Summary of Major Literature Related to COVID-19 (Aug 10-Sept 7)

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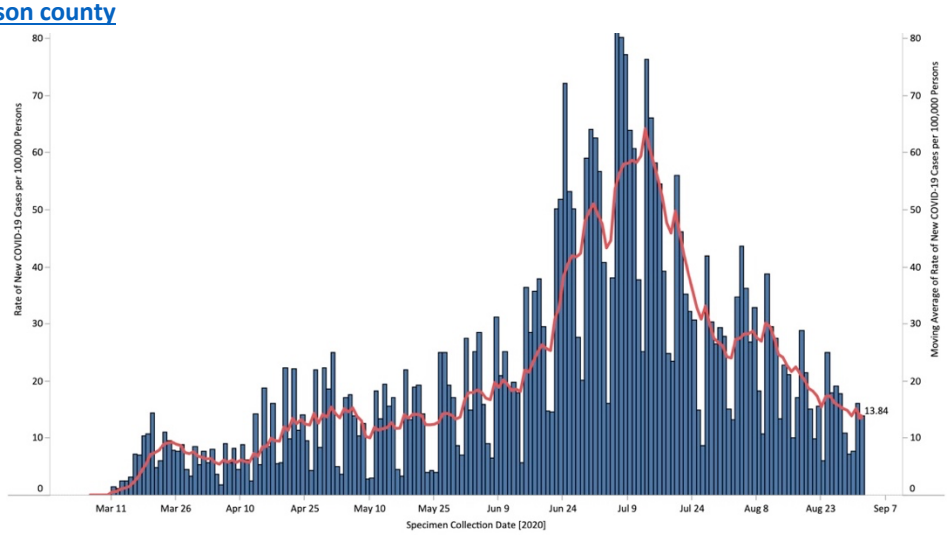
***This is informational and not intended to create variance from VUMC policies/guidance.**

STATISTICS – Daily new cases per 100,000 population

Tennessee

Davidson county



As of 09/07, in TN

- Total cases = 165,109
- Active cases = 18,896
- Ever hospitalized = 7,312
- Now hospitalized = 844
- Total deaths = 1,869
- Top counties:
  - Shelby = 27,947
  - Davidson = 26,686 (active cases = 1,134)
- Demographics:

Groups	Cases	%
By sex		
Female	83,565	50.6%
Male	79,507	48.2%
By race/ethnicity		
White	84,449	51.1%
Black	31,120	18.8%
Hispanic	23,435	14.2%
Asian	1,456	0.9%
Other	24,649	14.9%
By age (average: 39 years)		
0–10	8,162	4.9%
11–20	20,953	12.7%
21–30	35,605	21.6%
31–40	28,257	17.1%
41–50	24,831	15.0%
51–60	20,874	12.6%
61–70	13,805	8.4%
71–80	7,630	4.6%
80+	4,138	2.5%

ANTIBODY RESPONSE/CONVALESCENT PLASMA

Importance of these studies:

Further understanding of why some patients develop a stronger antibody response than others;
May provide information on selecting individuals who are likely to have high levels of neutralizing and anti-SARS-CoV-2 IgG antibodies to be preferred convalescent plasma donors;
Further understanding of the clinical implications of differing nAb titers for recovery from COVID-19 or protection against future infection

1. **Sex, age, and hospitalization drive antibody responses in a COVID-19 convalescent plasma donor population.** Klein et al. J Clin Invest. August 7.

- Humoral immune response to SARS-CoV-2 viral infection in 126 potential convalescent plasma donors was measured by virus neutralization assay, commercial IgG and IgA ELISAs to the spike (S) protein S1 domain, IgA, IgG and IgM indirect ELISAs to the full-length S or S-receptor binding domain (S-RBD), and an IgG avidity assay

    - Most donors had mild or moderate diseases; <10% were hospitalized
    - Mean age was 42y, and 56% were male
    - Median of 43 days (IQR 38-48) between initial PCR+ nasal swab test and plasma sample collection
- 80% had detectable nAb titers; IgG assays have a good ability to detect nAb positivity
- Substantial heterogeneity in the antibody response was observed
    - Male sex, older age, and hospitalization with COVID-19 (the strongest correlate) were associated with increased antibody responses
- nAb response reduced as the days increased from time of diagnostic PCR+ nasal swab collection
- Limitations: Kinetics of the complete antibody response over time could not be determined; whether the efficacy of convalescent plasma is correlated with nAb levels was not investigated

2. Evaluating the Association of Clinical Characteristics with Neutralizing Antibody Levels in Patients Who Have Recovered from Mild COVID-19 in Shanghai, China. Wu et al. JAMA Intern Med. August 18.

- Study of nAb response in 175 patients in Shanghai who had been hospitalized and recovered from mild PCR-confirmed COVID-19
    - Median age 50y (IQR 37-63) and 53% were female
    - Median length of hospital stay 16 days (IQR 13-21); median disease duration 22 days (18-26)
- nAb titers were measured using a validated single-round pseudovirus infection assay. Binding antibodies to SARS-CoV-2 spike (S) proteins, S1, receptor binding domain (RBD), and S2 were measured by ELISA. Plasma with high titers of nAbs was measured for cross-reactivity against SARS-associated CoV. To evaluate the kinetics of nAb development, sequential plasma samples were collected from admission to discharge at intervals of 2 to 4 days for 11 patients.
- Substantial variability in SARS-CoV-2-specific nAb titers was observed at the time of discharge
    - 50% inhibitory dose [ID50], 1076 [IQR, 448-2048]
    - 30% of patients developed nAbs with titers less than 500, and 10 patients had nAb titers below the detectable level of the assay (ID50, <40)
    - nAbs reached peak levels from day 10 to 15 after disease onset
- nAb titers were significantly higher in men, older patients, and those with a stronger immune response (higher plasma CRP levels and lower lymphocyte counts at the time of admission)
- nAb titers correlated significantly with the spike-binding antibodies targeting different domains of S protein, including S1, RBD and S2
- In 117 patients followed up at 2 weeks post discharge, median nAb titer at follow-up was 886 (IQR, 378-1658), significantly lower than that at the time of discharge (1110 [IQR, 447-2042]
    - Patients who did not generate nAbs at the time of discharge did not develop detectable nAbs at the time of follow-up
- Limitations: Patients with severe COVID-19 were not included; kinetics of nAB development were based on only 11 patients; substantial proportion with low or undetectable nABs may not be beneficial for convalescent plasma treatment

3. Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three Month Experience. Joyner et al. US EAP COVID- 19 Plasma Consortium. medRxiv preprint. August 12. (NCT04338360)

- Multicenter study, including 2,807 acute care facilities, of 35,322 adult participants transfused under the open-label US Convalescent Plasma Expanded Access Program (EAP) between April 4 and July 4, who were hospitalized with (or at risk of) severe or life threatening acute COVID-19 respiratory syndrome

    - Outcomes were 7- and 30-day mortality
    - Antibody levels in convalescent plasma units were unknown at time of transfusion
    - 52.3% of patients were in the ICU and 27.5% were receiving mechanical ventilation at the time of plasma transfusion
- 7-day mortality rate was lower (8.7% [95% CI 8.3%-9.2%]) in patients transfused within 3 days of COVID-19 diagnosis than in patients transfused 4 or more days after diagnosis (11.9% [11.4%-12.2%], p<0.001). Similar findings were observed for 30-day mortality (21.6% vs. 26.7%, p<0.0001)
- In a subset of 3,082 transfused patients who received only a single unit of plasma, for those patients who received high IgG plasma (>18.45 S/Co), 7-day mortality was 8.9% (6.8%, 11.7%); for recipients of medium IgG plasma (4.62 to 18.45 S/Co) mortality was 11.6% (10.3%, 13.1%); and for recipients of low IgG plasma (<4.62 S/Co) mortality was 13.7% (11.1%, 16.8%) (p=0.048). A similar unadjusted dose-response relationship with IgG was also observed for 30-day mortality (p=0.021)
    - The pooled relative risk of mortality among patients transfused with high antibody level plasma units was 0.65 [0.47-0.92] for 7 days and 0.77 [0.63-0.94] for 30 days compared to low antibody level plasma units
- Limitation: Exploratory analysis for signals of efficacy; not a randomized controlled trial; patients transfused early in study period were more critically ill and had different rates of concomitant medication use which may lead to an underestimation of effectiveness
- Implications: Observed associations of reduced mortality with earlier time to transfusion and higher IgG antibody levels are "consistent with efficacy for the use of convalescent plasma in the treatment of hospitalized COVID-19 patients"; **VUMC awarded $34 million to lead nationwide convalescent plasma randomized controlled trial**

4. **Rapid isolation and profiling of a diverse panel of human monoclonal antibodies targeting the SARS-CoV-2 spike protein. Zost et al. (VUMC paper, Crowe Senior Author). Nature. July 10.**
- Two rapid antibody discovery platforms were used in parallel to isolate hundreds of human monoclonal antibodies (mAbs) against the SARS-CoV-2 spike (S) protein (18-35 days)
    - single-B-cell antibody gene sequencing combined with high-throughput IgG isolation
    - screening assays included rapid antigen binding and functional (hACE2 blocking) and neutralization of authentic SARS-CoV2
    - many mAb inhibited infection of authentic SARS-CoV-2
- No antigen-specific B cells from patients 1 and 2 were isolated (cells collected 35 or 36 d after onset of symptoms); antigen-specific B cells were isolated from patients 3 and 4 (cells collected 50 d)
- 389 mAbs were placed into five major classes based on their reactivity to subdomains of S protein
    - 178 recognized the RBD and 43 recognized the amino-terminal domain (NTD)
    - most neutralizing mAbs recognized the RBD
    - among the 389, some neutralizing mAbs to SARS-CoV2 were also cross-reactive to SARS-CoV; cross-reactivity required recognition of the stabilized trimeric prefusion ectodomain of S protein ($S2P_{ecto}$)
- Of the 389 mAbs, 321 had unique amino acid sequences and 313 were unique clonotypes - with diverse usage of antibody variable genes
- Limitations: Patient samples from different times after disease onset could result in differential ability to have a memory B cell and/or differential amounts of affinity maturation
- Implications: This work defines sites of vulnerability on SARS-CoV-2 S and demonstrates the speed and robustness of advanced antibody discovery platforms

5. **Humoral Immune Response to SARS-CoV-2 in Iceland.** Gjudbjartsson et al. NEJM. September 1**.**

- Examination of SARS-CoV-2 seroprevalence in the population of Iceland as well as longitudinal changes in antibody levels within the first 4 months after SARS-CoV-2 infection
- SARS-CoV2- specific antibodies were measured in over 30,000 persons with either i) pan-Ig assays targeting Ab against nucleoprotein (N), receptor binding domain or the S1 subunit of spike and/or ii) assays targeting IgG & IgM against N and IgA & IgG against S1
    - low prevalence of infection in Iceland led authors to define seropositive as positive in both pan-Ig assays
- Among 1215 recovered qPCR-positive patients:
    - >90% (1107/1215) of samples were seropositive by 25 d after diagnosis
    - hospitalized persons (n=48) seroconverted more quickly and had higher Ab titer after qPCR diagnosis compared to non-hospitalized persons
    - 487 recovered patients had 2 or more samples assessed - only 19 had different pan-Ig results at different time points (one tested negative in a later sample)
    - pan-IgG antibody levels increased in first 2 months and remained at a plateau
- Among 4222 quarantined persons who had not tested qPCR-positive (they had received a negative qPCR result or had not been tested), 2.3% (95% CI, 1.9 to 2.8) were seropositive
    - Those who had household exposure (7.4% v 1.4%) and those who had symptoms during quarantine (7.2% v 2.4%) were five times and three times more likely to be seropositive, respectively
- Based on positive qPCR and seroconversion data, the authors estimate that 0.9% of the residents of Iceland were infected with SARS-CoV-2
    - 56% of all SARS-CoV-2 infections were diagnosed with qPCR, and 44% occurred without having been diagnosed by qPCR (14% occurred in quarantine and 30% outside quarantine)
- Among recovered persons, antibody levels were positively associated with older age, hospitalization and clinical severity, and higher body mass index, and inversely associated with smoking and use of anti-inflammatory medication
- Incidence of infection in Iceland was estimated to be 0.9% (95% CI, 0.8 to 0.9) and the infection fatality risk was 0.3% (95% CI, 0.2 to 0.6)
- Implications: Antiviral antibodies against SARS-CoV-2 did not decline up to 4 months after diagnosis; over 30% of infections were not detected, suggesting that many infected persons did not have substantial symptoms
- Limitation: Unknown relationship between seropositivity and protection against reinfection

EPIDEMIOLOGY

Asymptomatic infection

6. **Clinical Course and Molecular Viral Shedding Among Asymptomatic and Symptomatic Patients With SARS-CoV-2 Infection in a Community Treatment Center in the Republic of Korea.** Lee et al. JAMA Intern Med. August 6. PMID: 32780793.

- Retrospective cohort study of viral shedding in 303 patients with SARS-CoV-2 infection isolated in a community treatment center in the Republic of Korea
    - Median age 25y (IQR 22-36), 66% women, only 12 (4%) had comorbidities
    - 110 (36%) patients were asymptomatic at the time of isolation and 21 of these (19%) developed symptoms during isolation
    - Median interval from SARS-CoV-2 detection to symptom onset in pre-symptomatic patients was 15 (IQR 13-20) days
- Age, sex and comorbidity were similar among asymptomatic, pre-symptomatic and symptomatic patients

- Median time from diagnosis to the first negative conversion was similar for asymptomatic (17 days) and symptomatic (including pre-symptomatic) patients (19.5 days)
- Cycle threshold (Ct) values of RT-PCR for SARS-CoV-2 in asymptomatic patients were similar to those in symptomatic patients
    - However, Ct value for the *env* gene from lower respiratory tract (sputum) specimens showed that viral loads of asymptomatic patients tended to decrease more gradually than those of symptomatic (including pre-symptomatic) patients
- Implications:
    - Many individuals with SARS-CoV-2 infection remained asymptomatic for a prolonged period, and viral load was similar to that in symptomatic patients
    - Thus, symptom-based surveillance may be insufficient to control the spread of SARS-CoV-2, and quarantining of asymptomatic infected individuals is critical to curb the pandemic
    - Despite limited generalizability of this young, relatively healthy cohort, results have relevance for the spread of COVID-19 among college students
- Limitation: Infectiousness of asymptomatic patients was not evaluated

Children

7. **Multisystem Inflammatory Syndrome in U.S. Children and Adolescents.** Feldstein et al. N Engl J Med. July 23**.**

- Targeted surveillance for Multisystem Inflammatory Syndrome in Children (MIS-C) from March 15 to May 20 in 53 pediatric health centers across 26 states
- Among 186 seriously ill, hospitalized patients (median age 8.3 years), 135 (73%) had previously been healthy; 132 (71%) had involvement of ≥4 organ systems; 148 (80%) received intensive care, and 4 (2%) died
- Organ-system involvement included the gastrointestinal system in 171 (92%), cardiovascular in 149 (80%), hematologic in 142 (76%), mucocutaneous in 137 (74%), and respiratory in 131 (70%)
- Most patients had elevations in ≥4 biomarkers of inflammation; intravenous immune globulin was used in 144 (77%) and glucocorticoids in 91 (49%)
- Conclusion**:** MIS-C related to SARS-CoV-2 can lead to serious hyperinflammatory illness in previously healthy children and adolescents
- Limitations: Case definition of MIS-C may vary over time and/or among centers; the results may be not generalizable beyond the surveillance population

8. **Pediatric SARS-CoV-2: Clinical Presentation, Infectivity, and Immune Responses.** Yonker et al. J Pediatrics. August 13**.**

- Study of viral load, ACE2 expression and antibody responses in 192 children/young adults age ≤22y who presented to urgent care clinics or were hospitalized for confirmed/suspected SARS-CoV-2 infection and were enrolled in the MGH Pediatric COVID-19 Biorepository
    - Mean age 10.2 years
    - 49 (26%) were SARS-CoV-2 (+), 125 (65%) were SARS-CoV-2 (-) and 18 (9%) had Multisystem Inflammatory Syndrome in Children (MIS-C)
- Symptoms, when present, were generally non-specific and similar between groups, and only 51% of children with SARS-CoV-2 infection presented with fever
- 82% of SARS-CoV-2 (+) and 44% of MIS-C children had a known infected household contact
- Nasopharyngeal viral load was highest in children in the first 2 days of symptom appearance
    - Within the SARS-CoV-2 infected cohort, neither age nor ACE2 expression in the upper airway impacted viral load, although ACE2 expression was lower in younger children

- IgM and IgG to the receptor binding domain (RBD) of the SARS-CoV-2 spike protein were significantly increased in severe MIS-C, suggesting hyperactive antibody responses
- Limitations: Transmissibility was not assessed; uncertain generalizability of study population
- Implications: Children of all ages can carry high SARS-CoV-2 viral loads and have non-specific symptoms; thus, additional measures besides symptom screening, including social distancing and mask wearing, are needed to control infection in schools

9. **Clinical Characteristics and Viral RNA Detection in Children With Coronavirus Disease 2019 in the Republic of Korea.** Han et al. JAMA Pediatrics. August 28.

- Study of the clinical course and duration of SARS-CoV-2 RNA detection in a case series of 91 children under age 19 years with confirmed COVID-19 in 20 hospitals and 2 isolation facilities Korea
    - Median age 11 years (range, 27 days-18 years); 58% male; 7% had underlying diseases
    - Children were monitored for a mean (SD) of 21.9 (8) days
    - 85% of children did not receive treatment for COVID-19
- 20 (22%) remained asymptomatic throughout the observation period
- Among 71 (78%) symptomatic children, 66% had no symptoms before diagnosis, 25% developed symptoms after diagnosis, and only 9% were diagnosed at the time of symptom onset
    - Median duration of symptoms was 11 (range, 1-36) days
- SARS-CoV-2 viral RNA was detected in upper respiratory samples for a mean (SD) duration of 17.6 (6.7) days overall and 14.1 (7.7) days in asymptomatic children
- Implications: Symptom screening fails to identify most COVID-19 cases in children; SARS-CoV-2 RNA in children is detectable for a long time

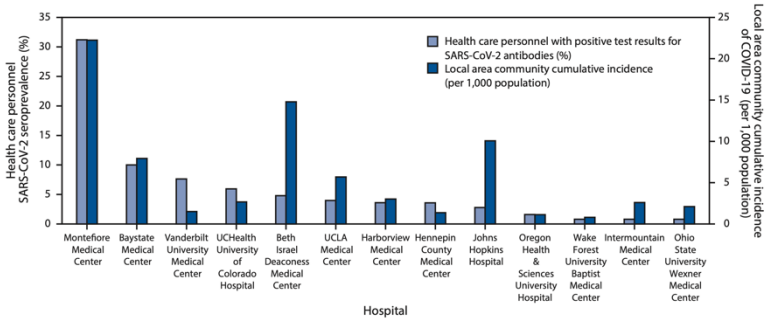
Seroprevalence among health care personnel

10. **Seroprevalence of SARS-CoV-2 Among Frontline Health Care Personnel in a Multistate Hospital Network — 13 Academic Medical Centers, April–June 2020.** Self et al. (**VUMC paper**) MMWR. 69(35);1221–26.

- Study of prevalence of and factors associated with SARS-CoV-2 infection among frontline healthcare personnel (HCP) who care for COVID-19 patients at 13 Influenza Vaccine Effectiveness in the Critically Ill (IVY) Network medical centers from 12 states
- Among 3,248 enrolled HCP (convenience sample), median age was 36y, and 80% reported no underlying medical conditions
    - 1,445 (44%) were nurses, 919 (28%) were physicians, nurse practitioners, or physician assistants, 235 (7%) were respiratory therapists, and 648 (20%) had other clinical roles
    - 1,292 (40%) reported working primarily in an ICU, 1,139 (35%) in an ED, and 817 (25%) in other locations
    - Participants were classified as having symptoms of acute viral illness if they reported any of the following symptoms from February 1, 2020, until the enrollment date: fever, cough, shortness of breath, myalgias, sore throat, vomiting, diarrhea, or change in sense of taste or smell
    - Participants self-reported PPE use and if they experienced shortage since February
- 6% of HCP (n=194) had antibody evidence of prior SARS-CoV-2 infection
    - Seroprevalence by hospital ranged from 0.8% to 31.2% (median = 3.6%) (see Figure)
    - 29% of personnel with SARS-CoV-2 antibodies were asymptomatic in the preceding months
    - 69% had not previously received a diagnosis of SARS-CoV-2 infection
- Seroprevalence was significantly lower among those who reported always wearing a face covering while caring for patients (6%), compared with those who did not (9%) (p=0.012)
    - Shortages of any PPE since February 1 were reported by 398 (12%) participants

- Seropositivity was lower among females (5.3%) than males (7.2%) (p = 0.03) and among non-Hispanic White participants (4.4%) than participants of other racial/ethnic groups (9.7%) (p<0.001)

FIGURE. SARS-CoV-2 seroprevalence among a convenience sample of frontline health care personnel and local area community cumulative incidence of COVID-19* — 13 academic medical centers, United States, April–June 2020†



- Implication: Consistent with the general population, a high proportion of SARS-CoV-2 infections among HCP appear to go undetected; universal use of face coverings and lowering clinical thresholds for testing could be important strategies for reducing hospital transmission
- Limitations: Potential for confounding in the absence of multivariable modeling; clinical role for ~600 HCP was classified as "other," hampering interpretation of overall significant difference in seroprevalence by clinical role

Health equity/vaccine disparities - commentaries

11. Covid's Color Line — Infectious Disease, Inequity, and Racial Justice. Evans MK. NEJM. July 30**.**

- Commentary from NIA Deputy Scientific Director and a call to action to confront individual and societal responsibility to fix health and other disparities
- African Americans and other minorities have a long history of being required to carry larger risks in outbreaks; 1793 yellow fever epidemic in which free Africans were used to perform nursing and essential duties with the false assumption that they had increased immunity
- Disparities are often ascribed to behavioral, educational, cultural, and psychological factors without addressing the root causes of injustice
- Immediate actions needed to address COVID-19 disparities: expand free minority-neighborhood-based COVID-19 testing; reduce wait time for test results; increase tracking; provide free housing for isolation for individuals with COVID living in crowded conditions
- See also: **Structural Racism, Social Risk Factors, and Covid-19 — A Dangerous Convergence for Black Americans.** Egede et al. NEJM. July 22**.**
    - Some effects of structural racism that affect health: food insecurity, housing instability, limited access to transportation, lack of health insurance, increased environmental exposures; psychological trauma

12. Addressing Influenza Vaccination Disparities During the COVID-19 Pandemic. Grohskopf et al. JAMA. August 20**.**

- Commentary from US CDC authors on need to remove vaccination disparities for influenza vaccination during COVID-19 pandemic
- Prevention of severe respiratory illness due to influenza will reduce mortality and conserve strained health care resources
- Less than 50% of US adults receive influenza vaccination
    - Hispanic, non-Hispanic Black, American Indian/Alaskan Native have lowest vaccination coverage
- Reasons for disparities are multifactorial including barriers to health care access, distrust based on history of discrimination and abuse, inequities in education, employment, sick leave, and other reasons
- Actions needed: 1) Clinicians should "strongly recommend influenza vaccination to all patients" for entirety of influenza season; 2) Tailored interventions and additional research on social determinants of vaccine acceptance and coverage

Male-female disparity

13. **Sex differences in immune responses that underlie COVID-19 disease outcomes.** Takahashi et al. Nature. August 26.

- To elucidate sex differences in immune responses against COVID-19, immune phenotypes (including viral loads, SARS-CoV-2 antibody levels, plasma cytokine/chemokines, and blood cell phenotypes) were assessed among confirmed COVID-19 patients from the Yale-New Haven Hospital
- Analyses were conducted among all patients (N=98), of whom 48 had serial samples, and after applying additional exclusion and matching criteria (e.g. age, BMI, and days from symptom onset (N=39)
- There were no differences in viral RNA concentrations or anti-SARS-CoV-2 S1-specific IgG or IgM antibodies between men and women
- In baseline samples from 39 patients, more robust T cell responses were seen in female than male COVID-19 patients, including significantly elevated CD8 T cells compared to healthy volunteers only among women
- Several proinflammatory chemokines and cytokines (IL-8 and IL-18 at baseline, and CCL5 in longitudinal analyses) were higher in male than female patients and were correlated with higher non-classical monocyte level at baseline
- In men, disease progression was associated with increasing age, BMI, and poor CD8 T cell activation; in women, disease progression was associated with higher innate immune cytokine levels (such as TNFSF10/TRAIL and IL-15)
- Implications: Data from this study suggests that that there may be key differences between men and women during SARS-CoV-2 infection and disease progression
- Limitations: Small population, limited sample collection, multiple comparisons; exploratory analyses, should be interpreted with caution

TREATMENT

14. **Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis.** WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. JAMA. Sep 2.

- A prospective meta-analysis of 7 randomized trials (PROSPERO CRD42020197242) conducted in 12 countries to estimate the effect of administration of corticosteroids compared with usual care or placebo on 28-day all-cause mortality among critically ill patients with COVID-19
- Hospitalized patients with COVID-19 who required respiratory support had been randomized to receive systemic dexamethasone, hydrocortisone, or methylprednisolone (678 patients) or to receive usual care or placebo (1025 patients)
- There were 222 deaths among the 678 patients randomized to corticosteroids and 425 deaths among the 1025 patients randomized to usual care or placebo (summary odds ratio (OR) 0.66 [95% CI, 0.53-0.82]; P < .001 based on a fixed-effect meta-analysis)
- The fixed-effect summary OR for the association with mortality was 0.64 (95% CI, 0.50-0.82) for dexamethasone compared with usual care or placebo (3 trials), 0.69 (95% CI, 0.43-1.12) for hydrocortisone (3 trials), and 0.91 (95% CI, 0.29-2.87; P = .87) for methylprednisolone (1 trial)
- Among the 6 trials that reported serious adverse events, 64 events occurred among 354 patients randomized to corticosteroids and 80 events occurred among 342 patients randomized to usual care
- Implication: Administration of corticosteroids was associated with reduced mortality for critically ill COVID-19 patients, with no suggestion of an increased risk of serious of adverse events
- Limitation: Optimal dose and duration of treatment could not be assessed
- **See also: Editorial: Corticosteroids in COVID-19 ARDS. Prescott and Rice. JAMA Sept 2.**

15. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. Spinner et al. JAMA. Aug 21. (NCT04292730)

- Randomized, open-label trial of 584 hospitalized patients with confirmed SARS-CoV-2 infection and moderate COVID-19 pneumonia (pulmonary infiltrates and room-air oxygen saturation >94%) to determine the efficacy of 5 or 10 days of remdesivir treatment compared with standard care
    - Patients were randomized in a 1:1:1 ratio to receive a 10-day course of remdesivir, a 5-day course of remdesivir, or standard care. Remdesivir was dosed intravenously at 200 mg on day 1 followed by 100 mg/d.
    - The primary end point was clinical status on day 11 on a 7-point ordinal scale ranging from death (category 1) to discharged (category 7)
- Median age 57 (IQR 46-66) years; 227 (39%) women; 56% had cardiovascular disease, 42% hypertension, and 40% diabetes
- On day 11, patients in the 5-day remdesivir group had statistically significantly higher odds of a better clinical status distribution than those receiving standard care (odds ratio, 1.65; 95% CI, 1.09-2.48; P = .02)
    - The clinical status distribution on day 11 between the 10-day remdesivir and standard care groups was not significantly different
- Limitation: Disease specific outcomes were not assessed; 6% of patients did not have clinical status reported on day 11; discharge decisions may have been influenced by assigned duration of remdesivir therapy

VACCINE DEVELOPMENT

16. Phase 1–2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine. Keech et al. NEJM. Sept 2.

- Randomized, placebo-controlled, phase 1–2 trial (131 healthy adults) to evaluate the safety and immunogenicity of the rSARS-CoV-2 vaccine candidate (full-length spike protein nanoparticle, NVX-CoV2373)
- Groups included: placebo (23 participants), Two 25-µg doses (25), Two 5-µg doses with Matrix-M1 adjuvant (29), Two 25-µg doses with Maxtrix-M1 (28), and One 25-µg dose with Matrix-M1 and one dose of placebo (26); given IM on days 0 and 21.
- Only 2 participants reported severe adverse events (headache, fatigue and malaise) and 2 reported fatigue, malaise, and tenderness; mild reactogenicity was more common with adjuvant;
- 10% (13) had some grade 2 or higher laboratory abnormalities; most common was transient reduction in hemoglobin and transient elevated liver enzymes.
- Geometric mean ELISA Units (GMEU; IgG anti–spike; day 0, 21 and 35) increased approximately 100 fold more in participants receiving 2 doses of the adjuvanted vaccine candidate; two-dose 5-µg and 25-µg adjuvanted vaccine regimens were similar; significantly higher than that in convalescent serum from outpatients with systematic; similar to that in convalescent serum from COVID inpatients. Neutralizing Ab (microneutralization assay) correlated with IgG anti-spike levels
- CD4 T-cell responses were assessed in response to spike in 4 random participants at day 0 and day 28 per group (intracellular cytokine staining). While there was a bias toward Th1 in adjuvanted groups, the results were not consistent between participants within groups.
- Limitations: Overall small trial with limited ethnic diversity; no long-term safety data; only adults 18-59 without underlying conditions; T cell assessment was on a small number of participants and no analysis of CD8 responses; how the day 35 time point relates to the COVID-19 convalescent serum is not clear.

- Implications: The benefit of the adjuvant was clear in the magnitude and functionality of the antibody response. The value of the second dose on day 21 for the two-dose rSARS-CoV-2 plus Matrix-M1 regimen is demonstrated and warrants the use of this vaccination schedule.

Animal models

Consistency across the vaccine candidate studies described below:

Intramuscular (IM) immunization can provoke systemic Ab/CMI response to S protein

Intranasal (IN) vaccination elicits a weaker systemic response, but stronger mucosal response than IM, but still largely protects the animals from challenge

17. A single-dose intranasal ChAd vaccine protects upper and lower respiratory tracts against SARS-CoV-2. Hassan et al. Cell. August 14**.**

- This report focuses on the effectiveness of a single dose of a chimpanzee adenovirus vectored vaccine candidate encoding a pre-fusion stabilized spike protein (ChAd-SARS-CoV-2-S, replication deficient) in challenge studies with SARS-CoV-2 in mice (expressing human ACE2 receptor)
- The intramuscular (IM) route [ChAd-SARS-CoV-2-S (10^{10} VP)] induced RBD and S specific IgG Ab in the serum, but IM did not induce IgA in serum (measured at 3w/6wk). IM immunization induced S specific IFNg producing and granzyme expressing T cells in spleens, but not in lungs (measured 4wk; 1wk after boost). After intranasal (IN) challenge ($4x10^5$ FFU; d35) the IM-group (2 doses) still had detectable viral RNA in lungs (4dpi/8dpi). Less pneumonia was detected in the immunized group compared to control and inflammatory cytokines were reduced in the lungs of the immunized group.
- The IN-immunization resulted in strong Ab responses after a single dose (d30) and development of a cellular immune response in both the spleens and the lungs after a booster (d37). A single dose of the ChAd-SARS-CoV-2-S (10^{10} VP) administered IN (d35) prevented SARS-CoV-2 infection in both the upper and lower respiratory tract
- 'Prevention of infection' was measured by presence of Abs against the nucleoprotein (NP) - presence suggests viral protein translation and active infection. No mice immunized IN with ChAD-SARS-CoV2-S had increases in anti-NP antibodies after challenge (IM-group had anti-NP Abs).
- An additional mouse model (C56Bl/6 background) which expresses 8 copies of the hACE2 receptor driven by the K18 cytokeratin epithelial cell promoter was used to evaluate efficacy of the ChAd-SARS-CoV2-S vaccine candidate. 4 weeks after immunization S protein and RBD specific IgG and IgA were significantly increased. Challenge was 28 days post immunization and resulted in no detectable infectious virus or viral RNA in the lungs; and significantly reduced viral RNA in the nasal turbinates and washes
- Limitations: Some inconsistency in experimental timelines and boost v. no boost between routes of immunization and mouse models; long term immunity cannot be assessed from these timelines
- Implications: Intranasal immunizations could be more efficient than intramuscular immunizations at activating the protective mucosal immune response against SARS-CoV2

18. A single dose of an adenovirus-vectored vaccine provides protection against SARS-CoV-2 challenge. Wu et al. Nature Communication. August 14**.**

- This report focuses on effectiveness of a single dose of replication-defective human type 5 adenovirus encoding the SARS-CoV-2 spike protein (Ad5-nCoV) in mice and ferret models following intramuscular and intranasal immunizations
- This vaccine candidate was constructed using replication-defective Ad5 (deletions of E1/E3 genes) encoding full-length Spike (sequence from the Wuhan-Hu-1 strain) led by the tissue plasminogen activation signal peptide. Ad5 alone served as the control immunization

- Mice were immunized either IM or IN and with one of 3 different doses ($5x10^7$, $5x10^8$, or $5x10^9$ VP). Higher IgG titers (sustained up to 8 weeks), higher NAb titers, and higher PNAb titers were reported in the high-dose IN groups compared to the IM groups. IFNg, TNF and IL-2 were higher in splenic CD8+ and CD4+ T cells of mice immunized IM than those immunized IN.
- Challenge was performed with $10^{3.6}$ PFU/mouse at 10 weeks post vaccination with a mouse adapted SARS-CoV2 virus. No detectible virus was detected by PCR or PFU assays on lungs or turbinates (upper respiratory) at 3 and 5 dpi in the IN-group (independent of immunization dose). Virus was detected in the turbinates of some mice of the IM group (PFU assays and qPCR) although reduced compared to control group.
- In the ferret model, the immunizations were either IM or IN + oral ($5x10^{10}$ VP per site) and challenge was done at 4 weeks post immunization (10^5 PFU). There were no differences in serological data between immunization sites. Virus was not detected in nasal washes of the IN+oral group at days 2-8 dpi; virus was detected in about ½ of the IM-group.
- Limitations: Cellular immune responses being assessed in the mouse spleen may not represent response at site of immunization or challenge; models could not assess pathological response.
- Implications: A similar vaccine candidate has been evaluated in Phase I trials; this study suggests that immunization route matters (mucosal vaccination is more efficacious), and this candidate should be considered further

19. **An adenovirus-vectored COVID-19 vaccine confers protection from SARS-COV-2 challenge in rhesus macaques** Feng et al. Nature. August 21**.**

- Short-term efficacy study in rhesus macaques of a vaccine candidate, a replication-deficient Adenovirus 5 vector which expresses the spike protein (Ad5-S-nb2). In this vector, the codon usage of the S gene is modified to increase S protein expression in human cells
- The two different doses of the vaccine candidate or empty vector control ($1x10^9$ VP or $5x10^9$ VP) were given either IM or IN in Balb/c mice. By day 28, IM injection with Ad5-S-nb2 induced dose dependent levels of systemic IgG but not pulmonary IgA to S protein; IN inoculation induced both systemic IgG and pulmonary IgA (BAL). Abs had neutralizing ability. More lymphocytes in the spleen responded to spike peptides in the high dose IM immunization than in lower doses or the IN immunized groups
- IM or IN immunizations were performed in the rhesus macaque model. Serum IgG was higher, developed faster in the IM-group compared to IN (+oral); IN did elicit serum IgG. (No assessment of neutralizing titers or pulmonary IgA). Elispot assay to assess CMI suggests only IM immunization (not IN route) consistently elicits IFNg producing PMBC
- Intratracheal challenge (d28 or d56 in IM low dose group) was performed with 2×10^4 50% tissue-culture infectious doses (TCID50) in 15 animals (3 per immunization route, 3 Ad5 vector only and 3 never immunized with any Ad5 vector). Immunized macaques were largely protected; most had transient viral loads in the pharyngeal swabs (but 2500-folds lower loads compared to controls by assessing area under the curve)
- Five animals were euthanized (at 7dpi). The nonvaccinated animals (2) had detectable viral genomes in biopsies and severe interstitial pneumonia; immunized animals (3) had no detectible virus in biopsies, and some were described as having mild histological changes
- Limitations: Challenge was shortly after immunizations; intratracheal challenge bypasses the upper respiratory tract; cell mediated immunity was assessed in spleen or PBMCs and not in respiratory lymphatics tissue; small sample size per group.

HUMAN IMMUNOLOGY

20. **Loss of Bcl-6-expressing T follicular helper cells and germinal centers in COVID-19.** Kaneko et al. Cell. August 19**.**

- Analysis of thoracic lymph nodes from persons who succumbed to COVID19 indicated that there was a loss of T follicular helper cells which express Bcl6; consistent with a loss of germinal centers (GC) in the tissue and accumulation of activated $IgD^{-}CD127^{-}$ B cells
- Postmortem tissues (LN and Spleen) also had evidence of an increase in % Th1 cells (but not No. of cells), a decrease in Th2 cells (but no difference in %), and increased TNFa compared to postmortem tissue from non COVID subjects.
- Severely ill COVID patients (hospitalized with CRP>200mg/L) have fewer naïve and early transitional B cells in their PBMCs, but increasing numbers of circulating activated B cells in comparison to convalescent patients and healthy controls
- These B cell findings correlate with severity of clinical parameters (CRP levels, symptom duration, days in the hospital)
- Many activated B cell subsets in the peripheral blood of patients with COVID-19 are specific for SARS-CoV-2-RBD of the spike protein.
- Limitations: No evidence that loss of GC in these patients is linked to durability of the antibody response; hard to define the postmortem tissue as 'acute' COVID19 based on available data; no serology data from patients linked to the postmortem tissues to address links between cellular findings and humoral response
- Implications: Lack of Bcl6+ Tfh cells and germinal center reactions may have implications for humoral immunity, but this is a limited data set