**Summary of Major Literature Related to COVID-19 (Jan 19-Feb 8)**

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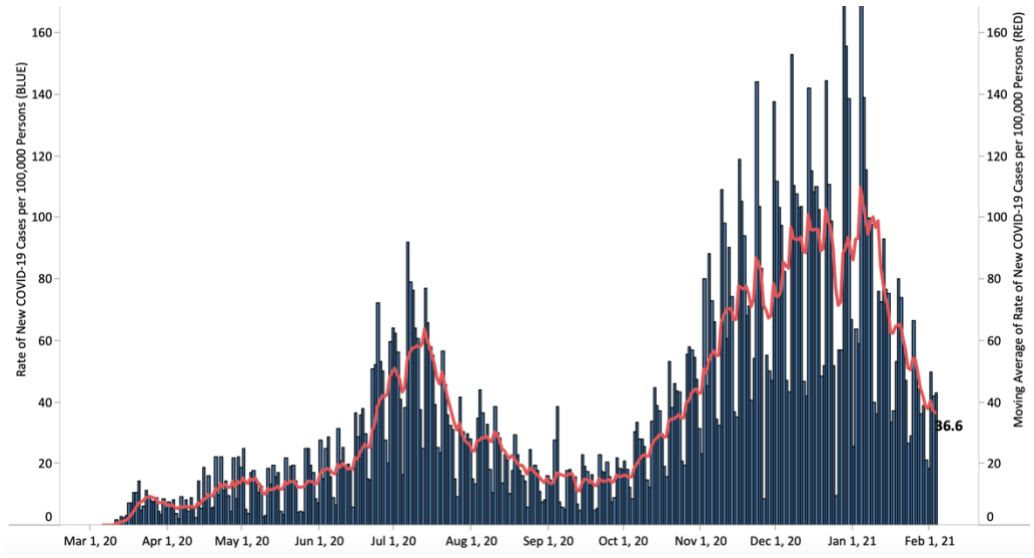
***This is informational and not intended to create variance from VUMC policies/guidance.**

## STATISTICS – Daily new cases per 100,000 population

### Tennessee


### Davidson county




As of Feb 8, 2021, in TN:

- Total cases = 745,826
- Active cases = 28,162
- Total deaths = 10,566
- Beds availability = 18%
- ICU availability = 15%
- Test positivity 7-d = 11%

Davidson county:

- Total cases = 86,648
- Active cases = 3,348
- Total deaths = 601
- Beds availability = 19%
- ICU availability = 14%
- Test positivity 7-d = 7%

Demographics:

| Groups | No. of Cases | No. of Deaths |
|---|---|---|
| By sex | | |
| Female | 395,731 | 4,881 |
| Male | 344,466 | 5,682 |
| By race/ethnicity | | |
| White | 450,289 | 7,882 |
| Black | 94,162 | 1,795 |
| Hispanic | 46,347 | 283 |
| Asian | 6,432 | 55 |
| Other | 61,185 | 363 |
| By age | | |
| 0–10 | 39,370 | 4 |
| 11–20 | 93,938 | 4 |
| 21–30 | 135,365 | 42 |
| 31–40 | 115,649 | 100 |
| 41–50 | 111,015 | 331 |
| 51–60 | 104,782 | 870 |
| 61–70 | 75,791 | 1,908 |
| 71–80 | 45,192 | 3,232 |
| 80+ | 23,678 | 4,075 |

## TN COVID-19 Vaccination Reporting

**9 Feb 2021**

| Total Vaccinations Reported | Vaccinations Reported on 2/8/2021 | Vaccinations Reported Since 2/1/2021 | % of People Statewide With at Least One Dose |
|---|---|---|---|
| 848,930 | 9,089 | 165,212 | 8.53% |

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 | 317,089 | 265,146 |
|---|---|---|

| Age Group | People Vaccinated | % of People Vaccinated |
|---|---|---|
| 16-20 years | 3,391 | 0.58 |
| 21-30 years | 46,386 | 7.97 |
| 31-40 years | 59,685 | 10.25 |
| 41-50 years | 64,045 | 11.00 |
| 51-60 years | 70,129 | 12.04 |
| 61-70 years | 67,833 | 11.65 |
| 71-80 years | 165,770 | 28.47 |
| 81+ years | 104,927 | 18.02 |
| Pending | 69 | 0.01 |
| Total | 582,235 | 99.99 |

| Patient Race | People Vaccinated | % of People Vaccinated |
|---|---|---|
| Asian | 6,212 | 1.11 |
| Black or African American | 40,121 | 6.58 |
| White | 398,592 | 69.23 |
| Other/Multiracial | 56,516 | 9.01 |
| Unknown | 80,794 | 14.06 |
| Total | 582,235 | 99.99 |

Note: An update was made to how data were being categorized, causing a decrease for the Other/Multiracial category. Individuals with multiple races where one was "Unknown" were removed from this category.

## EPIDEMIOLOGY

### Asymptomatic COVID-19

1. **Follow-up of SARS-CoV-2 Positive Subgroup from the Asymptomatic novel CORonavirus iNfection (ACORN) Study.** Meyers et al. J Med Virol. 19 Jan 2021**.**

- Longitudinal study nested within the community-based Asymptomatic novel CORonavirus iNfection (ACORN) study followed 86 participants who initially presented as asymptomatic for COVID-19 but who tested positive for SARS-CoV-2
    - Follow up for at least 14 days to assess symptom development and duration of positive RT-PCR test results
- 19 (22.1%) developed at least one symptom after the initial positive test
    - Median time to symptom development was 6 days (range 1-29)
    - Most frequently reported symptoms were fatigue or muscle aches (10.5%), headache (9.3%), fever (5.8%), shortness of breath (5.8%); no hospitalizations were reported
- Among 78 who were tested at Day 14, 17 (22%) remained positive; of these, 4 remained positive at Day 28
    - Viral loads were generally low throughout follow-up among those with asymptomatic infection
- Limitations: Potential selection bias as cohort was young, mostly White, and with over 95% self-reporting good/excellent health, and had access to COVID-19 knowledge and testing; symptoms reported were generally mild and non-specific
- Implications: Broad testing programs, as opposed to reliance on symptoms, are needed for slowing transmission

2. **Effect of Discontinuing vs Continuing Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers on Days Alive and Out of the Hospital in Patients Admitted With COVID-19.** Lopes et al. JAMA. 19 Jan 2021**.**

- There have been conflicting mechanistic hypotheses and observational findings regarding effect of ACEIs and ARBs on patients with COVID-19
- Multi-site, registry-based, open-label randomized clinical trial in Brazil (BRACE CORONA) of 659 patients hospitalized with mild to moderate COVID-19 who were taking ACEIs or ARBs prior to hospitalization
    - Randomized to discontinue (n=334) or continue (n=324) ACEI/ARBs for 30 days
    - Median age was 55.1 years (IQR, 46.1-65.0), 14.7% were aged 70+ years, 40.4% were women, and 52.2% were obese; 100% had hypertension and 1.4% had heart failure
    - 16.7% were taking an ACEI and 83.3% were taking an ARB for a median of 5 years (IQR, 3-8 years) prior to randomization
- Median time from symptom onset to hospital admission was 6 days (IQR, 4-9 days) and 27.2% of patients had an oxygen saturation of less than 94% of room air at baseline
    - 57.1% of patients were considered mild and 42.9% moderate severity at hospital admission
- Primary outcome:
    - No significant difference in mean number of days alive and out of the hospital for patients randomized to discontinue use of ACEIs or ARBs (21.9 days; SD, 8.0 days) vs those randomized to continue use (22.9 days; SD, 7.1 days)
- Secondary outcomes: There was no statistically significant difference in
    - death (2.7% for the discontinuation group vs 2.8% for the continuation group); OR 0.97 (95% CI, 0.38-2.52]
    - cardiovascular death (0.6% vs 0.3%, respectively); OR 1.95 (95% CI, 0.19-42.12)
    - COVID-19 progression (38.3% vs 32.3%, respectively); OR 1.30 (95% CI, 0.95-1.80)

- Limitations: Open label study; the study did not collect data on race, ethnicity, COPD, immunosuppression or use of mineralocorticoid receptor antagonists
- Implication: These findings do not support routinely discontinuing ACEIs or ARBs among patients hospitalized with mild to moderate COVID-19 if there is an indication for treatment

## VACCINE RESEARCH

3. **Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia.** Logunov et al. Lancet. 2 Feb 2021.

- Interim clinical efficacy results of the heterologous recombinant adenovirus rAd26 and rAd5 vector-based COVID-19 vaccine Gam-COVID-Vac (**Sputnik V**)
  - Randomized, double-blind, placebo-controlled phase 3 trial at 25 hospitals/clinics in Moscow
  - Participants aged ≥18 years with negative anti-SARS-CoV-2 IgM and IgG antibody and SARS-CoV-2 PCR tests and no history of COVID-19
  - rAd26 and rAd5 both carry the gene for SARS-CoV-2 full-length glycoprotein S and are administered intramuscularly (0.5 mL/dose) separately with a 21-day interval.
- 21,977 adults were randomly assigned to the vaccine group (n=16,501) or the placebo group (n=5,476); 14,964 and 4,902 received two doses of vaccine or placebo, respectively, and were included in this interim primary outcome analysis
  - 61% male, 98.5% White, mean age 45.3 years, ~11% age >60y
- Primary outcome: proportion of participants with PCR-confirmed COVID-19 from day 21 after receiving the first dose
  - Vaccine efficacy was 91.6% (95% CI 85.6 - 95.2%), with 16 cases confirmed in the vaccine group (0.1%) vs 62 cases in the placebo group (1.3%)
  - Efficacy was greater than 87% in all age and sex subgroups, including efficacy of 91.8% (67.1–98.3%) in participants older than 60 years
- Secondary outcome: severity of COVID-19
  - Vaccine efficacy against moderate or severe COVID-19 was 100% (94.4–100.0%), with 0 cases (vaccine group) and 20 cases (placebo group) of moderate or severe COVID-19 confirmed at least 21 days after dose 1
  - From day 15 to 21 after dose 1, efficacy was 73.6%

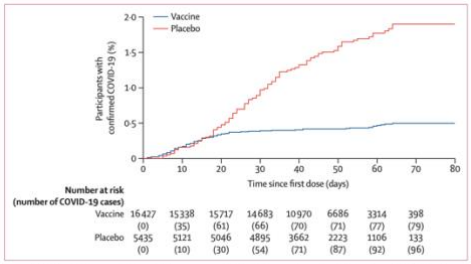


*Figure 2:* Kaplan-Meier cumulative incidence curves for the first symptomatic, PCR-positive COVID-19 after dose 1, in participants who received at least one dose of vaccine or placebo

- Adverse events:
  - 94% (7485/7966) of reported adverse events were grade 1
  - 0.3% and 0.4% of participants in the vaccine group and placebo group, respectively, had serious adverse events, and four deaths were reported during the study (<0·1% in both groups), none of which was considered related to the vaccine
- Humoral immune response (42 days from start of vaccination):
  - In the vaccine group, antibodies specific to the receptor-binding domain (RBD) of SARS-CoV-2 glycoprotein S (measured by ELISA) were detected in 336 (98%) of 342 samples, with a geometric mean titer (GMT) of 8996, and a seroconversion rate of 98.25%; in the placebo group, RBD-specific IgG was detected in 17 (15%) of 114 samples, with a GMT of 30.55, and a seroconversion rate of 14.91% (p<0·0001 *vs* vaccine group)
  - GMT of neutralizing antibodies (measured by neutralization assay with 100 $TCID_{50}$) was significantly higher in the vaccine group (44.5, N=72) than the placebo group (1.6, N=28); similar response across age groups

- Limitations: Virtually all participants were White; small sample size within age strata; median follow-up time was 48 days after first dose so duration of protection could not be assessed
- Implications:
    - Interim analysis of Gam-COVID-Vac vaccine showed >91% efficacy and robust humoral response, including among those age >60 years
    - Divergence of cumulative incidence curves around day 16-18 after the first immunization suggest partially protective effect after a single dose, but no conclusions can be drawn from this study

**Vaccination progress**

4. **COVID-19 Vaccination Intent, Perceptions, and Reasons for Not Vaccinating Among Groups Prioritized for Early Vaccination — United States, September and December 2020.** Nguyen et al. MMWR. 9 Feb 2021.

- Results of household panel surveys conducted among a nationally representative sample of US adults aged ≥18 years in Sept (n=3,541) and Dec (n=2,033) 2020 to examine perceptions towards COVID-19 vaccines
- Vaccination intent (defined as being absolutely certain or very likely to be vaccinated) increased from 39.4% to 49.1% overall from Sept to Dec
    - Largest increase was observed among adults aged ≥65 years (from 49.1% to 66.2%)
    - Observed increases also among essential workers (from 37.1% to 45.9%), and among adults aged 18–64 years with underlying medical conditions (from 36.5% to 41.8%)
- While vaccination non-intent decreased across most socioeconomic groups, younger adults, women, non-Hispanic Black individuals, adults living in nonmetropolitan areas, and those with lower educational attainment, with lower income, and without health insurance were most likely to report *lack of intent* to receive COVID-19 vaccine
    - Most frequently cited reasons were concerns about side effects and safety (29.8%), planning to wait to see if the vaccine is safe and consider receiving it later (14.5%), lack of trust in the government (12.5%), and concern that COVID-19 vaccines were developed too quickly (10.4%)
- Limitations: Most respondents were different for the two panels so longitudinal examination of changes in perception were not possible; respondents may not be representative of US population nationally or at state/local levels
- Implications: Although increased confidence in COVID-19 vaccines is encouraging, additional efforts to tailor messages to certain subpopulations are needed to ensure high and equitable vaccination

5. **Demographic Characteristics of Persons Vaccinated During the First Month of the COVID-19 Vaccination Program — United States, December 14, 2020–January 14, 2021.** Painter et al. MMWR. 1 Feb 2021.

- During Dec 14, 2020 - Jan 4, 2021, 12,928,749 persons in the US received at least one dose of COVID-19 vaccine
    - Represents 5% of US population aged ≥16 years
    - Data on sex were reported for 97.0%, age for 99.9%, and race/ethnicity for 51.9%
- Among persons who received the first vaccine dose and had reported demographic data:
    - 63.0% were women
    - 55.0% were aged ≥50 years
    - 60.4% were non-Hispanic White, 11.5% Hispanic/Latino, 6.0% Asian, 5.4% Black, 2.0% AI/AN, and 0.3% NH/PI, and 14.4% multiple or other race/ethnicity

- Limitation: Unknown proportions of priority groups (health care personnel, long-term care facility residents) among early vaccine recipients overall or by jurisdiction; data on neighborhood or community deprivation are not considered; missing data on race/ethnicity for almost half of vaccinations
- Implications: Demographic distribution may reflect *in part* the make-up of health care personnel and long-term care facility residents in the Phase 1a priority group; however, more complete real-time reporting of race/ethnicity and other community-level data is critical to detect and address disparities in distribution of COVID-19 vaccines
- **See also**: **Early COVID-19 First-Dose Vaccination Coverage Among Residents and Staff Members of Skilled Nursing Facilities Participating in the Pharmacy Partnership for Long-Term Care Program — United States, December 2020–January 2021.** Gharpure et al. MMWR. 1 Feb 2021**.**
    - Among 11,460 SNFs with at least one vaccination clinic conducted during the first month of the CDC Pharmacy Partnership for Long-Term Care Program, a median of 77.8% of residents and 37.5% of staff members received ≥1 vaccine dose; need to address barriers to vaccination among LCTF staff members

**IMMUNE RESPONSE**

6. **Immunological characteristics govern the transition of COVID-19 to endemicity.** Lavine et al. Science. 12 Jan 2021**.**

- Estimates of immunological and epidemiological parameters for endemic HCoVs were used to develop a model for endemic transmission of a virus with severity based on age of host
    - The model incorporates different components of immunological protection with respect to susceptibility, pathology and infectivity ($IE_S$, $IE_P$ and $IE_I$) and their different rates of waning
    - The derivation of the model (to be similar to SARS-CoV-2) included short $IE_S$, high $IE_P$ and moderate $IE_I$- representing susceptibility to reinfection possible within 1 year but reinfection pathology would be mild, and the virus is expected to be cleared more rapidly
- Mean age of primary infection of endemic HCoVs is 3.4-5.1 years (based on IgM titers); this may suggest high Ro, waning sterilizing immunity, significant transmission from reinfection of older individuals in the population
- This model predicts that at the beginning of an outbreak, age distribution would mirror the population and then after steady state, only new cases would be in babies and young children with low CFR and infection fatality ratio (IFR); further predicts that overall IFR will drop significantly as moves into endemicity
- Frequent boosting of immunity by ongoing virus circulation may be required to maintain protection from pathology and for the development of endemicity
- If the vaccine induces $IE_s$ and $IE_P$ immunity than the endemic regime may happen more quickly; the model predicts once endemic state is reached mass vaccination may no longer be necessary
- Limitations: This is a model based on endemic human coronaviruses and *R*o maybe quite different in different populations; may be affected by the rate of mutations and emerging variants; one assumption made is that age distribution would mirror the population at least in the US we don't know if that is occurring because testing is not widespread in children
- Implications: When weak physical distancing is practiced and the *R*o is approximately 2, the models suggest an initial peak is followed by a low-incidence endemic state after 5 to 10 *years*. A higher *Ro* would mean endemicity may be reached earlier but at the expense of more stress on the health care system and more deaths

7. **Mapping and role of T cell response in SARS-CoV-2 infected mice.** Zhaung et al. JEM. 19 January 2021**.**

- Using a mouse model for SARS-CoV-2 infection (Ad5-hACE2 transduction of C57Bl/6 or BALB/c), the SARS-CoV-2 specific T cell epitopes recognized by T helper cells and cytotoxic T cells were investigated
    - Candidate epitopes were identified by vaccinating mice with Venezuelan equine encephalitis replicon particles (VRPs) expressing SARS-CoV-2-S, SARS-CoV-2 N, SARS-CoV-2 M, SARS-CoV-2 E, ORF3a, ORF6, ORF7a, ORF8, ORF9b, and ORF9c and then screening for T cells which responded to peptide pools (this read out was focused on IFNg producing cells)
    - Several epitopes were confirmed from T cells in BALF in the SARS-CoV-2 model (8 days after intranasal inoculation); some epitopes identified in the pre-screen using the VRPs were not confirmed in the SARS-CoV-2 infected mice; only 4 dominant epitopes – one CD4+, one CD8+ per mouse stain were selected for further analysis
    - These SARS-CoV-2 specific T cells all peaked in numbers in the lung, draining lymph node, spleen and airways at 8 d.p.i.; airways had the highest frequency of these dominant epitopes
- Virus specific T cells had markers of activation, cytotoxicity and migration; they also expressed several cytokines (IFNg, TNF, IL-10 and IL-2)
- Using IFNAR (type I IFN receptor) KO BALB/c, the data indicate that Type I interferon was required for optimal T cell responses; epitope specific T cells had reduced frequency, reduced avidity and reduced cytokine production in IFNAR mice compared to WT mice (BALBc)
- Mice vaccinated with VRPs expressing only the SARS-CoV-2 epitopes were challenged with SARS-CoV-2; this T cell specific vaccination alone showed some reduction in viral titers (some epitopes had more of an impact than others)
- T cells from SARS-CoV-2 infected mice respond to a similar SARS-CoV epitopes by producing cytokine, but do not respond to MERS-CoV epitopes therefore some cross-reactivity exists
- Limitations: The frequency of these epitope 'dominant' T cells is highest in the airways, but the screening method was performed on BALF so it is biases towards cells that would be dominant in the airways and IFNg producing; Severity of disease in this mouse model is still mild- (& expression of ACE2 is transient) - only representative histological images are presented when discussing severity of disease (it is not quantitative); limited focus on 2 epitopes/mouse background
- Implications: A critical role for T cells has been described in many models; this manuscript demonstrates that the tools can be developed to address the functionality of T cells and the durability of their responses over time

## VIROLOGY/PATHOGENESIS

**8. Neuroinvasion of SARS-CoV-2 in human and mouse brain.** Song et al. JEM. 12 Jan 2021.

- 3 approaches were used to investigate the capacity of SARS-CoV-2 to infect the brain
- Using brain organoids (*in vitro*) it was demonstrated that SARS-CoV-2 can infect organoids; can be blocked with anti-ACE2 blocking Ab; CSF-containing antiviral antibodies blocked SARS-CoV-2 infection in organoids
    - Changes in gene expression related to cell division, organelle fission, and metabolic processes
    - Cell death is common in infected organoids (but a majority of dying cells are not infected)
    - No type I IFN detected
- Transgenic mice expressing human ACE2 were infected intranasally with SARS-CoV-2 and neuroinvasion of the virus was observed; vascular remodeling was observed in infected regions
- Expression of hACE2 was then directed to the brain of mice with intracisternal delivery of adenovirus associated virus vector (AAV-hACE2) followed by an intraventricular administration of SARS-CoV-2; this model of infection led to weight loss and death at a challenge dose 100x lower than that used to induce disease with intranasal route

- SARS-CoV-2 was detected in cortical neurons in the brains of patients who died of COVID-19; pathological noted included varying stages of infarction (near regions where SARS-CoV-2 is detected) and minimal immune cell infiltrate
- Limitations: Cannot make generalized conclusion about finding Ab in the CSF of COVID-19 yet with small sample size; unknown generalizability of the small number of autopsy samples
- Implications: SARS-CoV-2 has neurotropic properties and can infect neurons in patients, but it did not invoke an immune response typical of other neurotropic viruses, i.e. ZIKA (with SARS-CoV-2 in the brain there are minimal immune infiltrates and low type I IFN)

## PASSIVE IMMUNIZATION STRATEGIES

9. **Structure-guided multivalent nanobodies block SARS-CoV-2 infection and suppress mutational escape.** Koeing et al. Science. 12 Jan 2012.

- In this study, in depth analysis was performed on 4 neutralizing monovalent nanobodies (targeting the RBD of spike) and subsequent engineered multivalent nanobodies
    - Candidate nanobodies (heavy chain-only antibodies) were the result of immunizing an alpaca and a llama with the RBD of SARS-CoV-2 spike and formalin-inactivated SARS-CoV-2
    - Candidates were screened for binding by ELISA and for their ability to neutralize using pseudotyped virus (VSV) and using a plaque reduction neutralization test
    - X-ray crystal structures of complexes of nanobodies with SARS-CoV-2 RBD demonstrates that they target distinct epitopes, for example
        - VHH E binds in an orientation different from other neutralizing nanobodies
        - VHH U, VHH V and VHH W are expected to compete with ACE2 for the RDB due to its binding location
    - Cryo-EM was performed to look at the spike complex bound to individual nanobodies
        - VHH E bound to the trimeric spike revealed that the predominant complex (61%) contained all RBDs in the up conformation; this suggests it cannot move to the down confirmation
        - VHH V revealed that the predominant complex (42%) had all three RBDs bound by VHH V with 2 RBDs in the up conformation and 1 in the down conformation
- Multivalent nanobodies targeting 2 distinct binding epitopes improved neutralizing activity by 100x
- Biparatopic nanobody fusions were created (multivalent nanobody fusions were linked by flexible linkers, capitalizing on the relatively unrestrained N- and C-termini of VHHs)
    - biparatopic VHH VE stabilized all RBDs in the up conformation, and all six VHH binding sites were occupied on the spike
    - The fusions targeting 2 distinct epitopes suppressed the emergence of escape mutants
- Limitations: These have not been assessed in vivo; what route of administration would be effective and feasible is not addressed in this study
- Implications: Nanobodies may be an alternative to conventional antibody for passive immunization. These nanobodies have diverse mechanisms of neutralization including receptor binding competition or premature activation of spike fusion machinery (in the absence of a host cell); fusing or using multivalent antibodies increases neutralization efficiency and may suppress emergence of escape mutants