Summary of Major Literature Related to COVID-19 (September 16, 2021)

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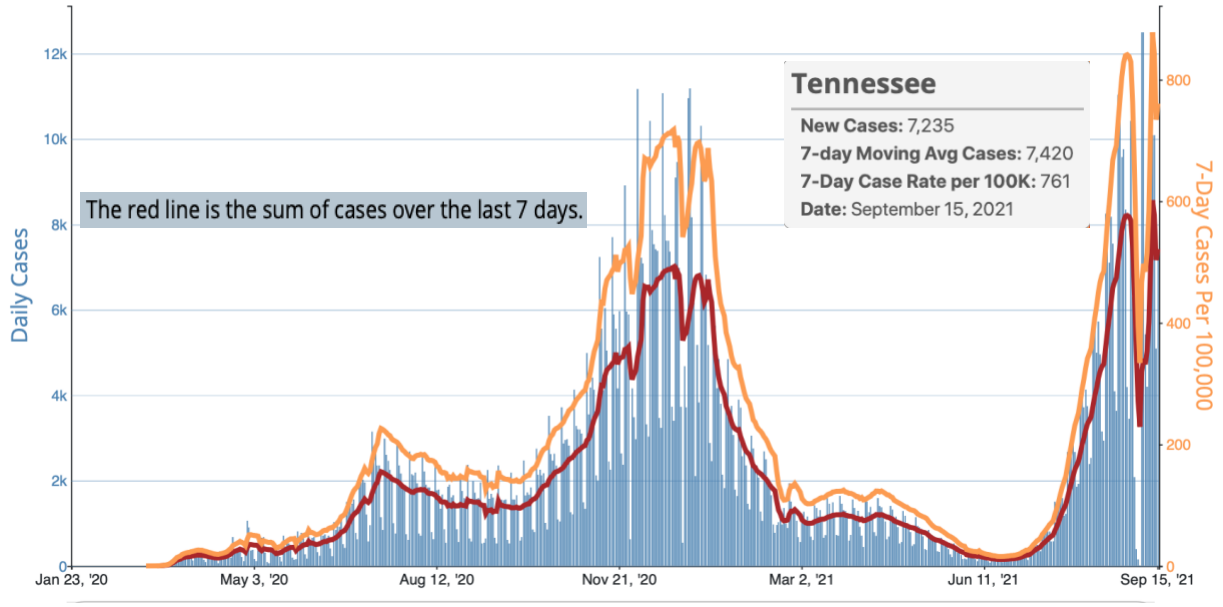
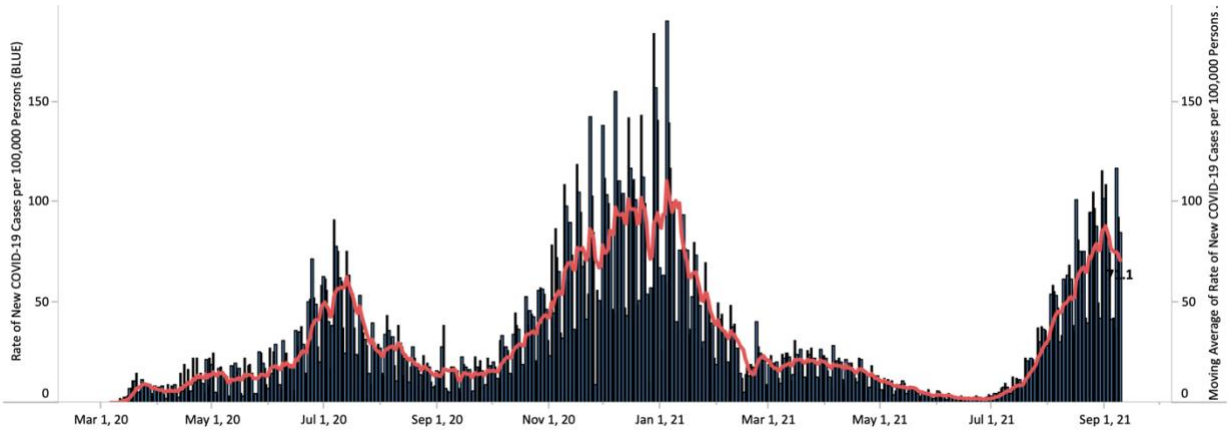
***This is informational and not intended to create variance from VUMC policies/guidance**

Tennessee

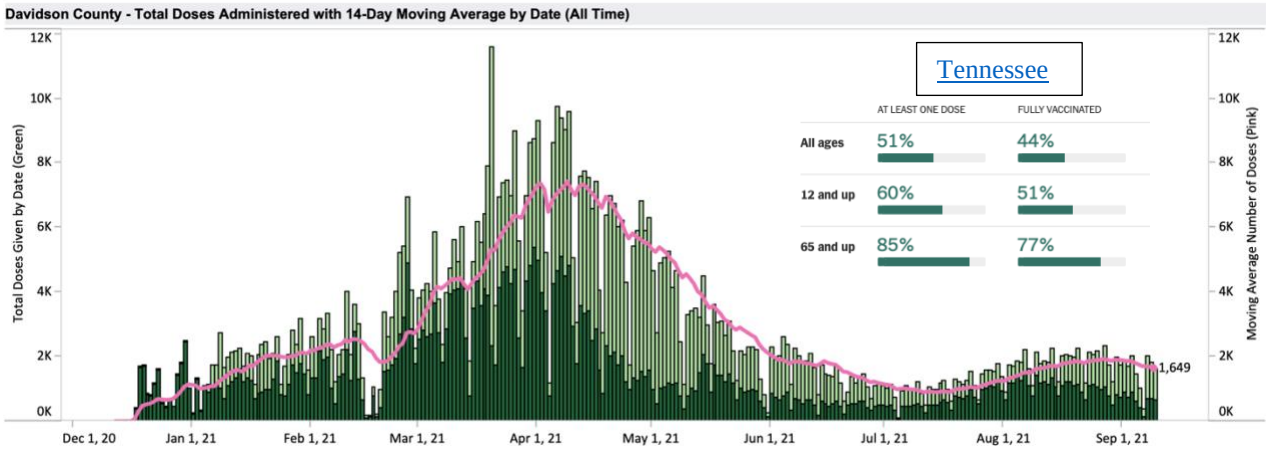
Daily Trends in Number of Cases and 7-Day Cumulative Incidence Rate of COVID-19 Cases in Tennessee Reported to CDC, per 100,000 population.



Davidson county



Davidson County Vaccination Curve

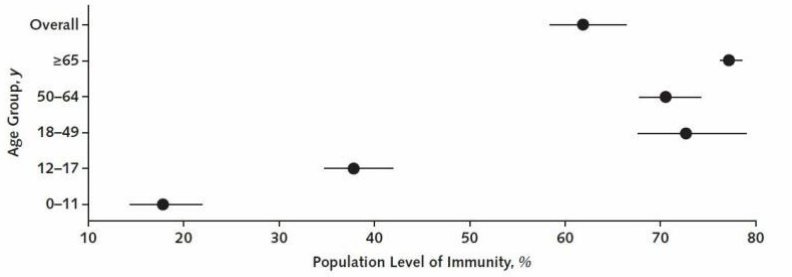


EPIDEMIOLOGY

Population immunity

1. **Population Immunity Against COVID-19 in the United States.** Moghadas et al. Ann Intern Med. 14 Sept 2021.

- Statistical and simulation modeling study to estimate the proportion of the population, overall and by age group, that is protected against SARS-CoV-2 infection due to either prior infection or vaccination
    - Used CDC-reported deaths and age-specific infection fatality rate (IFR) estimates from 21 Jan 2020 to 15 July 2021, combined with estimates of vaccine coverage (including among previously infected persons), real-world vaccine effectiveness, and naturally acquired protection against reinfection, derived from published studies and CDC
- As of 15 July 2021, 114.9 (95% credible interval [CrI], 103.2 to 127.4) million persons were estimated to have been infected with SARS-CoV-2 in the US
- Estimated mean overall population immunity was 62.0% (CrI, 58.4% to 66.4%)



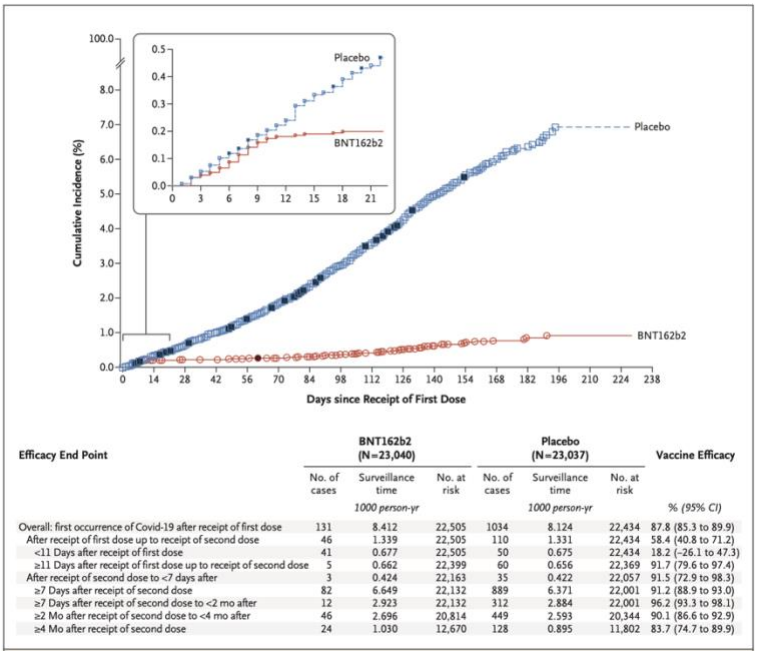
    - Adults aged 65 years or older were estimated to have the highest immunity level (77.2% [CrI, 76.2% to 78.6%])
    - Children younger than 12 years had the lowest immunity level (17.9% [CrI, 14.4% to 21.9%])
    - Similar results in sensitivity analyses, with overall population immunity ranging from ~52% to 71%, and with similar patterns of age-specific immunity
- Limitations: Geographic variation in immunity estimates is likely; as with any modeling/simulation study, many assumptions are needed, but sensitivity analyses were conducted; estimates are based on reported effectiveness of the two mRNA vaccines but not J&J vaccine; assumption that prior infection has a mean protection level of 80.5% against reinfection is not consistent across age groups
- Implications: Overall population immunity estimates, taking into account both natural infection and vaccination, are not sufficiently high to contain the pandemic or to remove mitigation behaviors; accelerated vaccination is needed, particularly in younger age groups

VACCINES

Safety/Efficacy

2. **Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine through 6 Months.** Thomas et al. NEJM. 15 Sept 2021.

- Prespecified analysis through 6 months of follow up of Pfizer-BioNTech (BNT162b2) vaccine efficacy trial; cases accrued through March 13, 2021
- Safety (N=9839 participants age ≥16y, including 364 with evidence of prior SARS-CoV-2 infection and 1656 newly enrolled after previous data cutoff)
    - Local and systemic reactogenicity and adverse events profiles were similar to previously reported
    - Vaccine recipients with previous infection reported systemic events more often after the first dose, and those without evidence reported systemic events more often after the second dose
    - New adverse events included decreased appetite, lethargy, asthenia, malaise, night sweats, and hyperhidrosis
    - No new serious adverse events or safety signals were identified during longer follow up



Efficacy End Point	BNT162b2 (N=23,040) No. of cases	Surveillance time 1000 person-yr	No. at risk	Placebo (N=23,037) No. of cases	Surveillance time 1000 person-yr	No. at risk	Vaccine Efficacy % (95% CI)
Overall: first occurrence of Covid-19 after receipt of first dose	131	8.412	22,505	1034	8.124	22,434	87.8 (85.3 to 89.9)
After receipt of first dose up to receipt of second dose	46	1.339	22,505	110	1.331	22,434	58.4 (40.8 to 71.2)
<11 Days after receipt of first dose	41	0.677	22,505	50	0.675	22,434	18.2 (−26.1 to 47.3)
≥11 Days after receipt of first dose up to receipt of second dose	5	0.662	22,399	60	0.656	22,369	91.7 (79.6 to 97.4)
After receipt of second dose to <7 days after	3	0.424	22,163	35	0.422	22,057	91.5 (72.9 to 98.3)
≥7 Days after receipt of second dose	82	6.649	22,132	889	6.371	22,001	91.2 (88.9 to 93.0)
≥7 Days after receipt of second dose to <2 mo after	12	2.923	22,132	312	2.884	22,001	96.2 (93.3 to 98.1)
≥2 Mo after receipt of second dose to <4 mo after	46	2.696	20,814	449	2.593	20,344	90.1 (86.6 to 92.9)
≥4 Mo after receipt of second dose	24	1.030	12,670	128	0.895	11,802	83.7 (74.7 to 89.9)

- Vaccine efficacy (N=42,094 age ≥12y without evidence of prior SARS-CoV-2 infection)
  - 91.3% (95% CI, 89.0-93.2) against confirmed COVID-19, based on 77 cases in vaccine group and 850 in placebo group; efficacy was virtually identical (91.1%) when analysis included those with or without prior SARS-CoV-2 infection
  - From 7 days to < 2 months after the second dose, vaccine efficacy against COVID-19 was 96.2% (95% CI, 93.3 to 98.1); from 2 months to less than 4 months after the second dose, 90.1% (95% CI, 86.6 to 92.9); and from 4 months after the second dose to the data cutoff date, 83.7% (95% CI, 74.7 to 89.9)
  - 96.7% (95% CI 80.3-99.9) against *severe disease*, based on 30 cases in placebo group and 1 in vaccine group
  - Efficacy estimates ranged from 86-100% in all subgroup analyses by age, sex, race/ethnic group, comorbidities, but some were under-powered
- Among 542 placebo recipients with positive N-binding antibodies at trial entry, 7 (1.3%) developed COVID, compared to 1015 of 21,521 (4.7%) placebo recipients without evidence of infection at trial entry, suggesting that previous infection conferred ~72.6% protection
- Limitations: No data on potential persistence of protection from single dose because 99% of participants received second dose
- Implications: Updated analyses through 6 months of follow up showed 91% vaccine efficacy of the Pfizer-BioNTech vaccine against COVID-19 and 97% efficacy against severe disease; efficacy peaked at 96% by 2 months after second dose and gradually declined but remained high (84%) at 4 months; no new safety signals were identified

Booster

3. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel. Bar-On et al. NEJM. 15 Sept 2021**.**

- Israel approved booster administration to high-risk populations on July 12 and to everyone age 60y and older on July 30
- This report presents real-world data on the effect of a third booster dose among 1,137,804 individuals 60y and older who had been fully vaccinated with BNT162b2 (Pfizer-BioNTech) at least 5 months earlier and had no confirmed SARS-CoV-2 infection prior to July 30
- Compared the rate of confirmed infection and rate of severe illness among fully vaccinated participants who had received the booster dose (booster group) and those who had received only two vaccine doses (non-booster group)
  - Used 12 days as the time window for outcome ascertainment after booster dose
  - Groups (and observation time) were dynamic, meaning participants transitioned from the non-booster group to the booster group 12 days after receiving the booster dose
  - 4439 confirmed infections (incidence rate: 85.5/100,000 person-days) and 294 cases of severe illness in non-booster group, 934 confirmed infections (8.8/100,000 p-d) and 29 cases of severe illness in the booster group
- In the (adjusted) primary analysis, the rate of confirmed infection overall was reported to be lower in the booster group than in the non-booster group by a factor of 11.3 (95% CI, 10.4-12.3)

    - However, in a secondary analysis attempting to account for behavioral biases in the two groups which may lessen with time after booster dose, the rate of confirmed infection at least 12 days after vaccination was lower than the rate after 4 to 6 days by a factor of 5.4 (95% CI, 4.8-6.1)
- The rate of severe illness was lower in the booster group than in the non-booster group by a factor of 19.5 (95% CI, 12.9 to 29.5)
    - However, among those who became infected, the proportion who developed severe illness was 6% in the non-booster group compared to 3% in the booster group, a 2-fold difference
- Limitations: Behavioral changes before and after boostering among dynamic cohorts and other potential biases may not have been fully accounted for; follow up only to day 25 so longer-term effects of boostering unknown; very wide confidence intervals for estimates beyond day 15; findings generalizable only to those ≥60y
- Implications: Evidence from this Israeli study lends support to administering boosters after 5 months to individuals 60y and older, but the true effectiveness of the booster both against *infection* and against *severe illness once infected* is likely substantially less than the factor reduction reported and the long-term effect on protection is unknown

Immune response

4. **Low-dose mRNA-1273 COVID-19 vaccine generates durable memory enhanced by cross-reactive T cells.** Mateus et al. Science. 14 Sept 2021.

- Examination to 7 months post-vaccination of CD4+ T cell, CD8+ T cell, binding and neutralizing antibody response data among 35 participants from the phase 1 trial of two doses of 25µg (low dose) Moderna mRNA-1273 vaccines given 28 days apart
- Antibody response
    - Anti-spike and anti-receptor binding domain (RBD) binding antibodies were maintained at detectable levels for at least 7 months after first vaccination for 100% of subjects
    - SARS-CoV-2 pseudovirus (PSV) neutralizing titers were detected in 100% of subjects after two vaccinations; 88% maintained detectable neutralizing antibodies for at least 6 more months
    - All three antibody measurements were highly correlated (r=0.89-0.90)
    - At 7 months, anti-spike IgG, anti-RBD IgG and PSV neutralizing titers were 6.8- to 9.5-fold lower than peak titers, and were comparable to antibodies from infected patients at similar time post-exposure
- T cell memory
    - Spike-specific CD4+ T cell responses were observed after second vaccination in 100% of subjects and were maintained 6 months later; less than twofold difference in frequencies between peak and 6 months post boost suggests durable vaccine T cell memory
    - Spike-specific memory CD4+ T cell frequencies at 7 months were similar to those observed for COVID-19 cases (170-195 days post symptom onset)
    - T follicular helper cells were detectable in 94% of subjects overall (71% and 75% after first and second vaccination, respectively) and were still detected in 63% at 7 months
    - Spike-specific CD8+ T cells were detectable in 67% of subjects 6 months after second vaccination, comparable to the response observed for COVID-19 cases
- Comparison with 100µg mRNA-1273 vaccine dose
    - Anti-spike IgG, anti-RBD IgG and PSV neutralizing titers were ~2-fold higher compared to 25µg dose
    - CD4+ T cell responses were ~1.4 to 2.0-fold higher compared to 25µg dose
    - CD8+ T cell responses were comparable between doses
- Subjects with pre-existing cross-reactive CD4+ T cell memory (17/35 25µg dose vaccinees) had:

    - Spike-specific CD4+ T cells, T follicular helper cell frequencies and anti-spike and anti-RBD IgG (but not CD8+ T cells) were significantly higher on day 15 after first vaccination
    - Significantly higher spike-specific CD4+ T cell frequencies and higher SARS-CoV-2 neutralizing titers were observed >6 months after second vaccination
- Implications:
    - Measurements of compartments of immune memory, including comparison of vaccination and natural infection, are necessary to determine durability of protective immunity
    - Low dose mRNA-1273 vaccination generated durable immune memory against spike for antibodies, CD4+ T cells, and CD8+ T cells, and may be considered for certain age strata or low-risk groups
    - Cross-reactive memory T cells may have biologic relevance for the speed and magnitude of immune responses to vaccination and/or SARS-CoV-2 infection
- Limitations: Small sample size; comparison groups from different studies (e.g. 100 μg dose, prior COVID infection) may limit direct comparisons