Summary of Major Literature Related to COVID-19 (August 18, 2021)

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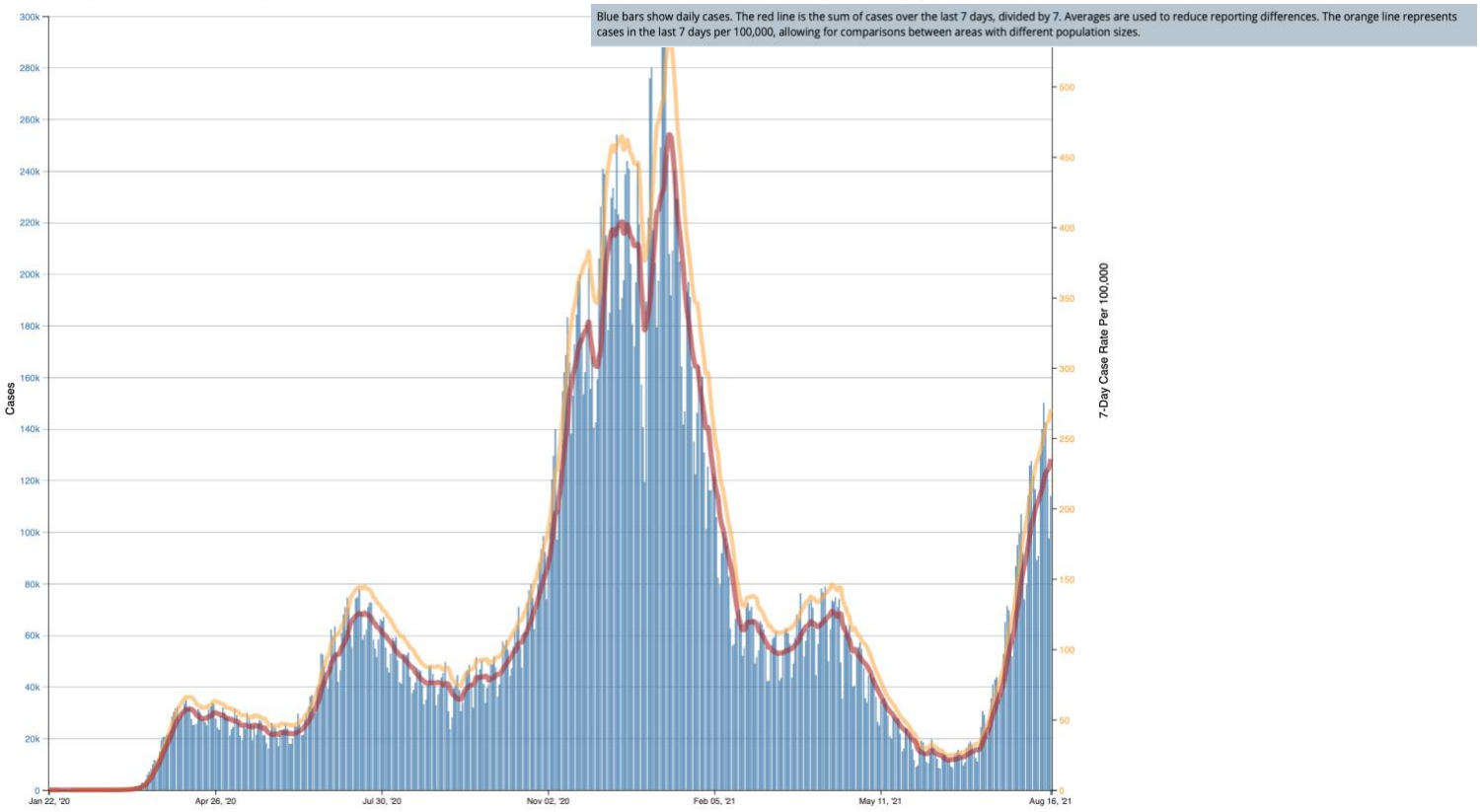
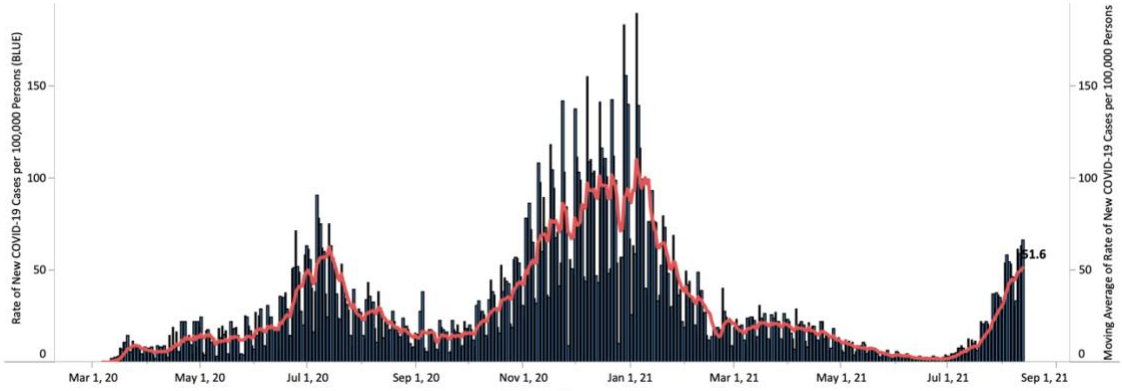
***This is informational and not intended to create variance from VUMC policies/guidance**

Tennessee

Trends in Daily COVID-19 Cases and 7-Day Cumulative Incidence Rate of COVID-19 Cases in the United States Reported to CDC, per 100,000 population



Davidson county



TN COVID-19 Vaccination Reporting

Total Vaccinations Reported	Vaccinations Reported Since 8/10/2021	% of People Statewide With at Least One Dose	% of People Statewide Fully Vaccinated
5,896,529	117,510	47.2%	40.5%

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.

Please note: The Summary Page includes all vaccinations reported to TennIIS from Tennessee providers, regardless of patient's state of residence. These numbers will differ from the Population Page, which contains data on Tennessee residents only.

Number of People with **Series Initiation** (1 dose of Pfizer / Moderna) **Series Completion** (2 doses of Pfizer / Moderna OR 1 dose of Janssen)	458,229	2,764,180

TREATMENT

Anticoagulation

1. **Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19.** The REMAP-CAP, ACTI-4a, ATTACC Investigators. NEJM. 4 Aug 2021.

- Randomized controlled trial of critically ill patients with severe COVID19 received either therapeutic -dose heparin or pharmacologic thromboprophylaxis in accordance with local usual care.
- Primary outcome was number of organ support-free days (on an ordinal scale up to 21 days where in hospital death was given a value of -1); data available for 1098 patients
- No marked difference in organ support-free days (1 (heparin) vs. 4 (usual-care), adjusted proportional odds ratio 0.83 [credible interval 0.67 to 1.03]
    - % of patients who survived to discharge was similar in the two groups
- Significant increase in major bleeding in patients who received the therapeutic-dose anticoagulation (3.8%) compared to those assigned usual-care pharmacologic thromboprophylaxis (2.3%)
- Limitations: A substantial majority of the patients who were enrolled were in the UK (practice guidelines changed during the trial to recommend that patients with COVID19 admitted to an ICU receive intermediate-dose anticoagulation for thromboprophylaxis (previously published that intermediate-dose is not superior to low-dose); open-label design
- Implications: Prophylactic dosing is as good as therapeutic dosing for critically ill COVID19 patients without the increased risk of major bleeding

Inhaled steroids

2. **Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial**. Yu et al, PRINCIPLE Trial Collaborative Group. Lancet. 10 August 2021.

- Prior evidence is inconsistent regarding benefit and potential harm of inhaled corticosteroids for COVID-19 patients with less severe illness or not admitted to hospital
- Multicenter, open-label, multi-arm randomized controlled trial in the UK
- Eligible participants were aged 65y+ or 50y+ with comorbidities, who had ongoing COVID-19 symptoms for up to 14 days but were not admitted to hospital
- Primary analysis population of participants randomly assigned to budesonide (n=787; 800 µg twice daily for 14 days), usual care alone (n=1069) and other treatments (n=974)
    - Mean age 64.2y, 92% White, 52% women, 81% had comorbidities, median duration of illness before randomization 6 days
- Co-primary endpoints at 28 days
    - Shorter time to first self-reported recovery by an estimated 2.94 days (95% CI 1.19 to 5.12) in the budesonide group (11.8 days) vs the usual care group (14.7 days), with a hazard ratio of 1.21 (95% CI 1.08 to 1.36)
    - For hospital admission or death, the estimated rate was 6.8% (95% CI 4.1 to 10.2) in the budesonide group versus 8.8% (5.5 to 12.7) in the usual care group; estimated absolute difference 2.0% (95% CI –0.2 to 4.5); odds ratio 0·75 (95% CI 0.55 to 1.03)
        - Did not meet prespecified superiority threshold
- No differences between groups in global self-rating of how patients felt at day 28 or in time to alleviation of all symptoms
- Limitations: Questionable reliability and validity of self-reported (online daily diary) time to recovery outcome due to potential placebo effect of inhalers; Longer follow up needed to examine effects on psychological well-being or long-term self-rated health; Data don't inform use in individuals <50y of age; largely unvaccinated population

- Implications: First randomized study in the primary care setting suggests that inhaled budesonide may improve time to recovery, and may also reduce hospital admissions or deaths, in people with COVID-19 who are at higher risk of complications
- **See also**: The use of inhaled corticosteroids in early-stage COVID-19. Mangin and Howard. Lancet. 10 August 2021.

VACCINES

General vaccine efficacy/effectiveness

3. **Determining the Incidence of Asymptomatic SARS-CoV-2 among Early Recipients of COVID-19 Vaccines: A Prospective Cohort Study of Healthcare Workers before, during and after Vaccination [DISCOVER-COVID-19]**. North et al. Clin Infect Dis. 7 Aug 2021.

- Prospective study of 2,247 healthcare workers before, during and after vaccination at Mass General Brigham Dec 30, 2020-April 2, 2021
    - 78% women, median age 37y, 84% White, 64% Moderna/36% Pfizer
- Weekly nasal swabs and symptom surveys; cycle thresholds, viral culture and sequencing determined for positive tests
- 19 participants (0.8%) had a positive test during the study period, 3 of whom were fully vaccinated
- Incidence was lower among those who were fully vaccinated [rate ratio 0.052 (95% CI 0.013–0.21)] and those who were partially vaccinated [rate ratio 0.11 (95% CI 0.040–0.30)], compared to those who were unvaccinated at the time of the positive test

eTable 3. Incidence of SARS-CoV-2 infection and vaccination status

Vaccination Status	*Total Participants*	*No. (%) positive tests*	*Observation Time*			*Incidence metrics*	
			Person days	*Person years*	*Median observation time per participant [IQR]*	*Rate per 1000 person years [95% CI][a]*	*Incidence Rate Ratio [95% CI][b]*
Before vaccination	593	6 (1.01)	3,289	9.0	5 days [3, 6]	666.3 [244.5, 1450.3]	REF
Partial vaccination	2036	10 (0.49)	50,159	137.3	26 days [15, 36]	72.8 [34.9, 133.9]	0.11 [0.040, 0.30][c]
Full vaccination	1923	3 (0.16)	31,661	86.7	17 days [12, 22]	34.6 [7.1, 101.1]	0.052 [0.013, 0.21][c]

- Two of 3 (67%) infections that occurred afer full vaccination were asymptomatic, compared with 4/10 (40%) infections in the partial vaccination period and 1/6 (17%) before vaccination (p=0.39)
- Cycle thresholds (CT) were available for 17/19 positive tests and did not differ significantly between those who tested positive before and after vaccination
- Virologic sub-study of 7 participants with positive tests
    - 4 asymptomatic, 3 symptomatic; all in partially or fully vaccinated period
    - All 4 individuals with asymptomatic infections had undetectable viral loads a median of 2 days (IQR 2,2) after their positive test and none had culturable virus at that time
    - 2 of 3 participants with symptomatic infection had prolonged viral shedding and culturable virus up to 7 days after initial positive test
- Limitation: Small sample size; follow up only until 8 weeks after first vaccine dose; young population
- Implications:
    - ~20-fold decrease in incidence of SARS-CoV-2 infection after vaccination
    - Results are suggestive of shorter duration of viral shedding in asymptomatic post-vaccination infections, but require confirmation
- ***See also***: Covid-19 Breakthrough Infections in Vaccinated Health Care Workers. Bergwerk et al. NEJM. 28 July 2021.
- Evaluation of 1497 fully vaccinated Israeli healthcare workers with symptomatic infection or known infection exposure

4. **Vaccine effectiveness against SARS-CoV-2 transmission and infections among household and other close contacts of confirmed cases, the Netherlands, February to May 2021**. De Gier et al. Euro Surveill. 5 August 2021.

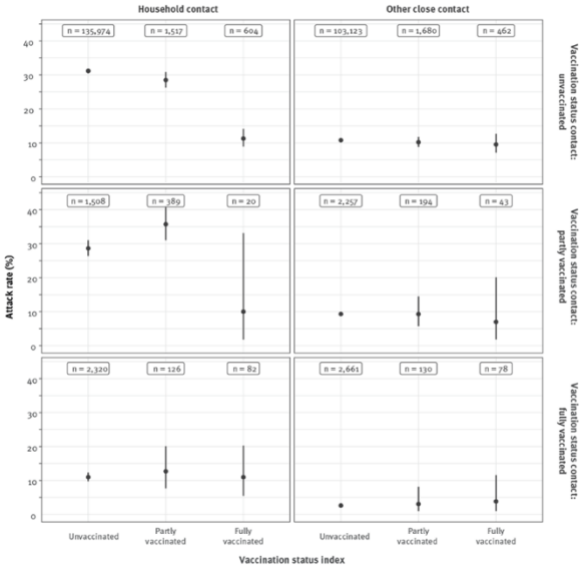
- Routine contact tracing and monitoring data were used to estimate vaccine efficacy against transmission (VET, calculated using secondary attack rate among close contacts) and vaccine efficacy against infection (VE) among household and other close contacts of confirmed cases of SARS-CoV-2 infections
- Study population:
    - 113,582 index cases; 622 (0.5%) full vaccinated and 2,088 (1.8%) partly vaccinated
    - 253,168 contacts; 5,397 (2.1%) fully vaccinated and 4,411 (1.7%) partly vaccinated
    - Included index cases 18y+ only, but contacts aged 0-17y were included in VET analyses

Vaccine efficacy against transmission

- Overall secondary attack rate was 31% among household contacts of unvaccinated index cases and 11% among household contacts of fully vaccinated index cases
- Adjusting for age of index and contact, vaccination status of the contact, and month, the VET to household contacts after full vaccination was 71% (95% CI 63 to 77)
- Transmission to an unvaccinated (Figure, top left panel) or partially vaccinated (middle left panel) household contact is substantially decreased if index case is vaccinated; if household contact is fully vaccinated, then vaccination status of index case is less important (bottom left panel)

Vaccine effectiveness among contacts

- The adjusted VE for fully vaccinated household contacts of confirmed cases was estimated at 75% (95% CI: 72 to 78) and for fully vaccinated other close contacts at 79% (95% CI: 74 to 83)
- Implication: Vaccination among adults provides strong protection against infection AND is critical in preventing spread to unvaccinated family members including children
- Limitations: Alpha variant was dominant during study period, thus applicability of results to Delta variant is unclear; relatively low proportion of study population was vaccinated leading to imprecise estimates; small sample sizes for analyses stratified by type of vaccine; incomplete information on negative tests may have led to underestimates of infection among contacts



Delta variant/duration of vaccine-induced immunity

Many recent analyses of vaccine effectiveness for the Delta variant and of potential for waning immunity have contributed to today's CDC recommendation for boosters but have not yet been peer-reviewed. These data from USA, Israel, Qatar, Canada, UK, etc will be reviewed here as they are published.

5. **New COVID-19 Cases and Hospitalizations Among Adults, by Vaccination Status — New York, May 3–July 25, 2021**. Rosenberg et al. MMWR. 18 August 2021.

- NY State Department of Health linked statewide immunization, testing and hospitalization databases to estimates rates of new cases and hospitalizations by vaccination status among adults from May 3-July

25, 2021, a period of universal adult vaccine eligibility and rising prevalence of the Delta variant from <2% to >80% of infections

- By July 25, 65.8% of New York adults aged ≥18 years were fully vaccinated and 10.4% were partially vaccinated
    - 51% Pfizer-BioNTech, 40% Moderna, 9% Janssen (Johnson & Johnson) vaccines.
- Infection:
    - A total of 9,675 new cases (1.31 per 100,000 person-days) occurred among fully vaccinated adults, compared with 38,505 (10.69 per 100,000 person-days) among unvaccinated adults
    - Overall age-adjusted VE against new COVID-19 cases declined from 91.7% to 79.8% during the study period
- Hospitalization:
    - A total of 1,271 new COVID-19 hospitalizations (0.17 per 100,000 person-days) occurred among fully vaccinated adults, compared with 7,308 (2.03 per 100,000 person-days) among unvaccinated adults
    - Overall age-adjusted VE against hospitalization was stable, ranging from 91.9% to 95.3% during the study period
- Implications: Current COVID-19 vaccines remained highly effective against hospitalization during a period of rising Delta prevalence, relaxation of restrictions, and 65% vaccine coverage; vaccine effectiveness against new infection also remained high but declines in recent months were observed

6. **Sustained Effectiveness of Pfizer-BioNTech and Moderna Vaccines Against COVID-19 Associated Hospitalizations Among Adults — United States, March–July 2021.** Tenforde, Self et al (IVY Network; **VUMC co-authors**). MMWR. 18 August 2021.

- Case-control study to evaluate duration of mRNA vaccine effectiveness (VE) against COVID-19 at 21 hospitals in 18 states from March 11-July 14, 2021
- 1,194 hospitalized COVID-19 case patients and 1,895 non-COVID hospital control patients
    - Median age 59 years, 48.7% female, 56.7% non-Hispanic White, 21.1% had immunocompromising conditions
    - 11.8% of cases and 52.1% of controls were fully vaccinated
- VE against COVID-19–associated hospitalization:
    - 86% (95% CI, 82%–88%) overall and 90% (95% CI, 87%–92%) among adults without immunocompromising conditions during the full surveillance period
    - 86% (95% CI, 82%–90%) 2–12 weeks and 84% (95% CI, 77%–90%) 13–24 weeks from receipt of the second vaccine dose (p = 0.854)
- Limitation: Follow up only to 24 weeks since full vaccination so longer duration of protection could not be assessed; only 16% of 454 sequenced samples belonged to Delta lineage so Delta-specific VE was not estimated, but VE was similar during June-July (when Delta circulation increased in US) and March-May
- Implication: High protection from mRNA vaccines against COVID-19–associated hospitalization was sustained over a 24-week period, overall and in subgroups including those at higher risk for severe COVID-19 (≥65y, immunocompromised, with multiple morbidities)

7. **Effectiveness of Pfizer-BioNTech and Moderna Vaccines in Preventing SARS-CoV-2 Infection Among Nursing Home Residents Before and During Widespread Circulation of the SARS-CoV-2 B.1.617.2 (Delta) Variant — National Healthcare Safety Network, March 1–August**. Nanduri et al. MMWR. 18 August 2021.

- Evaluation of mRNA vaccine effectiveness (VE) against infection among nursing home residents during three time periods using CDC's weekly National Healthcare Safety Network (NHSN) data
- 75% of residents were fully vaccinated with Pfizer-BioNTech or Moderna
- Total of 6879 COVID-19 cases identified
- Adjusted VE in fully vaccinated vs. unvaccinated:
    - Pre-Delta period (March 1-May 9, 2021): 74.7% (95% CI, 70.0%–78.8%)
    - Intermediate period (May 10-June 20): 67.5% (95% CI, 60.1%–73.5%)
    - Delta period (June 21-August 1): 53.1% (95% CI, 49.1%–56.7%)
- VE estimates did not differ significantly for Pfizer-BioNTech and Moderna vaccines
- Limitations: Did not distinguish between symptomatic and asymptomatic infections, and more data are needed to examine VE against severe disease in this population; Study was unable to disentangle effects of Delta variant from those of time since vaccination, as nursing home residents were among the first to be vaccinated; In the absence of individual-level data, potential for confounding by age, comorbidities, and other clinical factors cannot be ruled out; No data on staff vaccination status
- Implications: mRNA vaccines provide protection against SARS-CoV-2 infection among nursing home residents, but lower VE observed after Delta became the predominant strain in the US lends support to consideration of booster dose and continued layered prevention strategies among nursing home residents

8. **Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant**. Bernal et al. NEJM. 12 August 2021.

- Test-negative case–control study in the UK to estimate the effectiveness of vaccination against symptomatic disease caused by the Delta variant or the predominant strain; symptomatic sequenced cases of COVID19 in England were used to estimate the proportion of cases with either variant according to the patients' vaccination status
    - 19,109 sequenced cases linked to vaccine status in persons >16 yo were included in this study (14,837 were alpha variant and 4272 were Delta variant)
- Pfizer vaccine: the effectiveness of two doses was 93.7% (95% CI, 91.6 to 95.3) among persons with the alpha variant and 88.0% (95% CI, 85.3 to 90.1) among those with the Delta variant
- AstraZeneca vaccine: the effectiveness of two doses was 74.5% (95% CI, 68.4 to 79.4) among persons with the alpha variant and 67.0% (95% CI, 61.3 to 71.8) among those with the Delta variant
- Effectiveness after one dose of either vaccine was lower among persons with the Delta variant (30.7%; 95% CI, 25.2 to 35.7) than among those with the alpha variant (48.7%; 95% CI, 45.5 to 51.7)
- Limitations: This study is observational; differences among the populations that received each vaccine (i.e. clinical high risk received AZ; younger or HCW received Pfizer)
- Implications: Pfizer and AZ vaccines are highly effective against the Delta variant; two doses are important for protection against disease independent of vaccine type; VE for Pfizer vaccine against new diagnosed infections in this UK study was higher than that reported in Israel (65%) from June 20-July 17

Boosters

9. **August 16**: Pfizer and Biontech announce submission of initial data to U.S. FDA to support booster dose of COVID-19 vaccine
   August 18: Joint Statement from HHS Public Health and Medical Experts on COVID-19 Booster Shots.

- "The COVID-19 vaccines authorized in the United States continue to be remarkably effective in reducing risk of severe disease, hospitalization, and death, even against the widely circulating Delta variant...The available data make very clear that protection against SARS-CoV-2 infection begins to decrease over time following the initial doses of vaccination, and in association with the dominance of

the Delta variant, we are starting to see evidence of reduced protection against mild and moderate disease."

- Booster shots will require FDA independent evaluation and determination of the safety and effectiveness of a third dose of the Pfizer and Moderna mRNA vaccines and CDC's Advisory Committee on Immunization Practices (ACIP) issuing booster dose recommendations

10. **Antibody Response After a Third Dose of the mRNA-1273 SARS-CoV-2 Vaccine in Kidney Transplant Recipients With Minimal Serologic Response to 2 Doses**. Bentmane et al. JAMA. 23 July 2021.

- This study examined the antibody responses using the anti-receptor binding domain assay (ARCHITECT IgG II Quant Test) of 159 kidney transplant recipients who did not respond to 2 doses (< 50 AU/mL) and received a third dose (100 µg) of the mRNA-1273 vaccine [median of 51d after 2nd dose, Moderna]
- 78 patients (49%) had antibody levels greater than 50 AU/mL after the 3rd dose (measured at median of 28d [IQR 27-33d])
- Patients taking tacrolimus, mycophenolate, and steroids were less likely to develop anti–SARS-CoV-2 antibodies in response to the third dose than those treated with other regimens
- No severe adverse events were observed after the third dose
- Limitations: No assays for neutralizing antibody, B-cell memory, and T-cell responses
- Implications: A third dose of vaccine may increase spike Ab in transplant patients (this has been examined in two other studies; for more information on safety and immunogenicity, see Safety and immunogenicity of a third dose of SARS-CoV-2 vaccine in solid organ transplant recipients: a case series and Three doses of an mRNA Covid-19 vaccine in solid-organ transplant recipients.)

Immune response

11. **Rapid and stable mobilization of CD8+ T cells by SARS-CoV-2 mRNA vaccine.** Obernardt et al. Nature. 28 July 2021.

- The induction of functional spike specific-CD8+ T cells in response to the bnt162b2 (Pfizer) prime and boost vaccinations was examined and compared to other arms of immunity including neutralizing antibody and CD4+ T cell responses.
- Longitudinal assessment of PBMC and sera was done in 32 health care workers (not previously infected with SARS-CoV2) from before vaccination to 80-120 d after boost
    - Spike-specific CD8+ T effector cells detected in >1/2 of tested donors at 6-8d; peaked in most 9-12d; boost increased frequency and expression of T effector markers (Ki67, Cd38,TBET, PD-1)
    - 20-30% of spike-specific CD8+ T cells were CD127+ after prime (memory precursor marker); increased after boost and remained constant through time points
    - Functional production of IFNγ, TNF and degranulation capacity of CD8+ T cells remained stable after boost
    - Spike-specific CD4+ T cells (targeting DRB1*15:01//S_{236}) had "limited increase" and only a small percentage activated (activated TH1 phenotype)
    - Progressive maturation of the serum S1-Ab response observed IgM after prime, then S1-specific IgG detectable after boost correlated with a high neutralization capacity (plaque reduction assay); delayed appearance of circulating S1-specific B cells was confirmed by polyclonal restimulation in vitro
    - S1-specific B cells were largely producing IgM production upon polyclonal restimulation then acquired a memory phenotype after boost vaccination (also expressed transferrin receptor (CD71) and CD95)
- Neutralization capacity of post-boost sera was elevated compared to time point-matched mild infection

- Vaccine-associated spike-specific early memory CD8+ T cell populations exhibit similar capacity to expand and produce cytokines compared to natural infection- but a different subset distribution (higher frequencies of effector memory 1 T cells (TEM1) were detectable after vaccination; higher expression of TCF-1 and BCL-1 and prolonged CD38 expression after natural infection)
- Limitations: CD8+ T cell effector functions had to be assessed after ex vivo expansion (limited to 3 epitopes); CD4+ spike specific responses were limited to one epitope in only 8 subjects; other forms of immunity (e.g., non-neutralizing antibody) may contribute to protection and were not assessed in this study
- Implications: Early protection from prime vaccination (although limited) may be mediated by CD8+ T cell response; Boost vaccination is required for maturation of B cell responses and results in increased neutralization capacity compared to natural infection