Providence

COVID-19 Resource Desk

#45 | 2.24.2021 to 3.2.2021

Prepared by System Library Services Retraction Watch

New Research

*note, **PREPRINTS** have not undergone formal peer review

COVID-19 related publications by Providence caregivers – see Digital Commons

Basic Science / Virology / Pre-clinical

1. **Circulating SARS-CoV-2 spike N439K variants maintain fitness while evading antibody-mediated immunity.** Thomson EC, Rosen LE, Shepherd JG, et al. *Cell.* 2021 Jan 28:S0092-8674(21)00080-5. doi: 10.1016/j.cell.2021.01.037.
https://www.sciencedirect.com/science/article/pii/S0092867421000805
Findings: SARS-CoV-2 can mutate and evade immunity, with consequences for efficacy of emerging vaccines and antibody therapeutics. Here, we demonstrate that the immunodominant SARS-CoV-2 spike (S) receptor binding motif (RBM) is a highly variable region of S and provide epidemiological, clinical, and molecular characterization of a prevalent, sentinel RBM mutation, N439K. We demonstrate N439K S protein has enhanced binding affinity to the hACE2 receptor, and N439K viruses have similar in vitro replication fitness and cause infections with similar clinical outcomes as compared to wild type. We show the N439K mutation confers resistance against several neutralizing monoclonal antibodies, including one authorized for emergency use by the US FDA, and reduces the activity of some polyclonal sera from persons recovered from infection. Immune evasion mutations that maintain virulence and fitness such as N439K can emerge within SARS-CoV-2 S, highlighting the need for ongoing molecular surveillance to guide development and usage of vaccines and therapeutics.

2. **SARS-CoV-2 spike D614G change enhances replication and transmission.** Zhou B, Thi Nhu Thao T, Hoffmann D, et al. *Nature.* 2021 Feb 26. doi: 10.1038/s41586-021-03361-1.
https://www.nature.com/articles/s41586-021-03361-1
Findings: During the evolution of SARS-CoV-2 in humans a D614G substitution in the spike (S) protein emerged and became the predominant circulating variant (S-614G) of the COVID-19 pandemic. However, whether the increasing prevalence of the S-614G variant represents a fitness advantage that improves replication and/or transmission in humans or is merely due to founder effects remains elusive. Here, we generated isogenic SARS-CoV-2 variants and demonstrate that the S-614G variant has (i) enhanced binding to human host cell surface receptor angiotensin-converting enzyme 2 (ACE2), (ii) increased replication in primary human bronchial and nasal airway epithelial cultures as well as in a novel human ACE2 knock-in mouse model, and (iii) markedly increased replication and transmissibility in hamster and ferret

models of SARS-CoV-2 infection. Collectively, our data show that while the S-614G substitution results in subtle increases in binding and replication in vitro, it provides a real competitive advantage in vivo, particularly during the transmission bottle neck, providing an explanation for the global predominance of S-614G variant among the SARS-CoV-2 viruses currently circulating.

Clinical Syndrome

3. **Characteristics and Factors Associated with COVID-19 Infection, Hospitalization, and Mortality Across Race and Ethnicity.** Dai CL, Kornilov SA, Roper RT, Cohen-Cline H, Jade K, Smith B, Heath JR, Diaz G, Goldman JD, Magis AT, Hadlock JJ. **[Providence authors].** *Clin Infect Dis.* 2021 Feb 20:ciab154. doi: 10.1093/cid/ciab154. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab154/6145124
   Findings: 570,298 patients with known race/ethnicity were tested for SARS-CoV-2, of whom 27.8% were non-White minorities. 54,645 individuals tested positive, with minorities representing 50.1%. Hispanics represented 34.3% of infections but only 13.4% of tests. While generally younger than White patients, Hispanics had higher rates of diabetes but fewer other comorbidities. 8,536 patients were hospitalized and 1,246 died, of whom 56.1% and 54.4% were non-White, respectively. Racial/ethnic distributions of outcomes across the health system tracked with state-level statistics. Increased odds of testing positive and hospitalization were associated with all minority races/ethnicities. Hispanic patients also exhibited increased morbidity, and Hispanic race/ethnicity was associated with in-hospital mortality. Major healthcare disparities were evident, especially among Hispanics who tested positive at a higher rate, required excess hospitalization and mechanical ventilation, and had higher odds of in-hospital mortality despite younger age. Targeted, culturally-responsive interventions and equitable vaccine development and distribution are needed to address the increased risk of poorer COVID-19 outcomes among minority populations.

4. **Arterial and venous thromboembolism in COVID-19: a study-level meta-analysis.** Tan BK, Mainbourg S, Friggeri A, et al. *Thorax.* 2021 Feb 23:thoraxjnl-2020-215383. doi: 10.1136/thoraxjnl-2020-215383. https://thorax.bmj.com/content/early/2021/02/22/thoraxjnl-2020-215383
   Findings: We analysed findings from 102 studies (64 503 patients). The frequency of COVID-19-related VTE was 14.7% (95% CI 12.1% to 17.6%, I2=94%; 56 studies; 16 507 patients). The overall prevalence rates of pulmonary embolism (PE) and leg deep vein thrombosis were 7.8% (95% CI 6.2% to 9.4%, I2=94%; 66 studies; 23 117 patients) and 11.2% (95% CI 8.4% to 14.3%, I2=95%; 48 studies; 13 824 patients), respectively. Patients admitted in the ICU for severe COVID-19 had a high risk of VTE. Conversely, further studies are needed to determine the specific effects of COVID-19 on the risk of ATE or VTE in less severe forms of the disease.

5. **Cardiac arrhythmias in critically ill patients with coronavirus disease 2019: a retrospective population-based cohort study.** Wetterslev M, Jacobsen PK, Hassager C, et al. *Acta Anaesthesiol Scand*. 2021 Feb 27. doi: 10.1111/aas.13806. https://onlinelibrary.wiley.com/doi/10.1111/aas.13806

Findings: From the 7 ICUs we included 155 patients with COVID-19. The incidence of cardiac arrhythmias in the ICU was 57/155 (37%, 95% confidence interval 30-45), and 39/57 (68%) of these patients had this as new-onset arrhythmia. Previous history of tachyarrhythmias and higher disease severity at ICU admission were associated with cardiac arrhythmias in the adjusted analysis. New-onset supraventricular arrhythmias were frequent in ICU patients with COVID-19 and related to previous history of tachyarrhythmias and severity of the acute disease. The mortality was high in these patients despite the frequent use of interventions against arrhythmias.

6. **ST-segment elevation in patients with COVID-19: a systematic review.** Diaz-Arocutipa C, Torres-Valencia J, Saucedo-Chinchay J, Cuevas C. *J Thromb Thrombolysis*. 2021 Mar 1. doi: 10.1007/s11239-021-02411-9. https://link.springer.com/article/10.1007/s11239-021-02411-9
Findings: Forty-two studies (35 case reports and seven case series) involving 161 patients were included. The mean age was 62.7 ± 13.6 years and 75% were men. The most frequent symptom was chest pain (78%). Eighty-three percent of patients had obstructive CAD. Patients with non-obstructive CAD had more diffuse ST-segment elevation (13% versus 1%, p = 0.03) and diffuse left ventricular wall-motion abnormality (23% versus 3%, p = 0.02) compared to obstructive CAD. In patients with previous coronary stent (n = 17), the 76% presented with stent thrombosis. In the majority of cases, the main reperfusion strategy was primary percutaneous coronary intervention instead of fibrinolysis. The in-hospital mortality was 30% without difference between patients with (30%) or without (31%) obstructive CAD. Our data suggest that a relatively high proportion of COVID-19 patients with ST-segment elevation had non-obstructive CAD. The prognosis was poor across groups. However, our findings are based on case reports and case series that should be confirmed in future studies.

Diagnostics & Screening

7. **Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19.** Cochrane COVID-19 Diagnostic Test Accuracy Group. *Cochrane Database Syst Rev.* 2021 Feb 23;2:CD013665. doi:10.1002/14651858.CD013665.pub2. Update of Cochrane Database Syst Rev. 2020 Jul 7;7:CD013665.
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013665/full
AUTHORS' CONCLUSIONS: The majority of individual signs and symptoms included in this review appear to have very poor diagnostic accuracy, although this should be interpreted in the context of selection bias and heterogeneity between studies. Based on currently available data, neither absence nor presence of signs or symptoms are accurate enough to rule in or rule out COVID-19. The presence of anosmia or ageusia may be useful as a red flag for COVID-19. The presence of fever or cough, given their high sensitivities, may also be useful to identify people for further testing. Prospective studies in an unselected population presenting to primary care or hospital outpatient settings, examining combinations of signs and symptoms to evaluate the syndromic presentation of COVID-19, are still urgently needed. Results from such studies could inform subsequent management decisions.

8. **Lessons from applied large-scale pooling of 133,816 SARS-CoV-2 RT-PCR tests.** Barak N, Ben-Ami R, Sido T, et al. *Sci Transl Med.* 2021 Feb 22:eabf2823. doi: 10.1126/scitranslmed.abf2823. https://stm.sciencemag.org/content/early/2021/02/19/scitranslmed.abf2823
   Findings: Here we report an analysis of 133,816 samples collected between April-September 2020 and tested by Dorfman pooling for the presence of SARS-CoV-2. We spared 76% of RNA extraction and RT-PCR tests, despite the frequently changing prevalence (0.5%-6%). We observed pooling efficiency and sensitivity that exceeded theoretical predictions, which resulted from the non-random distribution of positive samples in pools. Overall, our findings support the use of pooling for efficient large-scale SARS-CoV-2 testing.

9. **Association of SARS-CoV-2 Seropositive Antibody Test with Risk of Future Infection.** Harvey RA, Rassen JA, Kabelac CA, et al. *JAMA Intern Med*. 2021 Feb 24. doi: 10.1001/jamainternmed.2021.0366.
   https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2776810
   Findings: The cohort included 3 257 478 unique patients with an index antibody test; 56% were female with a median (SD) age of 48 (20) years. Of these, 2 876 773 (88.3%) had a negative index antibody result, and 378 606 (11.6%) had a positive index antibody result. In this cohort study, patients with positive antibody test results were initially more likely to have positive NAAT results, consistent with prolonged RNA shedding, but became markedly less likely to have positive NAAT results over time, suggesting that seropositivity is associated with protection from infection. The duration of protection is unknown, and protection may wane over time.

10. **Performance and Implementation Evaluation of the Abbott BinaxNOW Rapid Antigen Test in a High-throughput Drive-through Community Testing Site in Massachusetts.** Pollock NR, Jacobs JR, Tran K, et al. *J Clin Microbiol*. 2021 Feb 23:JCM.00083-21. doi: 10.1128/JCM.00083-21. https://jcm.asm.org/content/early/2021/02/19/JCM.00083-21.long
    Findings: BinaxNOW had very high specificity in both adults and children and very high sensitivity in newly symptomatic adults. Overall, 95.8% sensitivity was observed with Ct ≤ 30. These data support public health recommendations for use of the BinaxNOW test in adults with symptoms for ≤7 days without RT-PCR confirmation. Excellent inter-operator agreement indicates that an individual can perform and read the BinaxNOW test alone. A skilled laboratorian can perform and read 20 tests per hour. Careful attention to temperature is critical.

11. **CT findings and dynamic imaging changes of COVID-19 in 2908 patients: a systematic review and meta-analysis.** Zhou X, Pu Y, Zhang D, et al. *Acta Radiol*. 2021 Feb 25:284185121992655. doi: 10.1177/0284185121992655.
    https://journals.sagepub.com/doi/full/10.1177/0284185121992655
    The aim of the review was to explore the chest CT findings and dynamic CT changes of COVID-19 using systematic evaluation methods, instructing the clinical imaging diagnosis. A systematic literature search was performed. The quality of included literature was evaluated with a quality assessment tool, followed by data extraction and meta-analysis. Homogeneity and publishing bias were analyzed. A total of 109 articles were included, involving 2908 adults with COVID-19. The lesions often occurred in bilateral lungs (74%) and were multifocal (77%) with subpleural

distribution (81%). Lesions often showed ground-glass opacity (GGO) (68%), followed by GGO with consolidation (48%). The thickening of small vessels (70%) and thickening of intralobular septum (53%) were also common. The dynamic changes of chest CT manifestations showed that lesions were absorbed and improved gradually after reaching the peak (80%), had progressive deterioration (55%), were absorbed and improved gradually (46%), fluctuated (22%), or remained stable (26%). The review showed the common and key CT features and the dynamic imaging change patterns of COVID-19, helping with timely management during COVID-19 pandemic.

Epidemiology & Public Health

12. **COVID-19 Outbreak among Attendees of an Exercise Facility — Chicago, Illinois, August–September 2020.** Lendacki FR, Teran RA, Gretsch S, Fricchione MJ, Kerins JL. *MMWR Morb Mortal Wkly Rep.* ePub: 24 February 2021. DOI: http://dx.doi.org/10.15585/mmwr.mm7009e2
Findings: In August 2020, 55 COVID-19 cases were identified among 81 attendees of indoor high-intensity classes at a Chicago exercise facility. Twenty-two (40%) persons with COVID-19 attended on or after the day symptoms began. Most attendees (76%) wore masks infrequently, including persons with (84%) and without COVID-19 (60%). What are the implications for public health practice? To reduce SARS-CoV-2 transmission in fitness facilities, attendees should wear a mask, including during high-intensity activities when ≥6 ft apart. In addition, facilities should enforce physical distancing, improve ventilation, and encourage attendees to isolate after symptom onset or receiving a positive SARS-CoV-2 test result and to quarantine after a potential exposure to SARS-CoV-2 and while awaiting test results. Exercising outdoors or virtually could further reduce SARS-CoV-2 transmission risk.
***See also*: **Community Transmission of SARS-CoV-2 at Three Fitness Facilities — Hawaii, June–July 2020.** Groves LM, Usagawa L, Elm J, et al. MMWR Morb Mortal Wkly Rep. ePub: 24 February 2021. DOI: http://dx.doi.org/10.15585/mmwr.mm7009e1

13. **Impact of the Influenza Vaccine on COVID-19 Infection Rates and Severity.** Conlon A, Ashur C, Washer L, Eagle KA, Hofmann Bowman MA. *Am J Infect Control*. 2021 Feb 22:S0196-6553(21)00089-4. doi: 10.1016/j.ajic.2021.02.012. https://www.ajicjournal.org/article/S0196-6553(21)00089-4/fulltext
Findings: A total of 27,201 patients received laboratory testing for COVID-19. The odds of testing positive for COVID-19 was reduced in patients who received an influenza vaccine compared to those who did not (odds ratio 0.76, 95% CI 0.68 to 0.86; P < 0.001). Vaccinated patients testing positive for COVID-19 were less likely to require hospitalization, or mechanical ventilation and had a shorter hospital length of stay. Influenza vaccination is associated with decreased positive COVID-19 testing and improved clinical outcomes and should be promoted to reduce the burden of COVID-19.

14. **Coronavirus Disease 2019 Hospitalizations Attributable to Cardiometabolic Conditions in the United States: A Comparative Risk Assessment Analysis.** O'Hearn M, Liu J, Cudhea F, Micha R, Mozaffarian D. *J Am Heart Assoc.* 2021 Feb 25:e019259. doi: 10.1161/JAHA.120.019259. https://www.ahajournals.org/doi/10.1161/JAHA.120.019259

Findings: As of November 18, 2020, an estimated 906 849 COVID-19 hospitalizations occurred in US adults. Of these, an estimated 20.5% of COVID-19 hospitalizations were attributable to diabetes mellitus, 30.2% (UI, 28.2-32.3) to total obesity (body mass index ≥30 kg/m2), 26.2% (UI, 24.3-28.3) to hypertension, and 11.7% (UI, 9.5-14.1) to heart failure. Considered jointly, 63.5% (UI, 61.6-65.4) or 575 419 (UI, 559 072-593 412) of COVID-19 hospitalizations were attributable to these 4 conditions. Large differences were seen in proportions of cardiometabolic risk-attributable COVID-19 hospitalizations by age and race/ethnicity, with smaller differences by sex. A substantial proportion of US COVID-19 hospitalizations appear attributable to major cardiometabolic conditions. These results can help inform public health prevention strategies to reduce COVID-19 healthcare burdens.

15. **Suspected Recurrent SARS-CoV-2 Infections among Residents of a Skilled Nursing Facility during a Second COVID-19 Outbreak — Kentucky, July–November 2020.** Cavanaugh AM, Thoroughman D, Miranda H, Spicer K. *MMWR Morb Mortal Wkly Rep* 2021;70:273–277. DOI: http://dx.doi.org/10.15585/mmwr.mm7008a3
Findings: Five residents of a skilled nursing facility received positive SARS-CoV-2 nucleic acid test results in two separate COVID-19 outbreaks separated by 3 months. Residents received at least four negative test results between the two outbreaks, suggesting the possibility of reinfection. Severity of disease in the five residents during the second outbreak was worse than that during the first outbreak and included one death. What are the implications for public health practice? Skilled nursing facilities should use strategies to reduce the risk for SARS-CoV-2 transmission among all residents, including among those who have previously had a COVID-19 diagnosis. Vaccination of residents and health care personnel in this setting is particularly important to protect residents.

16. **Changes in SARS CoV-2 Seroprevalence over Time in Ten Sites in the United States, March - August, 2020.** Lim T, Delorey M, Bestul N, et al. *Clin Infect Dis.* 2021 Feb 26:ciab185. doi: 10.1093/cid/ciab185. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab185/6152134
Findings: We performed serologic testing on a convenience sample of residual sera obtained from persons of all ages, at ten sites in the United States from March 23 through August 14, 2020, from routine clinical testing at commercial laboratories. Seroprevalence remained below 10% at all sites except New York and Florida, where it reached 23.2% and 13.3%, respectively. Statistically significant increases in seroprevalence followed peaks in reported cases in New York, South Florida, Utah, Missouri and Louisiana. In the absence of such peaks, some significant decreases were observed over time in New York, Missouri, Utah, and Western Washington. The estimated cumulative number of infections with detectable antibody response continued to exceed reported cases in all sites. CONCLUSIONS: Estimated seroprevalence was low in most sites, indicating that most people in the U.S. have not been infected with SARS-CoV-2 as of July 2020. The majority of infections are likely not reported. Decreases in seroprevalence may be related to changes in healthcare-seeking behavior, or evidence of waning of detectable anti-SARS CoV-2 antibody levels at the population level. Thus, seroprevalence estimates may underestimate the cumulative incidence of infection.

17. **Household Transmission of SARS-CoV-2.** Metlay JP, Haas JS, Soltoff AE, Armstrong KA. *JAMA Netw Open.* 2021 Feb 1;4(2):e210304. doi: 10.1001/jamanetworkopen.2021.0304. https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2776908
Findings: Our study showed an overall household infection risk of 10.1%, consistent with reported transmission risk based on more traditional contact tracing, including a recent meta-analysis that reported an overall transmission risk of 17.1%, although there was wide variation across studies.

Healthcare Delivery & Healthcare Workers

18. **Short-term Effects of Cancelled Elective Procedures due to COVID-19: Evidence from the Veterans Affairs Healthcare System.** Tran LD, Rose L, Urech T, Dalton A, Wu S, Vashi AA. *Ann Surg.* 2021 Feb 12. doi: 10.1097/SLA.0000000000004809. https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=ovft&AN=00000658-900000000-93719&PDF=y
Findings: Patients with elective surgical procedures cancelled due to COVID-19 were no more likely to have an ED visit in the 30- (Difference: -4.3% pts; 95% CI: -0.078, -0.007) and 90 days (-0.9% pts; 95% CI: -0.068, 0.05) following the expected case date. Patients with cancellations had no difference in 30- (Difference: 0.1% pts; 95% CI: -0.008, 0.01) and 90-day (Difference: -0.4% pts; 95% CI: -0.016, 0.009) mortality rates when compared to similar patients with similar procedures that were completed in previous years. CONCLUSIONS: The pause in elective surgical cases was not associated with short-term adverse outcomes in VA hospitals, suggesting appropriate surgical case triage and management. Further study will be essential to determine if the delayed cases were associated with longer-term effects.

19. **A multicenter analysis of the clinical microbiology and antimicrobial usage in hospitalized patients in the US with or without COVID-19.** Puzniak L, Finelli L, Yu KC, et al. *BMC Infect Dis.* 2021 Feb 27;21(1):227. doi: 10.1186/s12879-021-05877-3. https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-021-05877-3
Findings: This multicenter retrospective study included patients with > 1 day of inpatient admission and discharge/death between March 1 and May 31, 2020 at 241 US acute care hospitals in the BD Insights Research Database. We assessed microbiological testing data, antimicrobial utilization in admitted patients with ≥24 h of antimicrobial therapy, and length of stay (LOS). Despite similar rates of non-SARS-CoV-2 pathogens in SARS-CoV-2-positive, -negative, and -untested patients, SARS-CoV-2 was associated with higher rates of hospital-onset infections, greater antimicrobial usage, and extended hospital and ICU LOS. This finding highlights the heavy burden of the COVID-19 pandemic on healthcare systems and suggests possible opportunities for diagnostic and antimicrobial stewardship.

Prognosis

20. **Comorbid illnesses are associated with altered adaptive immune responses to SARS-CoV-2.** Yu KK, Fischinger S, Robert Y Choi **[Providence author]**. *JCI Insight*. 2021 Feb 23;146242. doi: 10.1172/jci.insight.146242. https://insight.jci.org/articles/view/146242

Findings: Comorbid medical illnesses, such as obesity and diabetes, are associated with more severe COVID-19, hospitalization, and death. However, the role of the immune system in mediating these clinical outcomes has not been determined. We used multi-parameter flow cytometry and systems serology to comprehensively profile the functions of T cells and antibodies targeting spike, nucleocapsid, and envelope proteins in a convalescent cohort of COVID-19 subjects who were either hospitalized (n=20) or not hospitalized (n=40). To avoid confounding, subjects were matched by age, sex, ethnicity, and date of symptom onset. Surprisingly, we found that the magnitude and functional breadth of virus-specific CD4 T cell and antibody responses were consistently higher among hospitalized subjects, particularly those with medical comorbidities. However, an integrated analysis identified more coordination between polyfunctional CD4 T-cells and antibodies targeting the S1 domain of spike among subjects that were not hospitalized. These data reveal a functionally diverse and coordinated response between T cells and antibodies targeting SARS-CoV-2, which is reduced in the presence of comorbid illnesses that are known risk factors for severe COVID-19.

21. **Association of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers with the Risk of Hospitalization and Death in Hypertensive Patients with Coronavirus Disease-19.** Khera R, Clark C, Lu Y, et al. *J Am Heart Assoc.* 2021 Feb 24:e018086. doi: 10.1161/JAHA.120.018086. https://www.ahajournals.org/doi/10.1161/JAHA.120.018086
Findings: In a concurrent inpatient cohort of 7,933 hospitalized with COVID-19, we tested their association with in-hospital mortality. The robustness of the observations was assessed in a contemporary cohort (May - August). In the outpatient study, neither ACE inhibitors (HR, 0.77, 0.53-1.13, P=0.18), nor ARBs (HR, 0.88, 0.61-1.26, P=0.48), were associated with hospitalization risk. ACE inhibitors were associated with lower hospitalization risk in the older Medicare group (HR, 0.61, 0.41-0.93, P=0.02), but not the younger commercially insured group (HR, 2.14, 0.82-5.60, P=0.12; P-interaction 0.09). Neither ACE inhibitors nor ARBs were associated with lower hospitalization risk in either population in the validation cohort. In the primary inpatient study cohort, neither ACE inhibitors (0.97, 0.81-1.16; P=0.74) nor ARBs (1.15, 0.95-1.38, P=0.15) were associated with in-hospital mortality. These observations were consistent in the validation cohort. Conclusions ACE inhibitors and ARBs were not associated with COVID-19 hospitalization or mortality. Despite early evidence for a potential association between ACE inhibitors and severe COVID-19 prevention in older individuals, the inconsistency of this observation in recent data argues against a role for prophylaxis.

22. **Efficacy of Serum Angiotensin II Levels in Prognosis of Patients with Coronavirus Disease 2019.** Ozkan S, Cakmak F, Konukoglu D, et al. *Crit Care Med*. 2021 Feb 26. doi: 10.1097/CCM.0000000000004967.
https://journals.lww.com/ccmjournal/Abstract/9000/Efficacy_of_Serum_Angiotensin_II_Levels_in.95319.aspx
Findings: Angiotensin II levels were studied by enzyme-linked immunosorbent assay method. A total of 112 patients were included in the study, of which 63.4% of the patients were men. The serum angiotensin II levels were statistically significantly lower in the patients with coronavirus disease 2019 compared with the healthy control group ($p < 0.001$). CONCLUSIONS: The serum

angiotensin II levels decrease significantly in patients with coronavirus disease 2019, and this decrease is correlated with lung damage.

23. **Elevated glucose level leads to rapid COVID-19 progression and high fatality.** Wang W, Shen M, Tao Y, et al. *BMC Pulm Med.* 2021 Feb 24;21(1):64. doi: 10.1186/s12890-021-01413-w. https://bmcpulmmed.biomedcentral.com/articles/10.1186/s12890-021-01413-w
Findings: Among 1,758 mild or moderate patients at admission, 474 (27.0%) progressed to a severe or critical stage. Age above 60 years, elevated levels of blood glucose, respiratory rate, fever, chest tightness, c-reaction protein, lactate dehydrogenase, direct bilirubin, and low albumin and lymphocyte count were significant risk factors for progression. Of 675 severe or critical patients at admission, 41 (6.1%) died. Age above 74 years, elevated levels of blood glucose, fibrinogen and creatine kinase-MB, and low plateleta count were significant risk factors for fatality. Patients with elevated blood glucose level were 58% more likely to progress and 3.22 times more likely to die of COVID-19. CONCLUSIONS: Older age, elevated glucose level, and clinical indicators related to systemic inflammatory responses and multiple organ failures, predict both the disease progression and the fatality of COVID-19 patients.

24. **Lipid metabolism changes in patients with severe COVID-19.** Li Y, Zhang Y, Lu R, et al. *Clin Chim Acta*. 2021 Feb 24:S0009-8981(21)00052-8. doi: 10.1016/j.cca.2021.02.011. https://www.sciencedirect.com/science/article/pii/S0009898121000528
Findings: Altogether, 424 severe COVID-19 patients, including 34 non-survivors and 390 survivors, were included in the final analyses. During hospitalization, low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-I (apoA-I) showed an increasing trend in survivors, but showed a downward trend in non-survivors. During severe COVID-19, HDL-C and apoA-I concentrations are dramatically decreased in non-survivors. Moreover, High CRP/HDL-C ratio is significantly associated with an increase in mortality and a poor prognosis.

25. **Association between antecedent statin use and decreased mortality in hospitalized patients with COVID-19.** Gupta A, Madhavan MV, Poterucha TJ, et al. *Nat Commun*. 2021 Feb 26;12(1):1325. doi: 10.1038/s41467-021-21553-1. https://www.nature.com/articles/s41467-021-21553-1
Findings: This is a retrospective analysis of patients admitted with COVID-19 from February 1st through May 12th, 2020 with study period ending on June 11th, 2020. Antecedent statin use was assessed using medication information available in the electronic medical record. We constructed a multivariable logistic regression model to predict the propensity of receiving statins, adjusting for baseline sociodemographic and clinical characteristics, and outpatient medications. The primary endpoint includes in-hospital mortality within 30 days. A total of 2626 patients were admitted during the study period, of whom 951 (36.2%) were antecedent statin users. Among 1296 patients (648 statin users, 648 non-statin users) identified with 1:1 propensity-score matching, statin use is significantly associated with lower odds of the primary endpoint in the propensity-matched cohort (OR 0.47, 95% CI 0.36-0.62, $p < 0.001$). We conclude that antecedent statin use in patients hospitalized with COVID-19 is associated with lower inpatient mortality.

26. **Lactate-dehydrogenase associated with mortality in hospitalized patients with COVID-19 in Mexico: a multi-centre retrospective cohort study.** Vidal-Cevallos P, Higuera-De-La-Tijera F, Chávez-Tapia NC, et al. *Ann Hepatol*. 2021 Feb 26:100338. doi: 10.1016/j.aohep.2021.100338. https://www.sciencedirect.com/science/article/pii/S1665268121000375
Findings: We performed a retrospective multi-centre cohort study with 377 hospitalized patients with confirmed SARS-CoV-2 in three centres in Mexico City, Mexico, who were ≥18 years old and died or were discharged between April 1 and May 31, 2020. A total of 377 patients were evaluated, 298 (79.1%) patients were discharged, and 79 (20.9%) patients died during hospitalization. Non-survivors were older, with a median age of 46.7 ± 25.7 years old, most patients were male. An ALT > 61 U/l (OR 3.45, 95% CI 1.27-9.37; p = 0.015), C-reactive protein (CRP) > 231 mg/l (OR 4.71, 95% CI 2.35-9.46; p = 0.000), LDH > 561 U/l (OR 3.03, 95% CI 1.40-6.55; p = 0.005) were associated with higher odds for in-hospital death. CONCLUSIONS: Our results indicate that higher levels of LDH, CRP, and ALT are associated with higher in-hospital mortality risk in Mexican patients admitted with COVID-19.

27. **Development of Severe COVID-19 Adaptive Risk Predictor (SCARP), a Calculator to Predict Severe Disease or Death in Hospitalized Patients with COVID-19.** Wongvibulsin S, Garibaldi BT, Antar AAR, et al. *Ann Intern Med*. 2021 Mar 2. doi: 10.7326/M20-6754. https://www.acpjournals.org/doi/full/10.7326/M20-6754
OBJECTIVE: To develop the Severe COVID-19 Adaptive Risk Predictor(SCARP) (https://rsconnect.biostat.jhsph.edu/covid_trajectory/), a novel tool that can provide dynamic risk predictions for progression from moderate disease to severe illness or death in patients with COVID-19 at any time within the first 14 days of their hospitalization. Findings: A clinical registry for patients hospitalized with COVID-19 was the primary data source; data included demographic characteristics, admission source, comorbid conditions, time-varying vital signs, laboratory measurements, and clinical severity. Random forest for survival, longitudinal, and multivariate (RF-SLAM) data analysis was applied to predict the 1-day and 7-day risks for progression to severe disease or death for any given day during the first 14 days of hospitalization. RESULTS: Among 3163 patients admitted with moderate COVID-19, 228 (7%) became severely ill or died in the next 24 hours; an additional 355 (11%) became severely ill or died in the next 7 days. CONCLUSION: Using the predictive power of RF-SLAM and longitudinal data from more than 3000 patients hospitalized with COVID-19, an interactive tool was developed that rapidly and accurately provides the probability of an individual patient's progression to severe illness or death on the basis of readily available clinical information.

28. **Medical vulnerability of individuals with Down syndrome to severe COVID-19-data from the Trisomy 21 Research Society and the UK ISARIC4C survey.** T21RS COVID-19 Initiative. *EClinicalMedicine.* 2021 Feb 22:100769. doi: 10.1016/j.eclinm.2021.100769. https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00049-3/fulltext
FINDINGS: Similar to the general population, the most frequent signs and symptoms of COVID-19 were fever, cough, and shortness of breath. Joint/muscle pain and vomiting or nausea were less frequent ($p < 0.01$), whereas altered consciousness/confusion were more frequent ($p < 0.01$). Risk factors for hospitalization and mortality were similar to the general population with

the addition of congenital heart defects as a risk factor for hospitalization. Mortality rates showed a rapid increase from age 40 and were higher in patients with DS (T21RS DS versus non-DS patients: risk ratio (RR) = 3.5 (95%-CI=2.6;4.4), ISARIC4C DS versus non-DS patients: RR = 2.9 (95%-CI=2.1;3.8)) even after adjusting for known risk factors for COVID-19 mortality. INTERPRETATION: Leading signs/symptoms of COVID-19 and risk factors for severe disease course are similar to the general population. However, individuals with DS present significantly higher rates of medical complications and mortality, especially from age 40.

Survivorship & Rehabilitation

29. **A Review of Persistent Post-COVID Syndrome (PPCS).** Terese C Hammond, Santosh Kesari, et al. **[Providence authors]**. *Clin Rev Allergy Immunol.* 2021 Feb 20;1-9. doi: 10.1007/s12016-021-08848-3. https://link.springer.com/article/10.1007/s12016-021-08848-3
Persistent post-COVID syndrome, also referred to as long COVID, is a pathologic entity, which involves persistent physical, medical, and cognitive sequelae following COVID-19, including persistent immunosuppression as well as pulmonary, cardiac, and vascular fibrosis. Pathologic fibrosis of organs and vasculature leads to increased mortality and severely worsened quality of life. Inhibiting transforming growth factor beta (TGF-β), an immuno- and a fibrosis modulator, may attenuate these post-COVID sequelae. Current preclinical and clinical efforts are centered on the mechanisms and manifestations of COVID-19 and its presymptomatic and prodromal periods; by comparison, the postdrome, which occurs in the aftermath of COVID-19, which we refer to as persistent post-COVID-syndrome, has received little attention. Potential long-term effects from post-COVID syndrome will assume increasing importance as a surge of treated patients are discharged from the hospital, placing a burden on healthcare systems, patients' families, and society in general to care for these medically devastated COVID-19 survivors. This review explores underlying mechanisms and possible manifestations of persistent post-COVID syndrome, and presents a framework of strategies for the diagnosis and management of patients with suspected or confirmed persistent post-COVID syndrome.

30. **Persistence of antibodies to SARS-CoV-2 in relation to symptoms in a nationwide prospective study.** den Hartog G, Vos ERA, van den Hoogen LL, et al. *Clin Infect Dis.* 2021 Feb 24:ciab172. doi: 10.1093/cid/ciab172. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab172/6149064
Findings: Participants from a prospective representative serological study in the Netherlands were included based on IgG seroconversion to the Spike S1 protein of SARS-CoV-2 (N=353), with up to three consecutive serum samples per seroconverted participant (N=738). While SARS-CoV-2-specific IgM and IgA antibodies declined rapidly after the first month post onset of disease, specific IgG was still present in 92% of the participants after 7 months. SARS-CoV-2-specific IgG antibodies persist and show increasing avidity over time, indicative of underlying immune maturation. These data support development of immune memory against SARS-CoV-2 providing insight into protection of the general unvaccinated part of the population.

31. **Seasonal human coronavirus antibodies are boosted upon SARS-CoV-2 infection but not associated with protection.** Anderson EM, Goodwin EC, Verma A, et al. *Cell*. 2021 Feb 9:S0092-

8674(21)00160-4. doi: 10.1016/j.cell.2021.02.010.
https://www.sciencedirect.com/science/article/pii/S0092867421001604
Findings: SARS-CoV-2 has rapidly spread within the human population. Although SARS-CoV-2 is a novel coronavirus, most humans had been previously exposed to other antigenically distinct common seasonal human coronaviruses (hCoVs) before the COVID-19 pandemic. Here, we quantified levels of SARS-CoV-2-reactive antibodies and hCoV-reactive antibodies in serum samples collected from 431 humans before the COVID-19 pandemic. We then quantified pre-pandemic antibody levels in serum from a separate cohort of 251 individuals who became PCR-confirmed infected with SARS-CoV-2. Finally, we longitudinally measured hCoV and SARS-CoV-2 antibodies in the serum of hospitalized COVID-19 patients. Our studies indicate that most individuals possessed hCoV-reactive antibodies before the COVID-19 pandemic. We determined that ⍰20% of these individuals possessed non-neutralizing antibodies that cross-reacted with SARS-CoV-2 spike and nucleocapsid proteins. These antibodies were not associated with protection against SARS-CoV-2 infections or hospitalizations, but they were boosted upon SARS-CoV-2 infection.

32. **Patients with uncomplicated COVID-19 have long-term persistent symptoms and functional impairment similar to patients with severe COVID-19: a cautionary tale during a global pandemic.** Jacobson KB, Rao M, Bonilla H, et al. *Clin Infect Dis*. 2021 Feb 7:ciab103. doi: 10.1093/cid/ciab103. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab103/6129932
Findings: To assess the prevalence of persistent functional impairment after COVID-19, we assessed 118 individuals 3-4 months after their initial COVID-19 diagnosis with a symptom survey, work productivity and activity index questionnaire, and 6-minute walk test. We found significant persistent symptoms and functional impairment, even in non-hospitalized patients with COVID-19.

33. **A Follow-Up Study of Lung Function and Chest Computed Tomography at 6 Months after Discharge in Patients with Coronavirus Disease 2019.** Wu Q, Zhong L, Li H, et al. *Can Respir J*. 2021 Feb 13;2021:6692409. doi: 10.1155/2021/6692409. eCollection 2021.
https://www.hindawi.com/journals/crj/2021/6692409/
Findings: The main symptoms 6 months after discharge were fatigue and exertional dyspnea, experienced by 24.1% and 18.5% of patients, respectively, followed by smell and taste dysfunction (9.3%) and cough (5.6%). One patient dropped out of the pulmonary function tests. Of the remaining 54 patients, 41.5% had pulmonary dysfunction. Specifically, 7.5% presented with restrictive ventilatory dysfunction (forced vital capacity <80% of the predicted value), 18.9% presented with small airway dysfunction, and 32.1% presented with pulmonary diffusion impairment (diffusing capacity for carbon monoxide <80% of the predicted value). Of the 54 patients enrolled, six patients dropped out of the chest CT tests. Eleven of the remaining 48 patients presented with abnormal lung CT findings 6 months after discharge. Patients with residual lung lesions were more common in the severe group (52.6%) than in the moderate group (3.4%); a higher proportion of patients had involvement of both lungs (42.1% vs. 3.4%) in the severe group. The residual lung lesions were mainly ground-glass opacities (20.8%) and linear opacities (14.6%). Semiquantitative visual scoring of the CT findings revealed significantly

higher scores in the left, right, and both lungs in the severe group than in the moderate group. COVID-19 patients 6 months after discharge mostly presented with fatigue and exertional dyspnea, and their pulmonary dysfunction was mostly characterized by pulmonary diffusion impairment. As revealed by chest CT, the severe group had a higher prevalence of residual lesions than the moderate group, and the residual lesions mostly manifested as ground-glass opacities and linear opacities.

34. **Longitudinal follow-up of IgG anti-nucleocapsid antibodies in SARS-CoV-2 infected patients up to eight months after infection.** Van Elslande J, Oyaert M, Ailliet S, et al. *J Clin Virol.* 2021 Feb 18;136:104765. doi: 10.1016/j.jcv.2021.104765. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7891078/
Findings: Most SARS-CoV-2 infected patients develop IgG antibodies within 2-3 weeks after symptom onset. Antibody levels have been shown to gradually decrease in the first months after infection, but few data are available at six months or later. 22.2 % of mild and 2.6 % of severe COVID-19 cases never seroconverted ($p < 0.001$). Of the mild patients who seroconverted 0-59 days after PCR; 18.8 %, 40.0 % and 61.1 % were seronegative in the windows 60-119 days, 120-179 days and 180-240 days after PCR, respectively. In severe patients, these numbers were 1.9 %, 10.8 % and 29.4 % respectively ($p < 0.05$ each). Antibody levels were significantly higher in severe patients compared to mild patients in each 60 day window ($p < 0.001$ each). CONCLUSIONS: SARS-CoV-2 anti-N IgG antibody levels steadily decreased after 2 months up to 8 months post PCR. Of severe COVID-19 patients, 70.6 % remained positive up to eight months after infection. Antibody levels were significantly lower in mild SARS-CoV-2 infected patients and 61.1 % became seronegative within 6 months after the first positive PCR.

Therapeutics

35. **Progesterone in Addition to Standard of Care Versus Standard of Care Alone in the Treatment of Men Hospitalized with Moderate to Severe COVID-19: A Randomized, Controlled Pilot Trial.** Ghandehari S, Matusov Y, Pepkowitz S, et al. Chest. 2021 Feb 20:S0012-3692(21)00289-0. doi: 10.1016/j.chest.2021.02.024. https://journal.chestnet.org/article/S0012-3692(21)00289-0/fulltext
Findings: Severity of illness in COVID-19 is consistently lower in women. We assessed whether adding progesterone to standard of care would improve clinical outcomes of hospitalized men with moderate to severe COVID-19. Forty-two patients were enrolled from April - August 2020; 22 were randomized to the control group and 20 to the progesterone group. Two patients from the progesterone group withdrew from the study prior to receiving progesterone. There was a 1.5-point overall improvement in median clinical status score on a seven-point ordinal scale from baseline to Day 7 in patients in the progesterone group as compared to controls (95%CI:0.0-2.0; P=0.024). There were no serious adverse events attributable to progesterone. Patients treated with progesterone required 3 fewer days of supplemental oxygen (median of 4.5 vs 7.5 days) and were hospitalized for 2.5 fewer days (median of 7.0 vs 9.5 days) as compared to controls. Progesterone at a dose of 100 mg, twice daily by subcutaneous injection

in addition to SOC may represent a safe and effective approach for treatment in hypoxemic men with moderate to severe COVID-19.

36. **Effect of a genetically engineered interferon-alpha versus traditional interferon-alpha in the treatment of moderate-to-severe COVID-19: a randomised clinical trial.** Li C, Luo F, Liu C, et al. *Ann Med.* 2021 Dec;53(1):391-401. doi: 10.1080/07853890.2021.1890329. https://www.tandfonline.com/doi/full/10.1080/07853890.2021.1890329
Findings: In this multicenter randomized (1:1) trial, patients hospitalized with moderate-to-severe COVID-19 received either rSIFN-co nebulization or interferon-alpha nebulization added to baseline antiviral agents for no more than 28 days. The primary endpoint was the time to clinical improvement. A total of 94 patients were included in the safety set (46 patients assigned to rSIFN-co group, 48 to interferon-alpha group). The time to clinical improvement was 11.5 days versus 14.0 days (95% CI 1.10 to 2.81, p = .019); the overall rate of clinical improvement on day 28 was 93.5% versus 77.1% (difference, 16.4%; 95% CI 3% to 30%); the time to radiological improvement was 8.0 days versus 10.0 days (p = .002), the time to virus nucleic acid negative conversion was 7.0 days versus 10.0 days (p = .018) in the rSIFN-co and interferon alpha arms, respectively. Adverse events were balanced with no deaths among groups. CONCLUSIONS AND RELEVANCE: rSIFN-co was associated with a shorter time of clinical improvement than traditional interferon-alpha in the treatment of moderate-to-severe COVID-19 when combined with baseline antiviral agents. rSIFN-co therapy alone or combined with other antiviral therapy is worth to be further studied.

37. **Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19.** Singh B, Ryan H, Kredo T, Chaplin M, Fletcher T. *Cochrane Database Syst Rev.* 2021 Feb 12;2:CD013587. doi: 10.1002/14651858.CD013587.pub2. https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013587.pub2/full
AUTHORS' CONCLUSIONS: HCQ for people infected with COVID-19 has little or no effect on the risk of death and probably no effect on progression to mechanical ventilation. Adverse events are tripled compared to placebo, but very few serious adverse events were found. No further trials of hydroxychloroquine or chloroquine for treatment should be carried out. These results make it less likely that the drug is effective in protecting people from infection, although this is not excluded entirely. It is probably sensible to complete trials examining prevention of infection, and ensure these are carried out to a high standard to provide unambiguous results.

38. **Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19.** REMAP-CAP Investigators. *N Engl J Med.* 2021 Feb 25. doi: 10.1056/NEJMoa2100433. https://www.nejm.org/doi/full/10.1056/NEJMoa2100433
Findings: Adult patients with Covid-19, within 24 hours after starting organ support in the intensive care unit (ICU), were randomly assigned to receive tocilizumab (8 mg per kilogram of body weight), sarilumab (400 mg), or standard care (control). The primary outcome was respiratory and cardiovascular organ support-free days, on an ordinal scale combining in-hospital death (assigned a value of -1) and days free of organ support to day 21. RESULTS: Both tocilizumab and sarilumab met the predefined criteria for efficacy. CONCLUSIONS: In critically ill

patients with Covid-19 receiving organ support in ICUs, treatment with the interleukin-6 receptor antagonists tocilizumab and sarilumab improved outcomes, including survival.

39. **Time to Cannulation after ICU Admission Increases Mortality for Patients Requiring Veno-Venous ECMO for COVID-19 Associated Acute Respiratory Distress Syndrome.** Raff LA, Gallaher JR, Johnson D, et al. *Ann Surg*. 2020 Dec 22. doi: 10.1097/SLA.0000000000004683. https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=ovft&AN=00000658-900000000-93830&PDF=y
    Findings: We conducted a retrospective review from April 1 to July 31 2020 of the first 25 patients with COVID-19 associated ARDS placed on V-V ECMO at our institution. 44% of patients (11/25) survived to hospital discharge. Survivors were significantly younger (40.5 years vs. 53.1 years; $p < 0.001$) with no differences between cohorts in mean body mass index, diabetes, or PaO2:FiO2 at cannulation. Survivors had shorter duration from symptom onset to cannulation (12.5 days vs. 19.9 days, $p = 0.028$) and shorter duration of intensive care unit (ICU) length of stay (LOS) prior to cannulation (5.6 days vs. 11.7 days, $p = 0.045$). Each day from ICU admission to cannulation increased the adjusted risk of death by 4% and each year increase in age increased the adjusted risk 6%. ECMO has a role in severe, refractory ARDS associated with COVID-19. Increasing age and time from ICU admission were risk factors for mortality and should be considered in patient selection. Further studies are needed to define best practices for V-V ECMO use in COVID-19.

40. **Extracorporeal Membrane Oxygenation for Coronavirus Disease 2019: Crisis Standards of Care.** Agerstrand C, Dubois R, Takeda K, et al. *ASAIO J.* 2021 Mar 1;67(3):245-249. doi: 10.1097/MAT.0000000000001376. https://journals.lww.com/asaiojournal/Fulltext/2021/03000/Extracorporeal_Membrane_Oxygenation_for.5.aspx
    The coronavirus disease 2019 (COVID-19) pandemic has placed extraordinary strain on global healthcare systems. Use of extracorporeal membrane oxygenation (ECMO) for patients with severe respiratory or cardiac failure attributed to COVID-19 has been debated due to uncertain survival benefit and the resources required to safely deliver ECMO support. We retrospectively investigated adult patients supported with ECMO for COVID-19 at our institution during the first 80 days following New York City's declaration of a state of emergency. The primary objective was to evaluate survival outcomes in patients supported with ECMO for COVID-19 and describe the programmatic adaptations made in response to pandemic-related crisis conditions. Twenty-two patients with COVID-19 were placed on ECMO during the study period. Median age was 52 years and 18 (81.8%) were male. Twenty-one patients (95.4%) had severe ARDS and seven (31.8%) had cardiac failure. Fifteen patients (68.1%) were managed with venovenous ECMO while 7 (31.8%) required arterial support. Twelve patients (54.5%) were transported on ECMO from external institutions. Twelve patients were discharged alive from the hospital (54.5%). Extracorporeal membrane oxygenation was used successfully in patients with respiratory and cardiac failure due to COVID-19. The continued use of ECMO, including ECMO transport, during crisis conditions was possible even at the height of the COVID-19 pandemic.

41. **Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia.** Rosas IO, Bräu N, Waters M, et al. *N Engl J Med.* 2021 Feb 25. doi: 10.1056/NEJMoa2028700. https://www.nejm.org/doi/full/10.1056/NEJMoa2028700
Findings: In this phase 3 trial, we randomly assigned patients who were hospitalized with severe Covid-19 pneumonia in a 2:1 ratio receive a single intravenous infusion of tocilizumab (at a dose of 8 mg per kilogram of body weight) or placebo. Of the 452 patients who underwent randomization, 438 (294 in the tocilizumab group and 144 in the placebo group) were included in the primary and secondary analyses. The median value for clinical status on the ordinal scale at day 28 was 1.0 (95% confidence interval [CI], 1.0 to 1.0) in the tocilizumab group and 2.0 (non-ICU hospitalization without supplemental oxygen) (95% CI, 1.0 to 4.0) in the placebo group (between-group difference, -1.0; 95% CI, -2.5 to 0; P = 0.31 by the van Elteren test). In this randomized trial involving hospitalized patients with severe Covid-19 pneumonia, the use of tocilizumab did not result in significantly better clinical status or lower mortality than placebo at 28 days.

42. **High flow nasal oxygen therapy to avoid invasive mechanical ventilation in SARS-CoV-2 pneumonia: a retrospective study.** Bonnet N, Martin O, Boubaya M, et al. *Ann Intensive Care*. 2021 Feb 27;11(1):37. doi: 10.1186/s13613-021-00825-5. https://annalsofintensivecare.springeropen.com/articles/10.1186/s13613-021-00825-5
Findings: This was a bicenter retrospective study which took place in two intensive care units (ICU) of tertiary hospitals in the Paris region from March 11, to May 3, 2020. We enrolled consecutive patients hospitalized for COVID-19 and acute respiratory failure (ARF) who did not receive IMV at ICU admission. The primary outcome was the rate of IMV after ICU admission. Secondary outcomes were death at day 28 and day 60, length of ICU stay and ventilator-free days at day 28. Among 138 patients who met the inclusion criteria, 62 (45%) were treated with SOT alone, and 76 (55%) with HFNO. In HFNO group, 39/76 (51%) patients received IMV and 46/62 (74%) in SOT group (OR 0.37 [95% CI, 0.18-0.76] p = 0.007). After weighted propensity score, HFNO was still associated with a lower rate of IMV (OR 0.31 [95% CI, 0.14-0.66] p = 0.002). Length of ICU stay and mortality at day 28 and day 60 did not significantly differ between HFNO and SOT groups after weighted propensity score. Ventilator-free days at days 28 was higher in HNFO group (21 days vs 10 days, p = 0.005). In the HFNO group, predictive factors associated with IMV were SAPS2 score (OR 1.13 [95%CI, 1.06-1.20] p = 0.0002) and ROX index > 4.88 (OR 0.23 [95%CI, 0.008-0.64] p = 0.006). High flow nasal canula oxygen for ARF due to COVID-19 is associated with a lower rate of invasive mechanical ventilation.

43. **Association of Convalescent Plasma Treatment with Clinical Outcomes in Patients With COVID-19: A Systematic Review and Meta-analysis.** Janiaud P, Axfors C, Schmitt AM, et al. *JAMA.* 2021 Feb 26. doi: 10.1001/jama.2021.2747. https://jamanetwork.com/journals/jama/fullarticle/2777060
Findings: A total of 1060 patients from 4 peer-reviewed RCTs and 10 722 patients from 6 other publicly available RCTs were included. The summary risk ratio (RR) for all-cause mortality with convalescent plasma in the 4 peer-reviewed RCTs was 0.93 (95% CI, 0.63 to 1.38), the absolute risk difference was -1.21% (95% CI, -5.29% to 2.88%), and there was low certainty of the evidence due to imprecision. Across all 10 RCTs, the summary RR was 1.02 (95% CI, 0.92 to

1.12) and there was moderate certainty of the evidence due to inclusion of unpublished data. Among the peer-reviewed RCTs, the summary hazard ratio was 1.17 (95% CI, 0.07 to 20.34) for length of hospital stay, the summary RR was 0.76 (95% CI, 0.20 to 2.87) for mechanical ventilation use (the absolute risk difference for mechanical ventilation use was -2.56% [95% CI, -13.16% to 8.05%]), and there was low certainty of the evidence due to imprecision for both outcomes. Limited data on clinical improvement, clinical deterioration, and serious adverse events showed no significant differences. CONCLUSIONS AND RELEVANCE: Treatment with convalescent plasma compared with placebo or standard of care was not significantly associated with a decrease in all-cause mortality or with any benefit for other clinical outcomes. The certainty of the evidence was low to moderate for all-cause mortality and low for other outcomes.

Transmission / Infection Control

44. **Importance of non-pharmaceutical interventions in lowering the viral inoculum to reduce susceptibility to infection by SARS-CoV-2 and potentially disease severity.** Spinelli MA, Glidden DV, Gennatas ED, et al. *Lancet Infect Dis.* 2021 Feb 22:S1473-3099(20)30982-8. doi: 10.1016/S1473-3099(20)30982-8. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30982-8/fulltext
Adherence to non-pharmaceutical interventions to prevent the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been highly variable across settings, particularly in the USA. In this Personal View, we review data supporting the importance of the viral inoculum (the dose of viral particles from an infected source over time) in increasing the probability of infection in respiratory, gastrointestinal, and sexually transmitted viral infections in humans. We also review the available evidence linking the relationship of the viral inoculum to disease severity. Non-pharmaceutical interventions might reduce the susceptibility to SARS-CoV-2 infection by reducing the viral inoculum when there is exposure to an infectious source. Data from physical sciences research suggest that masks protect the wearer by filtering virus from external sources, and others by reducing expulsion of virus by the wearer. Social distancing, handwashing, and improved ventilation also reduce the exposure amount of viral particles from an infectious source. Maintaining and increasing non-pharmaceutical interventions can help to quell SARS-CoV-2 as we enter the second year of the pandemic. Finally, we argue that even as safe and effective vaccines are being rolled out, non-pharmaceutical interventions will continue to play an essential role in suppressing SARS-CoV-2 transmission until equitable and widespread vaccine administration has been completed.

Vaccines

45. **SARS-CoV-2 B.1.1.7 sensitivity to mRNA vaccine-elicited, convalescent and monoclonal antibodies.** Collier DA, De Marco A, Ferreira IATM, et al. *medRxiv. PREPRINT*. 2021 Feb 15:2021.01.19.21249840. doi: 10.1101/2021.01.19.21249840. https://www.medrxiv.org/content/10.1101/2021.01.19.21249840v4
Findings: SARS-CoV-2 transmission is uncontrolled in many parts of the world, compounded in some areas by higher transmission potential of the B1.1.7 variant now seen in 50 countries. It is

unclear whether responses to SARS-CoV-2 vaccines based on the prototypic strain will be impacted by mutations found in B.1.1.7. Here we assessed immune responses following vaccination with mRNA-based vaccine BNT162b2. We measured neutralising antibody responses following a single immunization using pseudoviruses expressing the wild-type Spike protein or the 8 amino acid mutations found in the B.1.1.7 spike protein. The vaccine sera exhibited a broad range of neutralising titres against the wild-type pseudoviruses that were modestly reduced against B.1.1.7 variant. This reduction was also evident in sera from some convalescent patients. Decreased B.1.1.7 neutralisation was also observed with monoclonal antibodies targeting the N-terminal domain (9 out of 10), the Receptor Binding Motif (RBM) (5 out of 31), but not in neutralising mAbs binding outside the RBM. Introduction of the E484K mutation in a B.1.1.7 background to reflect newly emerging viruses in the UK led to a more substantial loss of neutralising activity by vaccine-elicited antibodies and mAbs (19 out of 31) over that conferred by the B.1.1.7 mutations alone. E484K emergence on a B.1.1.7 background represents a threat to the vaccine BNT162b.

46. **Circulating SARS-CoV-2 variants escape neutralization by vaccine-induced humoral immunity.** Garcia-Beltran WF, Lam EC, et al. *medRxiv. PREPRINT.* 2021 Feb 18:2021.02.14.21251704. doi: 10.1101/2021.02.14.21251704.
https://www.medrxiv.org/content/10.1101/2021.02.14.21251704v1
Findings: Vaccination elicits immune responses capable of potently neutralizing SARS-CoV-2. However, ongoing surveillance has revealed the emergence of variants harboring mutations in spike, the main target of neutralizing antibodies. To understand the impact of globally circulating variants, we evaluated the neutralization potency of 48 sera from BNT162b2 and mRNA-1273 vaccine recipients against pseudoviruses bearing spike proteins derived from 10 strains of SARS-CoV-2. While multiple strains exhibited vaccine-induced cross-neutralization comparable to wild-type pseudovirus, 5 strains harboring receptor-binding domain mutations, including K417N/T, E484K, and N501Y, were highly resistant to neutralization. Cross-neutralization of B.1.351 variants was weak and comparable to SARS-CoV and bat-derived WIV1-CoV, suggesting that a relatively small number of mutations can mediate potent escape from vaccine responses. While the clinical impact of neutralization resistance remains uncertain, these results highlight the potential for variants to escape from neutralizing humoral immunity and emphasize the need to develop broadly protective interventions against the evolving pandemic.

47. **BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting.** Dagan N, Barda N, Kepten E, ET AL. *NEJM* 2021 Feb 24. DOI: 10.1056/NEJMoa2101765
https://www.nejm.org/doi/full/10.1056/NEJMoa2101765
Findings: In this study, data from Israel's largest health care organization were used to evaluate the effectiveness of the BNT162b2 mRNA vaccine. All persons who were newly vaccinated during the period from December 20, 2020, to February 1, 2021, were matched to unvaccinated controls in a 1:1 ratio according to demographic and clinical characteristics. Each study group included 596,618 persons. Estimated vaccine effectiveness for the study outcomes at days 14 through 20 after the first dose and at 7 or more days after the second dose was as follows: for documented infection, 46% (95% confidence interval [CI], 40 to 51) and 92% (95% CI, 88 to 95);

for symptomatic Covid-19, 57% (95% CI, 50 to 63) and 94% (95% CI, 87 to 98); for hospitalization, 74% (95% CI, 56 to 86) and 87% (95% CI, 55 to 100); and for severe disease, 62% (95% CI, 39 to 80) and 92% (95% CI, 75 to 100), respectively. Estimated effectiveness in preventing death from Covid-19 was 72% (95% CI, 19 to 100) for days 14 through 20 after the first dose. Estimated effectiveness in specific subpopulations assessed for documented infection and symptomatic Covid-19 was consistent across age groups, with potentially slightly lower effectiveness in persons with multiple coexisting conditions. CONCLUSIONS This study in a nationwide mass vaccination setting suggests that the BNT162b2 mRNA vaccine is effective for a wide range of Covid-19–related outcomes, a finding consistent with that of the randomized trial.

48. **Antibody response to first BNT162b2 dose in previously SARS-CoV-2-infected individuals.** Manisty C, Otter AD, Treibel TA, et al. *Lancet*. 2021 Feb 25:S0140-6736(21)00501-8. doi: 10.1016/S0140-6736(21)00501-8. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00501-8/fulltext Findings: Rapid vaccine-induced population immunity is a key global strategy to control COVID-19. To enable larger numbers of people to receive the first dose, delayed administration of the second dose has been advocated and implemented by some. The impact of previous SARS-CoV-2 infection on the need for boosting is not known. We reasoned that previous infection could be analogous to immune priming. As such, a first prime vaccine dose would effectively act as boost, so a second dose might not be needed. To test this, we undertook a nested case-control analysis of 51 participants of COVIDsortium, an ongoing longitudinal observational study of health-care workers (HCWs) in London who underwent weekly PCR and quantitative serology testing from the day of the first UK lockdown on March 23, 2020, and for 16 weeks onwards. 24 of 51 HCWs had a previous laboratory-confirmed mild or asymptomatic SARS-CoV-2 infection, as confirmed by positive detection of antibodies against the SARS-CoV-2 nucleocapsid or the receptor binding domain of the SARS-CoV-2 S1 subunit of the spike protein, whereas 27 HCWs remained seronegative. A median of 12·5 sampling timepoints per participant permitted the identification of peak antibody titres in seropositive individuals while avoiding false negatives.

    ***See also*: **Effect of previous SARS-CoV-2 infection on humoral and T-cell responses to single-dose BNT162b2 vaccine.** Prendecki M, Clarke C, Brown J, et al. *Lancet.* 2021 Feb 25:S0140-6736(21)00502-X. doi: 10.1016/S0140-6736(21)00502-X. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00502-X/fulltext

    ***See also*:**Binding and Neutralization Antibody Titers After a Single Vaccine Dose in Health Care Workers Previously Infected With SARS-CoV-2.** Saadat S, Tehrani ZR, Logue J, et al. *JAMA*. 2021 Mar 1. doi: 10.1001/jama.2021.3341. https://jamanetwork.com/journals/jama/fullarticle/2777171

49. **The Benefits of Vaccinating with the First Available COVID-19 Coronavirus Vaccine.** Bartsch SM, O'Shea KJ, Wedlock PT, et al. *Am J Prev Med.* 2021 Jan 19:S0749-3797(21)00021-0. doi: 10.1016/j.amepre.2021.01.001. https://www.ajpmonline.org/article/S0749-3797(21)00021-0/fulltext

Findings: During a pandemic, there are many situations in which the first available vaccines may not have as high effectiveness as vaccines that are still under development or vaccines that are not yet ready for distribution, raising the question of whether it is better to go with what is available now or wait. Except for a limited number of situations, mainly early on in a pandemic and for a vaccine that prevents infection, when an initial vaccine is available, waiting for a vaccine with a higher efficacy results in additional hospitalizations and costs over the course of the pandemic. For example, if a vaccine with a 50% efficacy in preventing infection becomes available when 10% of the population has already been infected, waiting until 40% of the population are infected for a vaccine with 80% efficacy in preventing infection results in 15.6 million additional cases and 1.5 million additional hospitalizations, costing $20.6 billion more in direct medical costs and $12.4 billion more in productivity losses. This study shows that there are relatively few situations in which it is worth foregoing the first COVID-19 vaccine available in favor of a vaccine that becomes available later on in the pandemic even if the latter vaccine has a substantially higher efficacy.

50. **Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in the UK: a test negative case control study.** *PREPRINT*. Bernal JL, Andrews N, Gower C, et al.
https://khub.net/documents/135939561/430986542/Early+effectiveness+of+COVID+vaccines.pdf/ffd7161c-b255-8e88-c2dc-88979fc2cc1b
Findings: Vaccination with either a single dose of BNT162b2 or ChAdOx1 COVID-19 vaccination was associated with a significant reduction in symptomatic SARS-CoV2 positive cases in older adults with even greater protection against severe disease. Both vaccines show similar effects. Protection was maintained for the duration of follow-up (>6 weeks). A second dose of BNT162b2 provides further protection against symptomatic disease but second doses of ChAdOx1 have not yet been rolled out in England. There is a clear effect of the vaccines against the UK variant of concern.

Women & Children

51. **Maternal and perinatal outcomes in high vs low risk-pregnancies affected by SARS-COV-2 infection (Phase-2): The WAPM (World Association of Perinatal Medicine) working group on COVID-19.** D'Antonio F et al. *Am J Obstet Gynecol MFM*. 2021 Feb 20:100329. doi:10.1016/j.ajogmf.2021.100329.
https://www.sciencedirect.com/science/article/pii/S2589933321000240
Findings: This was a multinational retrospective cohort study including women with laboratory-confirmed SARS-COV-2 from 76 centers from 25 different countries in Europe, United States, South America, Asia and Australia from 04 April 2020 till 28 October 2020. 887 singleton pregnancies tested positive to SARS-COV-2 at RT-PCR nasal and pharyngeal swab were included in the study. The risk of composite adverse maternal outcome was higher in high compared to low risk-pregnancies with an OR of 1.52. Likewise, women carrying a high risk-pregnancies were also at higher risk of hospital admission, presence of severe respiratory symptoms, admission to ICU and invasive mechanical ventilation. When exploring perinatal outcomes, high-risk

pregnancies were also at high risk of adverse perinatal outcome with an OR 0f 1.78. CONCLUSIONS: High-risk pregnancies complicated by SARS-COV-2 infection are at higher risk of adverse maternal outcome compared to low-risk gestations.

52. **Characteristics and Outcomes of US Children and Adolescents with Multisystem Inflammatory Syndrome in Children (MIS-C) Compared with Severe Acute COVID-19.** Overcoming COVID-19 Investigators. *JAMA*. 2021 Feb 24. doi: 10.1001/jama.2021.2091. https://jamanetwork.com/journals/jama/fullarticle/2777026
Findings: Of 1116 patients (median age, 9.7 years; 45% female), 539 (48%) were diagnosed with MIS-C and 577 (52%) with COVID-19. Compared with patients with COVID-19, patients with MIS-C were more likely to be 6 to 12 years old and non-Hispanic Black. Compared with patients with COVID-19, patients with MIS-C were more likely to have cardiorespiratory involvement cardiovascular without respiratory involvement and mucocutaneous without cardiorespiratory involvement. This case series of patients with MIS-C and with COVID-19 identified patterns of clinical presentation and organ system involvement. These patterns may help differentiate between MIS-C and COVID-19.

53. **Maternal, neonatal and placental characteristics of SARS-CoV-2 positive mothers.** Zhang P, Heyman T, Greechan M, et al. *J Matern Fetal Neonatal Med.* 2021 Feb 28:1-9. doi: 10.1080/14767058.2021.1892637.
https://www.tandfonline.com/doi/full/10.1080/14767058.2021.1892637
Findings: There were 142 SARS-CoV2 positive mothers within the study group, and 43 (36%) of them showed various degrees of COVID19 related clinical symptoms including fever (13.8%), cough (5.7%), loss of taste/smell (anosmia)(5.6%), shortness of breath (2.4%), muscle ache (2.4%), headache (1.6%) and pneumonia (0.8%). A total 142 neonates were born to the SARS-CoV-2 positive mothers, and only 1 neonate tested positive for SARS-CoV2 in the first 24 h. Two additional neonates were initially tested negative in first 24 h, and later tested positive on day 7 and the 1 month visit, and all these neonates were asymptomatic and had no sequelae. Although SARS-CoV2 is a significant risk to the pregnant women (mothers) and general population, there is no increased risk for neonates. Vertical transmission is rare, and perinatal transmission can also occur. There is no increased frequency of placental abnormalities in both maternal and fetal circulation.

GUIDELINES & CONSENSUS STATEMENTS

Multidisciplinary Recommendations Regarding Post-Vaccine Adenopathy and Radiologic Imaging: Radiology Scientific Expert Panel. Becker AS, Perez-Johnston R, Chikarmane SA, et al. *Radiology.* 2021 Feb 24:210436. doi: 10.1148/radiol.2021210436.

International Delphi Expert Consensus on Safe Return to Surgical and Endoscopic Practice: from the Coronavirus Global Surgical Collaborative. Asbun HJ et al. *Ann Surg*. 2020 Dec 29. doi: 10.1097/SLA.0000000000004674.

Multisystem inflammatory syndrome in children and adults (MIS-C/A): Case definition & guidelines for data collection, analysis, and presentation of immunization safety data. Vogel TP, Top KA, Karatzios C, et al. *Vaccine*. 2021 Feb 24:S0264-410X(21)00093-1. doi: 10.1016/j.vaccine.2021.01.054.

Vaccine-associated enhanced disease: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Brighton Collaboration Vaccine-associated Enhanced Disease Working Group. *Vaccine*. 2021 Feb 23:S0264-410X(21)00094-3. doi: 10.1016/j.vaccine.2021.01.055.

FDA / CDC / NIH / WHO Updates

CDC - Media Statement from CDC Director Rochelle P. Walensky, MD, MPH, on Signing the Advisory Committee on Immunization Practices' Recommendation to Use Janssen's COVID-19 Vaccine in People 18 and Older

FDA - Vaccines and Related Biological Products Advisory Committee Meeting, February 26, 2021: FDA Briefing Document: Janssen Ad26.COV2.S Vaccine for the Prevention of COVID-19

FDA Issues Emergency Use Authorization for Third COVID-19 Vaccine

FDA - Coronavirus (COVID-19) Update: FDA Allows More Flexible Storage, Transportation Conditions for Pfizer-BioNTech COVID-19 Vaccine

NIH - The COVID-19 Treatment Guidelines Panel's Statement on the Emergency Use Authorization of the Bamlanivimab Plus Etesevimab Combination for the Treatment of COVID-19

A living WHO guideline on drugs to prevent covid-19: Hydroxychloroquine

---

Commentary & News

Reassessing COVID-19 Vaccine Deployment in Anticipation of a US B.1.1.7 Surge: Stay the Course or Pivot? *CIDRAP* 2021 Feb 23.

Massive Google-funded COVID database will track variants and immunity. Maxmen A. *Nature.* 2021 Feb 24. doi: 10.1038/d41586-021-00490-5.

Covid-19: Single dose of Pfizer and Oxford vaccines cuts risk of hospital admission by 80% in over 80s, data suggest. *BMJ* 2021 March 2; 372 doi: https://doi.org/10.1136/bmj.n612

PFIZER AND BIONTECH INITIATE A STUDY AS PART OF BROAD DEVELOPMENT PLAN TO EVALUATE COVID-19 BOOSTER AND NEW VACCINE VARIANTS

A New Coronavirus Variant Is Spreading in New York, Researchers Report

New research shows California coronavirus variant is more transmissible

Executive summary: It's wrong not to test: The case for universal, frequent rapid COVID-19 testing. *EClinicalMedicine*. 2021 Feb 19:100759. doi: 10.1016/j.eclinm.2021.100759.

If you would like to receive a **customized COVID-19 Topic Alert** related to your specialty or area of interest, would like a **literature search** conducted, or have difficulty **accessing** any of the above articles please contact us at **librarian@providence.org**

Find previous weeks **here.**