Summary of Major Literature Related to COVID-19 (July 13-27)

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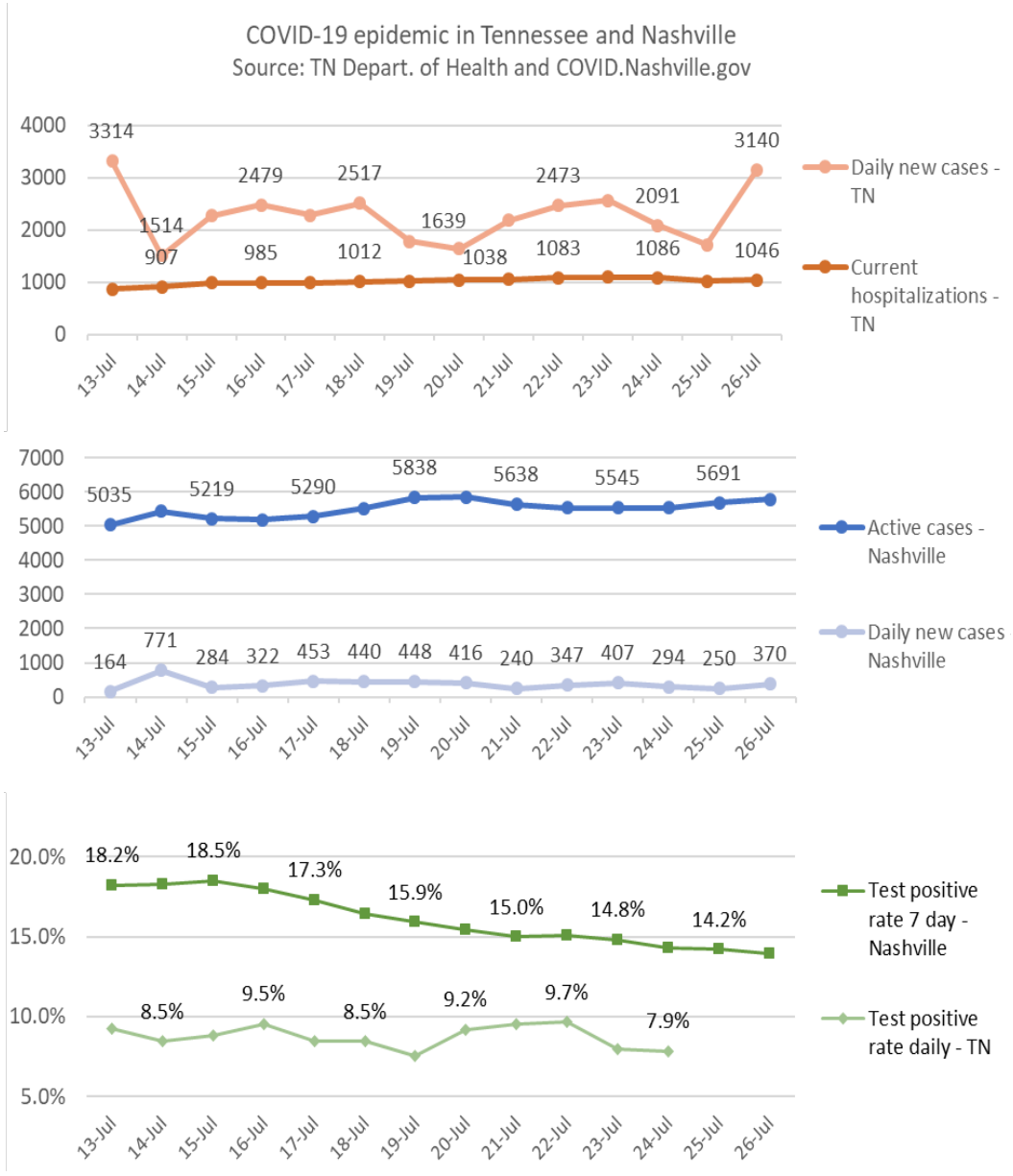
***This is informational and not intended to create variance from VUMC policies/guidance.**

STATISTICS – Tennessee and Nashville



As of July 26, in TN

- Total cases = 93,936
- Total hospitalizations = 4,244
- Total deaths = 967
- Top counties:
  - Davidson = 19,719
  - Shelby = 18,331
- Continued upward trend of current hospitalizations in TN
- Continued upward trend of current active cases in Nashville
- Downward trend of 7-day test positive rate in Nashville
- Demographics:

Groups	Cases	%
By sex		
Female	46,045	49.0%
Male	46,696	49.7%
By race/ethnicity		
White	39,810	42.4%
Black	18,149	19.3%
Hispanic	16,730	17.8%
Asian	898	1.0%
Other	12,970	13.8%
By age		
0–10	4,366	4.6%
11–20	10,555	11.2%
21–30	22,264	23.7%
31–40	17,465	18.6%
41–50	14,657	15.6%
51–60	11,664	12.4%
61–70	7,034	7.5%
71–80	3,708	3.9%
80+	2,047	2.2%

EPIDEMIOLOGY

1. **Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19).** Wiersinga et al. JAMA. July 10.

- Comprehensive summary of current evidence through June 15
- Case-fatality rate for COVID-19 varies markedly by age, ranging from 0.3 deaths/1000 among patients aged 5-17y to 304.9 deaths/1000 among patients aged ≥85y in US
  - Among patients hospitalized in the ICU, the case fatality is up to 40%

- Transmission
  - Most common transmission mode is via respiratory droplets during close face-to-face exposure
  - An estimated 48-62% of transmission occurs via presymptomatic carriers
  - Viral load in the upper respiratory tract appears to peak around the time of symptom onset and viral shedding begins approximately 2 to 3 days prior to symptom onset
  - Viral cultures are generally negative for SARS-CoV-2 8 days after symptom onset
- Clinical presentation/symptoms
  - Most common symptoms in hospitalized patients: fever (70-90%), dry cough (60-86%), and shortness of breath (53-80%); fatigue, myalgias, nausea/vomiting, weakness in up to 40%
  - Average time from exposure to symptom onset is 5 days, and 97.5% of people who develop symptoms do so within 11.5 days
  - Among patients hospitalized with COVID-19, 74-86% are aged ≥50 years
  - 25% of infected patients, but 60-90% of hospitalized patients, have comorbidities; diabetes, CVD, chronic pulmonary disease, chronic kidney disease most common
  - Complications include myocarditis, cardiomyopathy, ventricular arrhythmias, hemodynamic instability
  - 17-35% of hospitalized patients require intensive care, most commonly due to hypoxemic respiratory failure; among patients in the ICU, 29-91% require invasive mechanical ventilation
  - Venous and arterial thromboembolic events occur in 10-25% of hospitalized patients and 31-59% of ICU patients
- Treatment
  - Best practices for supportive management of acute hypoxic respiratory failure
  - Few randomized trials to date
  - Dexamethasone therapy reduces 28-day mortality in patients requiring supplemental oxygen compared with usual care
  - Remdesivir improves time to recovery (hospital discharge or no supplemental oxygen requirement) from 15 to 11 days
  - In a randomized trial of 103 COVID-19 patients, convalescent plasma did not shorten time to recovery

Factors associated with COVID-19 death, overall and after ICU admission

2. Characteristics of Persons Who Died with COVID-19 — United States, February 12–May 18, 2020. Wortham et al. MMWR. July 17**.**

- From surveillance data of 52,166 deaths among persons with laboratory-confirmed SARS-CoV-2: 55.4% male, 79.6% aged ≥65 years, 13.8% Hispanic/Latino (Hispanic), 21.0% Black, 40.3% White, 3.9% Asian, 0.3% American Indian/Alaska Native (AI/AN), 0.1% Native Hawaiian or other Pacific Islander (NHPI), 2.6% multiracial or other race, and race/ethnicity was unknown for 18.0%. Median decedent age was 78 years
- From supplemental data collection from health departments of 10,647 COVID-19 decedents with laboratory-confirmed SARS-CoV-2:
  - Median decedent age varied by race and ethnicity; Hispanic and non-White, non-Hispanic about 10 years younger than White
  - 76.4% had ≥ 1 comorbidity and percentage increased with age
  - 84.3% were hospitalized; median time from illness onset to death was 10 days; median interval from hospital admission to death was 5 days; younger ages more likely to die at home or in ED
- Limitations: Convenience samples, most decedents came from three jurisdictions; reporting practices and medical condition data collection varied by state

- Implications: Providers should consider possibility of severe disease among younger persons who are Hispanic, non-White, or have underlying medical conditions; public health campaigns should target messaging and interventions to populations most affected by severe outcomes

3. **Factors Associated With Death in Critically Ill Patients With Coronavirus Disease 2019 in the US.** Gupta et al. JAMA Internal Medicine. July 15**.**

- 2,215 adults admitted to ICUs at 65 institutions;
- Median time from symptom onset to ICU admission was 7 days; 83.9% received mechanical ventilation on ICU admission; 73.8% developed ARDS, 42.8% developed acute kidney injury without preexisting ESRD; 78.5% had ≥ 1 comorbidity
- 784 (35.4%) died within 28 days; most common causes of death were respiratory failure, septic shock, and kidney failure
- Increased risk of death was independently associated (adjusted odds ratio) with older age (≥80 vs. <40, 11.15), male sex (1.50), higher BMI (≥40 vs. <25, 1.51), coronary artery disease (1.47), active cancer (2.15), presence of hypoxemia (Pao_2:Fio_2<100 vs ≥300 mm Hg, 2.94), liver dysfunction (2.61) or kidney dysfunction (2.43) at admission, and admission to a hospital with fewer ICU beds (<50 vs. >=100, 3.28)
    - At least 15% of patients died in every age group, including <40y
    - Death was not associated with non-white race, hypertension, diabetes, lymphocyte count
- Hospitals varied widely in the risk-adjusted proportion of patients who died (range, 6.6%-80.8%) and in medications and supportive treatments that were given
- Implication: High mortality among patients admitted to ICU, wide variation in treatment approaches between institutions, and association between ICU size and patient mortality

4. **Risk Factors Associated with Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy.** Grasselli et al. JAMA Internal Medicine. July 15**.**

- 3,988 consecutive critically ill patients with laboratory-confirmed COVID-19 referred for ICU admission (at highest acuity level III centers); median follow-up of 70 days; 1926 deaths (48.3% mortality; mortality rate 12 per 1000 patient-days)
- Median time from symptom onset to ICU admission was 10 days; median ICU stay was 12 days, median hospital stay was 28 days
- 87.3% needed invasive mechanical ventilation with median duration of 10 days
- Risk factors for death included (adjusted hazard ratios) older age (1.75/10yr), male sex (2.57), the need for high levels of oxygen support on admission (1.14/10% Fi02), and comorbidities including COPD (1.68), hypercholesterolemia (1.25), type 2 diabetes (1.18)
    - Hypertension was not independently associated with increased risk of death
- Limitations: Due to crowding of ICUs at time of study, findings may be affected by compromised care
- Implications: Critically ill patients have high mortality, long ICU stays, and prolonged need for respiratory support

Asymptomatic transmission/contact tracing

5. **Outcomes of Universal COVID-19 Testing Following Detection of Incident Cases in 11 Long-term Care Facilities.** Bigelow et al. JAMA Intern Med. July 14**.**

- Testing in 11 Maryland long-term care facilities that had known positive cases
- Targeted symptom-based testing identified 153 cases, while universal screening identified an additional 354 cases (39.6% among the remaining residents)
- Among total 507 cases, 281 (55.4%) were asymptomatic
- Within 14 days of testing, 13.0% asymptomatic and 17.4% symptomatic cases were hospitalized, and 4.6% asymptomatic and 8.7% symptomatic cases died

- Implications**:** Symptom-based testing may miss a substantial number of cases in long-term care facilities. COVID-associated mortality in long-term care facilities may be lowered by increased testing and case detection
- Limitations: Unadjusted analyses; follow-up data were only available for 7 of the 11 universally tested sites

6. The implications of silent transmission for the control of COVID-19 outbreaks. Moghadas et al. PNAS. July 6**.**

- An analysis using COVID-19 transmission modes to estimate the contribution of presymptomatic and asymptomatic transmission to mitigation measures for future outbreak given that 18-31% of transmissions are thought to be from asymptomatic indivudals
- Assumptions: Average infectious period 5d, presymptomatic stage 3.2 d, infectious peak 0.7d before symptom onset, R_0 2.5 without control measures, % of asymptomatic patients varied by age and ranged from 20% (oldest) to 95% (youngest)
- Authors modeled isolation of presymptomatic and asymptomatic in addition to symptomatic individuals' days
- Asymptomatic infections were estimated to account for over 50% of COVID-19 (51.4%-53.6%) transmission
- Over one-third (33%-42%) of silent infections must be isolated to suppress a future outbreak below 1% of the population (outbreak control)
- Conclusion**:** Silent transmission alone can sustain outbreaks even if all symptomatic cases are immediately isolated
- Implication**:** Symptom-based isolation must be supplemented by rapid contact tracing and testing that identifies asymptomatic and presymptomatic cases, in order to safely lift current restrictions and minimize the risk of resurgence

7. Contact Tracing during Coronavirus Disease Outbreak, South Korea, 2020. Park et al. Emerg Infect Dis. July 16.

- Between January 20-March 27, South Korea's public health system enabled contact tracing for 5,706 COVID-19 patients with 59,073 contacts identified. During this time South Korea implemented social distancing, staying home except to perform essential tasks, and closed schools
- Index case was defined as first laboratory confirmed case. Detected cases were defined as a contact with symptom onset after that of confirmed index case
- 11.8% of household contacts had COVID-19 compared to 1.9% among non-household contacts
- In households with an index patient 10–19 years, 18.6% (43/231, 95% CI 14.0%–24.0%) of contacts had COVID-19. In households with an index patient 0-9 years, 5.3% (3/57, 95% CI 1.3%–13.7%) of contacts had COVID-19. In households with an index patient 40-49 years, 11.8% (206/1749, 95% CI 10.3-13.4) of contacts had COVID-19
- Implications:
    - Transmission occurs in all age brackets, including school age children, e.g., 0-9 and 10-19y
    - Outside of household contacts, transmission from young children was low, but the study was conducted when schools were closed
- Limitations: Low transmission occurred in two youngest age groupings, resulting in wide confidence intervals; Study could not determine actual index case given it was whomever was symptomatic first; grouping 10-19 years may not be ideal age grouping

See also: Podcast - IDSA Media Briefing: COVID-19's Impact on Public Schools

Mental health

8. **Mental health before and during the COVID-19 pandemic: a longitudinal probability sample survey of the UK population.** Pierce et al. Lancet Psychiatry. July 21.

- National UK Household Longitudinal Study (UKHLS) panel of 17,452 with repeated measures of the 12-item General Health Questionnaire (GHQ-12) prior to COVID-19 pandemic (2018/19) and in April 2020; ≥16 years and with documented address were recruited
- Clinically significant mental distress rose from 19% in 2018/19 to 27% in April 2020
    - particularly high among aged ≤ 34y (≥35%), women (33%), lowest income (32%), living without a partner (33%), living with children in home (≥30%), key worker (30%), advised by health system to isolate due to health condition (32%)
- Existing pre-pandemic inequalities in mental health remained but did not lead to an increased change in mental distress
- Limitations: 41% response rate; Pandemic effects on mental distress may be greater now and in the coming months with recession and continued changes in daily life
- Implications: With over a quarter of the population experiencing significant mental distress, mental health messaging and resources are needed; encounters with the healthcare system are an opportunity to address mental health

PPE

9. **Association Between Universal Masking in a Health Care System and SARS-CoV-2 Positivity Among Health Care Workers.** Wang et al. JAMA. July 14.

- 9850 health care workers with symptoms consistent with COVID-19 were tested for SARS-CoV-2 between March 1 and April 30 at Mass General Brigham
- Overall, 1271 (12.9%) had positive results for SARS-CoV-2 (median age, 39 years; 73% female; 7.4% physicians or trainees, 26.5% nurses or physician assistants, 17.8% technologists or nursing support, and 48.3% other)
- During the preintervention period before implementation of universal masking (March 1-24), the SARS-CoV-2 positivity rate increased exponentially from 0% to 21.3%, with a weighted mean increase of 1.16% per day and a case doubling time of 3.6 days (95% CI, 3.0-4.5 days).
- During the intervention period April 11-30, the positivity rate decreased linearly from 14.7% to 11.5%, with a weighted mean decline of 0.49% per day and a net slope change of 1.65% (95% CI, 1.13%-2.15%; P < .001) more decline per day compared with the preintervention period. This was despite continued increase in SARS-CoV-2 cases in MA during the study period
- Implication: These results provide strong support for universal masking as part of a multipronged infection reduction strategy in health care settings

VACCINE DEVELOPMENT

10. **An mRNA Vaccine against SARS-CoV-2 — Preliminary Report.** Jackson et al. NEJM. July 14.

- Phase 1, dose-escalation (25µg, 100µg, or 250µg), open-label trial including 45 healthy adults (15/dose), age 18 to 55y, who received two vaccinations, 28 days apart, with mRNA-1273 (which encodes the S-2P antigen)
- Across both vaccinations, solicited systemic and local adverse events that occurred in more than half the participants included fatigue, chills, headache, myalgia, and pain at the injection site. Reporting of these events increased with higher doses
- Dose-dependent antibody responses to the first and second vaccinations were evident
- Vaccine-induced neutralizing activity was assessed by a pseudotyped lentivirus reporter single-round-of-infection neutralization assay and by live wild-type SARS-CoV-2 plaque-reduction neutralization

testing assay. After the second vaccination, neutralizing responses were seen in all individuals tested and were greater in those receiving the 100µg dose than those receiving the 25µg dose

- T-cell responses against the spike protein were assessed by an intracellular cytokine–staining assay. CD4+ T cells responded to S-specific peptide pools by producing Th1 cytokines (i.e. TNF, IL2, IFNg). CD8+ T cell responses were low and only detected in individuals receiving the 100µg dose
- Results for the 250µg dose are not available in this preliminary report
- Limitations: Data are still limited, and the trial is ongoing with more timepoints planned; Further studies are required to assess the vaccine in various population groups including older age groups, those with comorbidities, and in ethnically and geographically diverse populations
- Implications: Safety and immunogenicity findings support advancement of the mRNA-1273 vaccine to later-stage clinical trials (phase 2 evaluating 50 and 100µg in 600 participants is ongoing; phase 3 expected to evaluate 100µg dose)

11. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Folegatti et al. Lancet. July 20.

- Preliminary report on safety, reactogenicity, and immunogenicity of a chimpanzee adenovirus-vectored coronavirus vaccine (ChAdOx1 nCoV-19) that expresses the spike protein of SARS-CoV-2. Phase 1/2, single-blind, randomized controlled trial
- >1000 healthy adults aged 18–55y with no history of laboratory confirmed SARS-CoV-2 infection or of COVID-19-like symptoms were randomly assigned (1:1) to receive ChAdOx1 nCoV-19 at a single dose of 5×10^{10} viral particles or the meningococcal conjugate vaccine (MenACWY)
- Pain, feeling feverish, chills, muscle ache, headache, and malaise were common in the ChAdOx1 nCoV-19 group; a protocol amendment adding use of prophylactic paracetamol (24h) reduced these local and systematic reactions (all $p<0.05$). There were no serious adverse events
- In the ChAdOx1 nCoV-19 group, spike-specific T-cell responses peaked on day 14 (ELIspot for IFNg; n=43). Anti-spike IgG responses rose by day 28 (median 157 ELISA units [EU], 96–317; n=127).
- 10 participants were enrolled in a nonrandomized prime-boost trial. Anti-spike IgG responses were boosted following a second dose (639 EU, 360–792; n=10) - a similar range of IgG responses in persons with natural exposure, and higher than participants receiving a single dose. After the second dose, all participants had neutralizing activity (n=9 in MNA80 at day 42 and n=10 in the Marburg VN assay on day 56). Neutralizing antibody responses correlated strongly with antibody levels measured by ELISA.
- Limitations: No cellular response data from convalescent persons for comparison; Very small subset of participants (n=10) were enrolled in the prime-boost trial; Further studies are required to assess the vaccine in various population groups
- Implications: ChAdOx1 nCoV-19 was safe, tolerated, and reactogenicity was reduced with paracetamol. A single dose elicited both humoral and cellular responses against SARS-CoV-2, with a booster immunization augmenting neutralizing antibody titers

12. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. Zhu et al. Lancet. July 20.

- This was a single-center (Wuhan) randomized, double-blind, placebo-controlled, phase 2 trial of the replication-deficient Ad5-vectored COVID-19 vaccine which contains the full-length spike gene
- >500 healthy adults aged ≥18y (12-13% were ≥55y) received either single dose of 1×10^{11} viral particles/mL, 5×10^{10} viral particles/ml, or placebo (2:1:1). Approximately 50% of participants had pre-existing high-Ab titers to Adenovirus 5 (Ad5). All participants' serum tested negative for antibodies (Ab) to the SARS-CoV-2 nucleocapsid protein at day 28 by IgG and IgM rapid test

- Safety data: Common systemic solicited reactions in both dose groups were fatigue (34-42%) and headache (28-29%). Fever was reported in 8% and 1% of participants in the 1×10^{11} and 5×10^{10} dose group, respectively. High pre-existing Ad5 immunity, increasing age, and male sex were associated with significantly lower occurrence of fever post vaccination.
- Antibody data:
    - Receptor Binding Domain (RBD) specific antibodies were measured by ELISA. Vaccination with either dose induced RBD-specific Ab by day 14 and there were significant increases by day 28
    - Neutralizing Ab were measured with 2 different assays - a live SARS-CoV-2 assay and a pseudovirus assay. By Day 28, neutralizing antibody responses to live SARS-CoV-2 occurred in 59% (1×10^{11} dose) and 47% (5×10^{10} dose) of participants. Neutralizing antibody responses in the pseudovirus assay were reported in 85% and 83% of participants, to the higher and lower dose vaccines, respectively. There was no significant impact of dose or gender on these measured responses and participants receiving placebo did not respond. Preexisting high Ab titers to Adenovirus 5 (the viral vector), reduced Ab titers approximately 2-fold. Vaccinated participants over age 55y had significantly reduced Ab responses compared to other age groups receiving vaccine, but they did have statistically significant responses relative to placebo.
- T cell data: At day 28 the Ad5-vectored vaccine had induced significant SARS-CoV-2 spike-specific IFNγ-ELISpot responses in 90% or 88% of those receiving the 1×10^{11} or the 5×10^{10} dose, respectively. The T cells response was not significantly impacted by age, gender, or pre-existing immunity to Ad5
- Limitations: No knowledge yet of durability of the response and no known correlates of protection are proven for COVID-19; This study only measured -RBD-specific Ab and performed no serology or T cell assays on samples from convalescent patients
- Implications: Phase 3 trials are likely to move forward at the 5×10^{10} viral particles dose because it had a better safety profile than, and comparable immunogenicity to, the vaccine at the 1×10^{11} viral particle dose. Age (>55yo) and pre-existing anti-Ad5 immunity of the participants could affect the Ad5-COVID-19 vaccine's safety and immunogenicity

VIRAL TROPISM/IN VITRO MODEL DEVELOPMENT

13. **SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls.** Le Bert et al. Nature. July 15**.**

- T cell responses to structural (nucleocapsid protein, NP) and non-structural (NSP-7 and NSP13 of ORF1) regions of SARS-CoV-2 were studied in COVID-19 convalescents (n=36) by evaluating PBMCs ability to produce IFNg in response to pools of peptides
- Of all individuals tested (36/36) IFNg was detected following stimulation with the pools of synthetic peptides covering the NP; Responses to NSP7 and NSP13 peptide pools were detected at very low levels (and in 12/36)
- Evaluation of memory T cells from SARS-recovered patients (2003, n=23) were reactive to the nucleocapsid protein (NP) from SARS-NP and exhibit cross-reactivity to SARS-CoV2- NP; they were not reactive to peptide pools from NSPs
- SARS-CoV-2 specific T cells were detected in individuals (19/37) with no history of SARS, COVID-19 or contact with SARS/COVID-19 patients. The immunodominance pattern was different in these uninfected controls, and the T cells responded to NP and NSP7/13.
- Limitation: Study does not provide evidence of whether pre-existing NP- and ORF-1-specific T cells present in the general population impact susceptibility and pathogenesis of SARS-CoV-2 infection; In a small subset (9 patients) they compared the frequency SARS-CoV-2-specific IFNg producing T cells with the presence of virus neutralizing antibodies, duration of infection and disease severity, but found no correlations.

- Implications: COVID-19 and SARS recovered patients can mount T cell responses against shared viral determinants; SARS-CoV-1 infection can induce T cells able to cross-react against SARS-CoV-2

14. Structural basis for translational shutdown and immune evasion by the Nsp1 protein of SARS-CoV-2, Thoms et al. Science. July 17.

- Building on previous data from SARS-CoV-1, which demonstrated that nonstructural protein 1 (Nsp1) inhibits all cellular anti-viral defense gene expression, this research explores whether the Nsp1 protein of SARS-CoV-2 inhibits translation of anti-viral host defense genes
- Recombinantly expressed Nsp1 from both CoVs associated strongly with 40S ribosomal subunits (not with 60S subunits); Nsp1 mutants (conserved residues K164 and H165 were mutated) showed no binding to ribosomal subunits
- Expression of the Nsp1 proteins in HEK293 cells leads to association with 40S ribosomal subunits and 80S ribosomes. Nsp1 disrupts cap-dependent translation in HEK cells (and requires K164/H165 conserved residues)
- A complex of purified, recombinant Nsp1 and purified human 40S ribosomal subunits was reconstituted and its structure was determined by cryo-EM (ave. resolution of 2.6 Å)
- Nsp1 was found to bind to the mRNA entry channel of a set of translationally inactive 80S ribosomes, several of these ribosomes were in complexes that have never been described previously
- SARS-CoV-2 Nsp1 inhibited the cellular response to Sendai Virus - protein levels of endogenous IFN-β, IFN-λ1 and interleukin-8 were reduced in HEK293 cells expressing Nsp1 (but not those expressing Nsp7 as a negative control).
- Limitations: Does not address how the virus can overcome the Nsp1-mediated block of translation for the production of viral proteins; All studies are in vitro cell culture-based methods
- Implications: A major immune evasion factor of SARS-CoV-2, Nsp1, efficiently interferes with the cellular translation machinery resulting in a shut-down of host protein production. (The authors suggest that rational structure-based drug design could be used to counteract this evasion by targeting the Nsp1-ribosome interaction.