**Summary of Major Literature Related to COVID-19 (Dec 22-Jan 4)**

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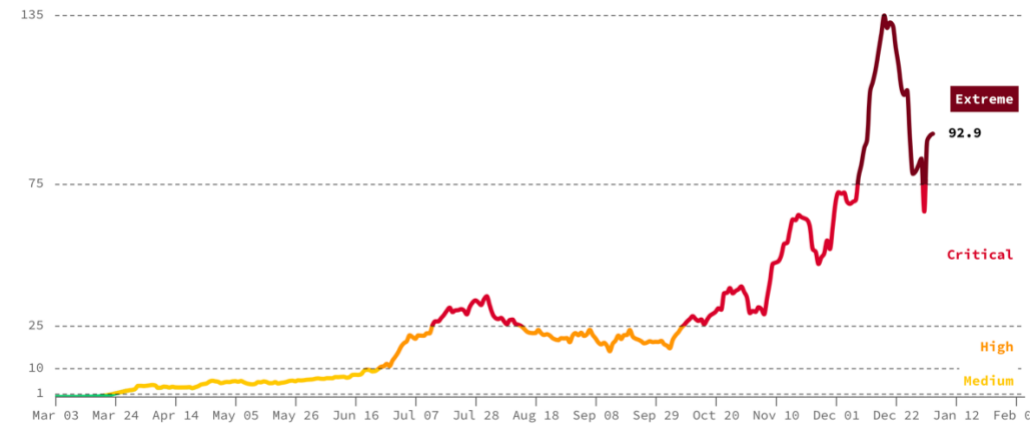
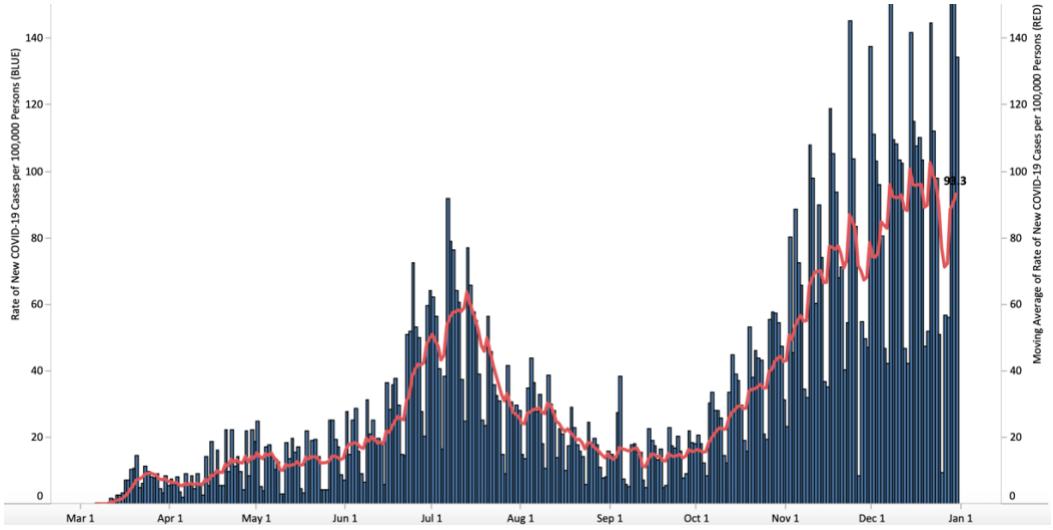
***This is informational and not intended to create variance from VUMC policies/guidance.**

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

### Tennessee




### Davidson county




As of Jan 5, 2021, in TN:

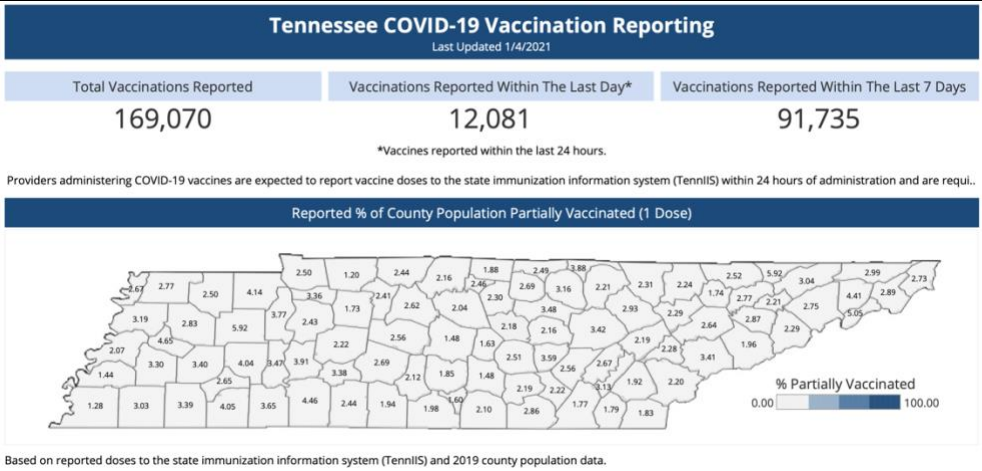
- Total cases = 617,649
- Active cases = 71,175
- Total deaths = 7,267
- Beds availability = 14%
- ICU availability = 9%
- Test positivity 7-d = 19%

In Davidson county:

- Total cases = 71,936
- Active cases = 6,684
- Total deaths = 495
- Beds availability = 12%
- ICU availability = 7%
- Test positivity 7-d = 21%

Demographics:

| Groups | No. of Cases | No. of Deaths |
|---|---|---|
| By sex | | |
| Female | 327,543 | 3,352 |
| Male | 285,002 | 3,910 |
| By race/ethnicity | | |
| White | 365,612 | 5,358 |
| Black | 78,347 | 1,311 |
| Hispanic | 40,812 | 228 |
| Asian | 4,946 | 37 |
| Other | 53,552 | 262 |
| By age | | |
| 0–10 | 31,474 | 4 |
| 11–20 | 78,029 | 3 |
| 21–30 | 112,895 | 41 |
| 31–40 | 96,462 | 73 |
| 41–50 | 92,681 | 237 |
| 51–60 | 86,401 | 626 |
| 61–70 | 61,940 | 1,307 |
| 71–80 | 37,099 | 2,206 |
| 80+ | 19,589 | 2,769 |




TN COVID-19 Vaccination Reporting

## TRANSMISSION

1. **Implications of Shortened Quarantine Among Household Contacts of Index Patients with Confirmed SARS-CoV-2 Infection — Tennessee and Wisconsin, April–September 2020.** Rolfs et al (**VUMC paper**). MMWR. 1 Jan 2021**.**

- CDC recently provided alternatives to reduce the duration of quarantine for close contacts without symptoms: 1) quarantine can end after day 10 without a test, or 2) quarantine can end after day 7 after receiving a negative test result
- An ongoing household contact study in TN and WI examined the probability of disease transmission after these shortened quarantine periods
    - among 105 index patients, 185 household contacts were enrolled, with a median of 4 days (IQR = 2–4 days) after the index patient's illness onset
- Overall, 109 (59%) household contacts had SARS-CoV-2 detected in respiratory specimens during the follow-up period, 76% within 7 days and 86% within 10 days after the index patient's illness onset
- The probability that a household contact who was *asymptomatic* and had *negative RT-PCR test results* through day 7 would become symptomatic or have a positive test result through 14 days after the index patient's illness onset was 19%; the probability decreased to 7% if the household contact remained asymptomatic with negative test results through day 10
- Implications: Although shortened quarantine may improve adherence, reducing quarantine to 7 or 10 days does not eliminate risk of spreading SARS-CoV-2; people released from a shortened quarantine should continue to monitor symptoms, avoid close contact with others, and wear a mask until 14 days

## VACCINE RESEARCH

**January 4: FDA Statement on Following the Authorized Dosing Schedules for COVID-19 Vaccines**

2. **National Trends in the US Public's Likelihood of Getting a COVID-19 Vaccine—April 1 to December 8, 2020.** Szilagyi et al. JAMA. 29 Dec 2020**.**

- Analysis of rolling biweekly survey data about COVID-19 from approximately 9,000 participants in the Understanding America Study; from April 1- Dec 8, participants were asked "How likely are you to get vaccinated for coronavirus once a vaccine is available to the public?"
- Self-reported likelihood of getting a COVID-19 vaccine declined from 74% in April to 56% in December
    - 10-20% declines were observed in all subgroups of age, gender, race/ethnicity and education
- In early December, the likelihood of getting a COVID-19 vaccine was lower among women than men (51% vs 62%) and Black vs White individuals (38% vs 59%), and higher among adults aged 65 years and older vs those 18-49 years (69% vs 51%) and those with at least a bachelor's degree vs a high school education or less (70% vs 48%)
- Limitations: Self-reported vaccine likelihood may or may not correlate with actual behavior now that vaccines are available
- Implications: Public health campaigns are critically needed to build trust and support for vaccination, and should be particularly targeted to groups such as Black individuals and those with lower educational levels

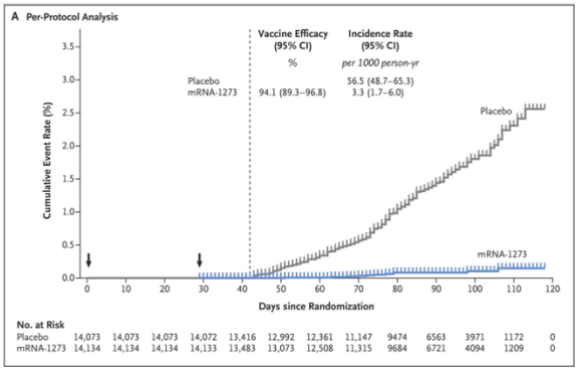
**See also: Maintaining Safety with SARS-CoV-2 Vaccines.** Castells and Phillips (**VUMC paper**). NEJM. 30 Dec 2020.

- In response to a small number of reported anaphylactic reactions following vaccination with Pfizer or Moderna mRNA vaccines, CDC has recommended exclusion of any person who has a history of severe or immediate (within 4 hours) allergic reaction associated with any of the vaccine components, including polyethylene glycol (PEG) and PEG derivatives

- "Maintenance of vaccine safety requires a proactive approach to maintain public confidence and reduce vaccine hesitancy." This 'safety roadmap' involves post-vaccination vigilance and documentation and characterization of these events, in order to heighten recognition, define causal mechanisms, identify populations at risk, and implement appropriate approaches to management and prevention.

**3.** **Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine.** Baden et al (**Creech, VUMC co-author**). NEJM. 30 Dec 2020.

- Report from the ongoing placebo-controlled, observer-blinded, Coronavirus Efficacy (COVE) phase 3 trial of mRNA-1273 vaccine candidate (**Moderna/NIAID**, 100 µg per dose). Individuals 18 years of age or older, were randomized to receive two doses, 28 days apart, of vaccine or placebo
    - Assignment was stratified based on age (<65, ≥65y) and risk for severe COVID-19 complications
    - Primary efficacy end point was efficacy of the vaccine in preventing a first occurrence of symptomatic COVID-19 with onset at least 14 days after the second dose
    - Secondary endpoints included efficacy against severe COVID-19 (needing hospitalization) and efficacy at preventing COVID-19 after a single dose
- 15,210 received mRNA-1273 and 15,210 received placebo
    - Mean age at vaccination = 51.4 years (range 18-95)
    - 47.3% were female, 24.8% were age ≥65 years, and 16.7% were age <65 years and had predisposing medical conditions that put them at risk for severe COVID-19
    - 79.2% were White, 10.2% Black or African American and 20.5% Hispanic or Latino
- Primary endpoint: 11 cases of COVID-19 were diagnosed in the vaccine group (3.3 per 1000 person-years; 95% CI, 1.7 to 6.0) and 185 cases in the placebo group (56.5 per 1000 person-years; 95% CI, 48.7 to 65.3)
    - 94.1% efficacy of the mRNA-1273 vaccine (95% CI, 89.3 to 96.8%; P<0.001) for the prevention of symptomatic SARS-CoV-2 infection (Figure)
    - Between days 1 and 42, 7 cases of COVID-19 were identified in the mRNA-1273 group compared with 65 in the placebo group (efficacy 93.0%; 95% CI, 88.9 to 95.6%)
    - Efficacy was consistent across subgroups stratified by demographic and baseline characteristics, including those over age 65y and those with prior SARS-CoV-2 infection




- Secondary endpoint: All 30 cases of severe COVID-19 were in the placebo group, and one death among these participants was attributed to COVID-19
- Interim analysis results provided to the FDA suggested vaccine efficacy of 92.1% (68.8 to 99.1%) >14 days after first dose; however, follow up was only to 28 days so no conclusions can be drawn about efficacy of one-dose strategy without longer term data
- Safety:
    - The most common injection-site event was pain (86%)
    - Solicited transient systemic adverse events occurred more often in the mRNA-1273 group than in the placebo group after both the first dose (54.9% vs. 42.2%) and the second dose (79.4% vs. 36.5%); the most common systemic events were fever, headache, and fatigue
    - Both solicited injection-site and systemic adverse events were more common among younger (18 to <65y) than older participants (≥65y)

- Frequency of serious adverse events reported throughout the trial was low and similar for mRNA-1273 and placebo (0.6% in both groups)

- Limitation: Not able to assess asymptomatic infection or viral shedding after infection
- Implications: The trial met primary efficacy endpoints, as well as the secondary endpoint of prevention of severe illness
  - Two-dose regimen of mRNA-1273 was found to be safe and 93% effective against COVID-19 illness, with a favorable safety profile
  - The trial was not designed to evaluate the efficacy of a single dose

4. **T cell and antibody responses induced by a single dose of ChAdOx1 nCoV-19 (AZD1222) vaccine in a phase 1/2 clinical trial.** Ewer et al. Nature Medicine. 17 Dec 2020.

- Results of analyses of the immune responses in adults (n=88), aged 18–55 years, up to 8 weeks after vaccination with a single dose of ChAdOx1 nCoV-19 (**AZD1222, AstraZeneca/Oxford University**)
- Phenotypic and cellular changes were assessed at 7d, 14d and 28d after vaccination in 26 persons by flow cytometry (tSNE analysis)
  - Activated, proliferating IgG+ B cells were seen at all time points, peaking at 7-14d
  - Increased expression of activation and proliferation markers CD69 and Ki67 were observed in CD4+ and CD8+ T cells (no increase in CD57 or KLRG1 in CD8+ T cells); CD4+ T cells produced TNF, IFNγ in response to restimulation with spike peptides
  - CD8+ T cells expressing the degranulation/cytotoxic function marker (CD107a) were detected
  - Non-specific stimulation of CD4+ T cells led to Th1 cytokines (IFNγ/IL-2) rather than Th2 (IL-5/13)
- Multiplex cytokine analysis (7d post-vaccination) demonstrated significant increases in IFNγ and IL-2 (a modest increase in IL-10) in PBMCs from those who received ChAdOx1 nCoV-19 vs control vaccination (MenAWY) in response to spike peptide pools (no increase in IL1β, IL12, IL-4, IL-13 and IL-18)
- Anti-SARS-CoV-2 IgG responses were detected at 14d and maintained at least to 56d
  - IgG avidity increased over time & comparable to convalescent samples by 56d
  - IgG3 responses were quantifiable in most vaccinated individuals (39-42/44); IgG1 responses were quantifiable in ~1/2 (22-24/44)
- Anti-SARS-CoV-2 IgM and IgA were also detected peaking at 14d and 28d, respectively
- PMBCs respond to pools of spike peptide by producing IFNγ in an ELISPOT assay by 14d
- No difference in the magnitude of cellular or antibody responses between males and females
- Limitations: It is still unknown what threshold and phenotype of immune responses are associated with protection; relatively small study
- Implications: Several methodologies suggest ChAdOx1 nCoV-19 induces a predominantly Th1 response (less likely to induce ADE); phase 2/3 trials are underway

5. **Randomized, Double-Blinded, Placebo-Controlled Phase 2 Trial of an Inactivated Severe Acute Respiratory Syndrome Coronavirus 2 Vaccine in Healthy Adults.** Che et al. Clin Infect Dis. 09 Nov 2020.

- Healthy adults (18-59 yo; n=742) received 2 injections of a medium dose (MD) or a high dose (HD) of the inactivated SARS-CoV-2 vaccine candidate at an interval of either 14d or 28 d
- In this trial, the inactivated SARS-CoV-2 antigen is administered adsorbed to the adjuvant aluminum hydroxide (and the placebo was $Al(OH)_3$)
- Primary endpoints:
  - Seroconversion rates of neutralizing antibody (NAb) in MD and HD groups receiving doses at 0, 14d were 92 and 96%, respectively (at 28d after immunization); NAb seroconversion was 95% for both groups receiving doses on 0, 28d schedule

    - anti-Spike (anti-S) and anti-nucleocapsid (anti-N) IgG were detected by ELISA; the 0, 14d group had seroconversion rates were near 95% for anti-S IgG and approximately 55% for anti-N IgG; the 0, 28d group had showed seroconversion rates of approximately 90% and 75%, respectively
- Secondary endpoints:
    - For 0, 14d group, overall adverse reactions occurred in 24%, 27.3%, and 17.3% of all individuals in the medium-dose, high-dose and placebo groups, respectively; of those systematic adverse reactions were reported in in 10%, 13%, and 14.7% of individuals in the medium-dose, high-dose, and placebo groups, respectively (similar findings in the 0, 28d group)
    - No significant adverse events were reported.
- Limitations: Still relatively small group sizes (between placebo and 2 doses and 2 schedules); as usual what level of NAb or titer correlate to protection are not known and in this case no comparison to convalescent samples.
- Implications: NAb was induced by the vaccine in >90% of individuals in this population; the elicited antibody response included anti-S and anti-N Ab; vaccine immunization in this population showed a tendency toward a dose-effect relationship for either seroconversion or GMTs of NAb in the 2 schedules- authors suggest a high dose with the 0, 14d schedule could be a better choice for phase 3 trials

**IMMUNE RESPONSE**

**6.** **Rapid generation of durable B cell memory to SARS-CoV-2 spike and nucleocapsid proteins in COVID-19 and convalescence**. Hartley et al. Science Immunol. 22 Dec 2020.

- In this study, fluorescently labeled tetramers of spike RBD and nucleocapsid protein were generated to track the longevity and immunophenotype of antigen specific memory B cells (Bmem) in 25 COVID-19 patients (days 4 to 242 days post-symptom onset[pso])
    - Tetramers were shown to be highly specific- not binding to samples from non-infected controls and binding to distinct B cell subsets in COVID-19 patients
    - Paired samples were taken from 11 patients between 21-106d and again at 116-224d pso
- Anti-RBD (25/25) and Anti-NCP IgG antibodies (24/25) were detected in patients and began decline at 20d pso (nearly all samples still had detectable antibody between 120-240d); 36 historic negative controls were negative
- Neutralizing Ab titers were detected in 22/25 patients using a pseudovirus neutralization assay; they were highest in those samples collected around 20d pso; in paired samples 7/11 repeat samples were at or below the *threshold of neutralizing* capacity (ID50)
- RBD- and NCP-specific Bmem cells were detected in all patients and predominantly IgM+ or IgG1+ and increased up to 150d
    - $CD38^{high}$ (plasmablasts) were only detected in 3 patients sampled in the first 2 weeks pso
    - $IgG^{+}$ Bmem cells were also mostly CD27+ (a marker of resting B cells) and correlated with circulating T follicular helper cells
    - $IgM^{+}$ Bmem cells in paired samples taken >200 days were lower than in the corresponding first samples; $IgG^{+}$ Bmem cells remained stable between paired samples
- Limitations: Fairly small study (25 patients) with only 11 paired samples; while disease severity is documented for these samples- the sample size is too small to attempt to correlate any findings with severity of disease; functionality of the Bmem cells was not assessed
- Implications: While the SARS-CoV-2 antibody response contracts during convalescence, antigen specific Bmem cells can persist at least up to 8 months.

7. **Antibody potency, effector function, and combinations in protection and therapy for SARS-CoV-2 infection in vivo.** Schafer et al. JEM. 19 Nov 2020.

- Properties of highly potent human monoclonal antibodies (hu-mAbs) were tested in a Syrian hamster model of SARS-CoV-2 and in a mouse-adapted model of SARS-CoV-2 infection (SARS-CoV-2 MA)
- There are 2 mutations in the spike of the SARS-CoV-2 MA (Q498T/P499Y) compared to wildtype SARS-CoV2; mouse-adapting mutations in the S protein did not significantly affect neutralization in 7 of 8 RBD-targeting IgG1 hu-mAbs tested in vitro using a pseudovirus neutralization assay.
- mAbs (8 mg/kg) were administered by intraperitoneal injection 12 h before intranasal infection of BALB/c mice with $10^5$ PFU of SARS-CoV-2 MA
    - In vitro antibody neutralization potency did not always correlate with in vivo protection, and some hu-mAbs were more protective in combination in vivo.
- To examine the role of Fc-effector function on the neutralization of SARS-CoV-2 MA in vivo two experiments were performed:
    1. A G236R/L328R (GRLR) mutation to abrogates antibody Fc receptor interaction was introduced to 3 of the hu-mAbs and their potency was tested in vivo; 2 of 3 of the mAb had significantly decreased potency with this mutation
    2. Grafting variable domains of one mAb (C104) onto either mouse IgG1 or IgG2aFc; the activity C104-IgG2a= C104- huIgG1 > C104-mIgG1 suggests engaging activating Fc receptors (rather than inhibitory Fc receptors) contributes to protection
- An antibody combination (targeting different areas of the RBD) was administered to Syrian hamsters 24 h before infection (prophylactic) or 12 h after infection (therapeutic) and prevented or significantly diminished SARS–CoV-2 replication at all Ab doses tested (as low as 2mg/kg prophylactic or 4mg/kg in the therapeutic dose)

8. **Afucosylated IgG characterizes enveloped viral responses and correlates with COVID-19 severity .** Larsen et al. Science. 23 Dec 2020.

- SARS-CoV-2 Ab studies have focused primarily on neutralization and kinetics – but this study investigates how a variability in the N-linked glycan within the IgG-Fc tail can potentially impact activation of the pro-inflammatory FcγRIIIa receptor
- Afucosylated IgG (~6% of total IgG in humans) are formed against enveloped viruses (i.e. HIV, CMV, measles, mumps, HBV and SARS-CoV-2) but generally not against other antigens (parvovirus B19, vaccination against HBV-protein subunit); high variability between individuals and types of antigen
- anti-S IgG responses against SARS-CoV-2 (S) (expressed on the cell surface and the viral envelope), were strongly skewed toward low levels of core fucosylation; responses against the nucleocapsid protein (N- not expressed on cell surface/viral envelope) were characterized by high levels of fucosylation
- Critically ill COVID-19 patients, but not those with mild symptoms, had high levels of afucosylated IgG antibodies against SARS-CoV-2
    - anti-S IgG1 responses of patients with ARDS recently in ICU (<5 days) were significantly less fucosylated than in convalescent plasma donors consisting of individuals who were asymptomatic or had relative mild symptoms
    - afucosylated IgG levels increasing in ARDS patients coorelated with increases in IL-6, c-reactive protein, and plasma D-dimer levels
    - Afucosylated IgG antibodies mediate stronger responses through the Fc receptor, FcγRIIIa; Afucosylated IgG (from ARDS patients), together with Toll-like receptor (TLR)3 ligand, increased ability of macrophages to produce IL-6 (in vitro)

- Limitations: hypothesis generating study still needs to address who different antigen context could produce altered IgG glycosylation; future studies should be designed to look at these glycosylation patterns in vaccination
- Implications: Ab glycosylation plays a critical role in immune responses to enveloped viruses, including SARS-CoV-2; high-titer Ig treatments should consider use of plasma enriched in fucosylated anti-SARS-CoV-2 antibodies

**9.** **Discordant neutralizing antibody and T cell responses in asymptomatic and mild SARS-CoV-2 infection** Reynolds et al. Science Immunol. 23 Dec 2020.

- T cell and neutralizing Ab (nAb) responses were analyzed in 136 healthcare workers (HCW) 16-18 wks after the UK's lockdown; 76 had mild/asymptomatic SARS-Co-2 infection (serology positive)
- HCW with laboratory confirmed SARS-CoV-2 infection had detectable S1 IgG and/or N IgG/IgM (97%); Peak S1 IgG tended to be lower with asymptomatic infection compared to those with symptoms
- nAb were present in 89% of previously infected HCW based on peudotyped virus neutralization assay; nAb titers were maintained irrespective of symptoms
- T cells responses were assessed to whole protein, mapped epitope peptide polls and overlapping peptide pools- largely only measuring frequency of IFNγ producing T cells
    - Various frequencies of antigen specific-IFNγ producing T cells were found depending on the antigen source (from 49% of persons with S specific T cells to 89% showing detectible t cell responses); Suggests that most HCW with infection had multi-specificity to their T cell responses
    - T cell responses were lower following asymptomatic infection than in those reporting case-definition symptoms of COVID-19 with laboratory confirmed SARS-CoV-2
    - There was a correlation with increasing age and T cell responses against spike, N1 OLP and ORF3a/7a mapped epitope polls; T cell immunity to spike increased with age in males
- The results suggest some discordant responses
    - 51% of the HCW were discordant for T cell and S1 IgG responses, making no T cell response to spike protein but having detectible anti-S IgG
    - 11% lacked nAb (only 8 HCW) and had undetectable T cell responses to S protein but had T cells reactive with other SARS-CoV-2 antigens
- Limitations: Measures are at a single time point; authors mention that they found no differences in terms of age, gender, ethnicity, symptom profile, clinical role or PPE use but these sub-studies would be underpowered
- Implications: A majority of individuals with mild or asymptomatic SARS-CoV-2 infection carry nAb and multispecific T cell responses at 16-18wks after their infection