to be from individuals who never have symptoms, total transmission from individuals without symptoms was higher than 50% with any value of peak infectiousness, up to 2 days after the median time of symptom onset
- Even the most conservative assumptions of peak infectiousness 2 days post–median onset and 0% transmission from individuals who never develop symptoms still resulted in more than 25% of transmission from asymptomatic individuals
- Implications: Under a range of plausible scenarios, more than half of SARS-CoV-2 transmission comes from individuals who do not have symptoms; thus, effective pandemic control needs to go beyond identification and isolation of symptomatic COVID-19 to include mask wearing, distancing, contact tracing and targeted testing
- Limitations: Simplified model which only varied 2 parameters; some imprecision in estimates used in models for incubation period or % transmission from asymptomatic individuals, even when derived from multiple studies

TREATMENT

Convalescent plasma

4. **Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults.** Libster et al. NEJM. 06 Jan 2021.

- Randomized, double-blind, placebo-controlled trial in Argentina of convalescent plasma with high IgG titers against severe COVID-19 in older adult patients within 72 hours after the onset of mild symptoms
    - Previous studies of convalescent plasma given later in the course of COVID-19 illness to patients aged 18y and older have not shown clear benefit
    - Patients were aged ≥75y (with or without comorbidities), or 65-74y with one or more comorbidities including hypertension, diabetes, obesity, chronic renal failure, CVD, and COPD
- 160 patients were randomized; 80 received 250 ml convalescent plasma with high IgG titer (>1:1000) against SARS-CoV-2 spike protein, and 80 received placebo infusion
    - Mean age 77.2y, 62% women, 55% age 75y or older, 81% had at least one comorbidity
- Primary end point was severe respiratory disease (respiratory rate of >30 breaths per minute, an oxygen saturation < 93% while the patient was breathing ambient air, or both)
    - 13/80 patients (16%) who received convalescent plasma developed severe respiratory disease, compared to 25/80 (31%) who received placebo (relative risk, 0.52; 95% CI, 0.29 to 0.94)
    - Donor titers at or above a median titer of 1:3200 showed a relative risk reduction of 73.3% compared to placebo
- Combined secondary end point (any of life-threatening respiratory disease, critical systemic illness, and death) occurred in 7 patients (9%) in the treatment arm and 12 (15%) in the placebo arm
- No solicited adverse events were observed
- Limitations: Small study; low statistical power to detect secondary end points or long-term outcomes; uncertain generalizability to younger patients or those without comorbidities; trial had to be stopped early due to decreasing numbers of cases in the area
- Implications: Convalescent plasma from recovered COVID-19 patients with high titers of antibodies against SARS-CoV-2 can reduce progression to severe illness if administered to older infected patients within 3 days after onset of symptoms

See also: Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19. Joyner et al. NEJM. 13 Jan 2021.

- Retrospective registry-based study of 3,082 patients. A lower risk of death within 30 days in the high-titer group than in the low-titer group was observed among patients who had *not* received mechanical ventilation before transfusion (relative risk, 0.66; 95% CI, 0.48 to 0.91); no benefit was observed among patients who had received mechanical ventilation
    - This observational study supports a potential benefit of high-titer convalescent plasma among patients who are not severely ill

See also: Trial of COVID-19 blood plasma finds no benefit in severely ill patients and Covid: 'Convalescent plasma no benefit to hospital patients'

- REMAP-CAP trial testing convalescent plasma in severely ill COVID-19 patients requiring intensive care and convalescent plasma arm of Recovery trial stopped due to lack of benefit in reducing death rates or decreasing number of days patients needed intensive care. The REMAP-CAP trial will continue to recruit hospitalized COVID-19 patients who are moderately ill but not in intensive care.

VACCINE RESEARCH

5. **Interim Results of a Phase 1–2a Trial of Ad26.COV2.S Covid-19 Vaccine (Johnson & Johnson vaccine)** Sadoff et al. NEJM. 13 Jan 2020.

- Interim results from the randomized, double-blind, placebo-controlled, phase 1–2a trial (COV1001), which randomized healthy adults between the ages of 18 and 55 years (cohort 1, n=402) and those 65 years of age or older (cohort 3, n=403) to receive the Ad26.COV2.S vaccine at a dose of 5×10^{10} viral particles (low dose) or 1×10^{11} viral particles (high dose) per milliliter or placebo in a single-dose or two-dose schedule (56 days apart) across 12 sites in the US and Belgium
    - Ad26.COV2.S is a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector encoding a full-length and stabilized SARS-CoV-2 spike (S) protein
    - Total of 5 study groups: low dose followed by low dose, low dose followed by placebo, high dose followed by high dose, high dose followed by placebo and placebo followed by placebo
    - Primary end points: safety and reactogenicity of each dose schedule; secondary end point: humoral and cellular immunity to the SARS-CoV-2 S protein
- Safety: Most frequent adverse events were fever, fatigue, headache, and myalgia
    - In cohort 1 (age 18-55y), solicited systemic adverse events after the first dose were reported in 65% of low-dose recipients, 84% of high-dose recipients, and 26% of placebo recipients (26%); corresponding percentages in older cohort 3 (age 65+), were 46%, 55%, and 23%, respectively
    - Safety data after second dose was available for 363 participants in cohort 1: the incidence of grade 3 solicited systemic adverse events was *lower* than after the first immunization in both the low-dose and high-dose groups; this is in contrast to higher reactogenicity of mRNA vaccines after second dose
- Humoral immunogenicity: Regardless of vaccine dose, neutralizing antibody titers (IC_{50}) measured in a random subgroup of participants in cohorts 1 and 3 showed wide variability, but were detected in ≥90% of participants at day 29 after the first dose and in 100% by day 57
    - Titers remained stable until day 71, but second dose provided an increase in the titer
    - Titers were lower in older than younger patients
    - Unclear whether neutralizing antibody titers were higher than those in human convalescent serum, particularly for cohort 3
- On day 14, CD4+ T-cell responses were detected in 76-83% of participants in cohort 1 and in 60-67% of those in cohort 3, and skewed toward type 1 helper T cells
    - CD8+ T-cell responses were robust overall but lower in cohort 3
- Limitation: Poor representation of minorities in study population; small sample sizes in subgroups by cohort and treatment regimen, particularly for humoral response data for cohort 3
- Implications:
    - Systemic adverse events were less commonly reported in the older cohort and in those who received the low dose vaccine
    - Single dose elicited strong and durable humoral response in a majority of participants
    - Phase 3 efficacy trials are underway, and cohort 2 has been enrolled to collect longer-term data comparing a single-dose regimen with a two-dose regimen, although the second dose did appear to enhance responses

IMMUNOLOGY

6. Circuits between infected macrophages and T cells in SARS-CoV-2 pneumonia. Grant et al. Nature. 11 Jan 2021.

- Bronchoalveolar lavage samples (BAL) from SARS-CoV-2 patients (88) and patients with non-COVID-19 pneumonia or intubated for other reasons (211) were analyzed by flow cytometry & bulk transcriptomic profiling; some samples from patients with severe COVID-19 (10) were analyzed by single cell RNA sequencing. All samples were from patients requiring mechanical ventilation

- Patients with SARS-CoV-2 pneumonia had longer stays in the ICU; had increased levels of CRP (other markers of inflammation were similar); mortality was not different between SARS-CoV-2 pneumonia and the entire cohort
- Flow cytometry data from BAL after intubation (day 1) suggests that COVID-19 pneumonia patients have < neutrophils, but significant enrichment of CD4+ T cells, CD8+ T cells and monocytes compare to pneumonias caused by other infections; PMN more predominant later if secondary infection
- RNAseq was performed on isolated alveolar macrophages comparing these cohorts; there is relative increased expression of genes involved in the response to IFN and chemokines (this pattern persisted in samples >48 h after intubation also) in COVID-19 samples
- Positive- and negative-strand SARS-CoV-2 transcripts were detected in epithelial cells, migratory CCR7+ dendritic cells, monocyte-derived alveolar macrophages (MoAM2) and tissue-resident alveolar macrophages (TRAM2-do not express ACE2)
- Single-cell RNAseq allowed for examining the transcription program in infected v. uninfected cells
    - tissue-resident alveolar macrophages (TRAM ACE2-) cells when infected expressed higher levels of chemokines *CCL2, CCL20, CXCL10* and *CXCL11*; *IL1B*, *DEFB1* and interferon-response genes.
- Limitations: While a model of alveolar macrophages driving T cell recruitment and IFNg production is proposed, how individual cell types contribute cannot be ascertained without more data; how TRAM cells become infected with SARS-CoV-2 is not clear if they are ACE2 negative
- Implications: Alveolar macrophages harbor SARS-CoV-2 and they may support viral replication (has been reported for SARS-CoV and MERS-CoV); the authors propose a model whereby SARS-CoV-2 pneumonia is a slowly progressive, spatially restricted infection in the alveolar spaces by infected macrophage recruiting pro-inflammatory T cells