Providence

COVID-19 Resource Desk

#44 | 2.17.2021 to 2.23.2021

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. **Intranasal fusion inhibitory lipopeptide prevents direct-contact SARS-CoV-2 transmission in ferrets.** de Vries RD, Schmitz KS, Bovier FT, et al. *Science*. 2021 Feb 17:eabf4896. doi: 10.1126/science.abf4896.https://science.sciencemag.org/content/early/2021/02/16/science.abf4896
   Findings: Containment of the COVID-19 pandemic requires reducing viral transmission. SARS-CoV-2 infection is initiated by membrane fusion between the viral and host cell membranes, mediated by the viral spike protein. We have designed lipopeptide fusion inhibitors that block this critical first step of infection, and based on in vitro efficacy and in vivo biodistribution selected a dimeric form for evaluation in an animal model. Daily intranasal administration to ferrets completely prevented SARS-CoV-2 direct-contact transmission during 24-hour co-housing with infected animals, under stringent conditions that resulted in infection of 100% of untreated animals. These lipopeptides are highly stable and thus may readily translate into safe and effective intranasal prophylaxis to reduce transmission of SARS-CoV-2.

Clinical Syndrome

2. **Ocular MRI Findings in Patients with Severe COVID-19: A Retrospective Multicenter Observational Study.** SFNR's COVID Study Group. *Radiology*. 2021 Feb 16:204394. doi: 10.1148/radiol.2021204394. https://pubs.rsna.org/doi/10.1148/radiol.2021204394
   Findings: COVID-19 may affect various organs. This paper reports 9 patients (1/9 [11%] woman and 8/9 [89%] men, mean age 56 ± 13 years) with globe MRI abnormalities obtained from a multicenter cohort of 129 patients presenting with severe COVID-19 from March 4th to May 1st, 2020. 9/129 (7%) patients had one or several FLAIR-WI hyperintense nodules of the posterior pole of the globe. All patients had nodules in the macular region, 8/9 (89%) had bilateral nodules, 2/9 (22%) had nodules outside the macular region. Screening of these patients might improve the management of potentially severe ophthalmological manifestations of the virus. See also the editorial by Kirsch.

3. **Musculoskeletal involvement of COVID-19: review of imaging.** Ramani SL, Samet J, Franz CK, et al. S*keletal Radiol*. 2021 Feb 18. doi: 10.1007/s00256-021-03734-7. https://link.springer.com/article/10.1007/s00256-021-03734-7
   The global pandemic of coronavirus disease 2019 (COVID-19) has revealed a surprising number of extra-pulmonary manifestations of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. While myalgia is a common clinical feature of COVID-19, other musculoskeletal manifestations of COVID-19 were infrequently described early during the pandemic. There have been emerging reports, however, of an array of neuromuscular and rheumatologic complications related to COVID-19 infection and disease course including myositis, neuropathy, arthropathy, and soft tissue abnormalities. Multimodality imaging supports diagnosis and evaluation of musculoskeletal disorders in COVID-19 patients. This article aims to provide a first comprehensive summary of musculoskeletal manifestations of COVID-19 with review of imaging.

4. **Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance.** Kotecha T, Knight DS, Razvi Y, et al. *Eur Heart J*. 2021 Feb 18:ehab075. doi: 10.1093/eurheartj/ehab075. https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab075/6140994
   Findings: One hundred and forty-eight patients (64 ± 12 years, 70% male) with severe COVID-19 infection [all requiring hospital admission, 48 (32%) requiring ventilatory support] and troponin elevation discharged from six hospitals underwent convalescent CMR (including adenosine stress perfusion if indicated) at median 68 days. Left ventricular (LV) function was normal in 89% (ejection fraction 67% ± 11%). Late gadolinium enhancement and/or ischaemia was found in 54% (80/148). This comprised myocarditis-like scar in 26% (39/148), infarction and/or ischaemia in 22% (32/148) and dual pathology in 6% (9/148). Myocarditis-like injury was limited to three or less myocardial segments in 88% (35/40) of cases with no associated LV dysfunction; of these, 30% had active myocarditis. Myocardial infarction was found in 19% (28/148) and inducible ischaemia in 26% (20/76) of those undergoing stress perfusion (including 7 with both infarction and ischaemia). Of patients with ischaemic injury pattern, 66% (27/41) had no past history of coronary disease. There was no evidence of diffuse fibrosis or oedema in the remote myocardium (T1: COVID-19 patients 1033 ± 41 ms vs. matched controls 1028 ± 35 ms; T2: COVID-19 46 ± 3 ms vs. matched controls 47 ± 3 ms). CONCLUSIONS: During convalescence after severe COVID-19 infection with troponin elevation, myocarditis-like injury can be encountered, with limited extent and minimal functional consequence. In a proportion of patients, there is evidence of possible ongoing localized inflammation. A quarter of patients had ischaemic heart disease, of which two-thirds had no previous history. Whether these observed findings represent pre-existing clinically silent disease or de novo COVID-19-related changes remain undetermined. Diffuse oedema or fibrosis was not detected.

5. **Hematologic autoimmune disorders in the course of COVID-19: a systematic review of reported cases.** Taherifard E, Taherifard E, Movahed H, Mousavi MR. *Hematology.* 2021 Dec;26(1):225-239. doi: 10.1080/16078454.2021.1881225. https://www.tandfonline.com/doi/full/10.1080/16078454.2021.1881225

Findings: A total of 58 documents were considered to be eligible for data extraction which described 94 patients with COVID-19 who developed hematologic autoimmune disorder in their course of infection. Of these patients with COVID-19, the most common hematologic autoimmune disorder was immune thrombocytopenic purpura (55 cases) followed by autoimmune hemolytic anemia (22 cases). Other hematologic autoimmune disorders include antiphospholipid syndrome, thrombotic thrombocytopenic purpura, Evans syndrome and autoimmune neutropenia. CONCLUSION: The current study would help us to always consider an autoimmune etiology for cases with abnormal hematologic finding which further lead to an appropriate treatment of the patients, especially when the symptoms present in about 1-2 weeks after the first manifestation of the infection symptoms. Maybe, at least in this pandemic, it should be recommended to evaluate patients with unexpected and unexplained decrease in their hemoglobulin or platelet count for COVID-19. Another challenging issue is the treatment options. Given the multiorgan involvement and multifaceted nature of the infection, an individualized approach should be taken for each patient.

6. **Markers of endothelial and epithelial pulmonary injury in mechanically ventilated COVID-19 ICU patients.** Spadaro S, Fogagnolo A, Campo G, et al. *Crit Care*. 2021 Feb 19;25(1):74. doi: 10.1186/s13054-021-03499-4. https://ccforum.biomedcentral.com/articles/10.1186/s13054-021-03499-4
Findings: This prospective study was performed in two COVID-19-dedicated ICU and one non-COVID-19 ICU at Ferrara University Hospital. A cohort of 31 mechanically ventilated patients with COVID-19 ARDS and a cohort of 11 patients with classical ARDS were enrolled. RESULTS: In COVID-19-related ARDS, the plasma levels of Ang-2 and ICAM-1 at T1 were statistically higher in non-survivors than survivors, ($p = 0.04$ and $p = 0.03$, respectively), whereas those of P-selectin, E-selectin and RAGE did not differ. Ang-2 and ICAM-1 at T1 were predictors of mortality (AUROC 0.650 and 0.717, respectively). At T1, RAGE and P-selectin levels were higher in classical ARDS than in COVID-19-related ARDS. Ang-2, ICAM-1 and E-selectin were lower in classical ARDS than in COVID-19-related ARDS (all $p < 0.001$). CONCLUSIONS: COVID-19 ARDS is characterized by an early pulmonary endothelial injury, as detected by Ang-2 and ICAM-1. COVID-19 ARDS and classical ARDS exhibited a different expression of biomarkers, suggesting different pathological pathways.

Diagnostics & Screening

7. **Multicenter evaluation of the Panbio™ COVID-19 rapid antigen-detection test for the diagnosis of SARS-CoV-2 infection.** Merino P, Guinea J, Muñoz-Gallego I, et al. *Clin Microbiol Infect*. 2021 Feb 15:S1198-743X(21)00076-8. doi: 10.1016/j.cmi.2021.02.001.
Findings: This prospective multicenter study was carried out in ten Spanish university hospitals including individuals with clinical symptoms or epidemiological criteria for COVID-19. Among the 958 patients studied, 325 (90.5%) had true-positives results. The overall sensitivity and specificity for the PanbioRT were 90.5% (CI 95%: 87.5-93.6) and 98.8% (CI 95%: 98-99.7), respectively. Sensitivity in participants who had a CT <25 for the RT-PCR test was 99.5% (CI 95%: 98.4-100), and in participants with ≤5 days of the clinical course was 91.8% (CI 95%: 88.8-94.8). Agreement between techniques was 95.7% (kappa score: 0.90; CI 95%: 0.88-0.93).

CONCLUSIONS: The PanbioRT provides good clinical performance, with even more reliable results for patients with a shorter clinical course of the disease or a higher viral load. The results must be interpreted based on the local epidemiological context.

8. **Self-Collected Oral Fluid Saliva Is Insensitive Compared with Nasal-Oropharyngeal Swabs in the Detection of Severe Acute Respiratory Syndrome Coronavirus 2 in Outpatients.** Manabe YC, Reuland C, Yu T, et al. *Open Forum Infect Dis*. 2020 Dec 30;8(2):ofaa648. doi: 10.1093/ofid/ofaa648. eCollection 2021 Feb.
https://academic.oup.com/ofid/article/8/2/ofaa648/6055600
Findings: We compared real-time reverse-transcription polymerase chain reaction Abbott m2000 results from matched salivary oral fluid (gingival crevicular fluid collected in an Oracol device) and nasal-oropharyngeal (OP) self-collected specimens in viral transport media from a nonhospitalized, ambulatory cohort of COVID-19 patients at multiple time points. RESULTS: There were 171 matched specimen pairs. Compared with nasal-OP swabs, 41.6% of the oral fluid samples were positive. Adding spit to the oral fluid percent collection device increased the percent positive agreement from 37.2% (16 of 43) to 44.6% (29 of 65). The positive percent agreement was highest in the first 5 days after symptoms and decreased thereafter. All of the infectious nasal-OP samples (culture positive on VeroE6 TMPRSS2 cells) had a matched SARS-CoV-2 positive oral fluid sample. CONCLUSIONS: In this study of nonhospitalized SARS-CoV-2-infected persons, we demonstrate lower diagnostic sensitivity of self-collected oral fluid compared with nasal-OP specimens, a difference that was especially prominent more than 5 days from symptom onset. These data do not justify the routine use of oral fluid collection for diagnosis of SARS-CoV-2 despite the greater ease of collection. It also underscores the importance of considering the method of saliva specimen collection and the time from symptom onset especially in outpatient populations.

Epidemiology & Public Health

9. **Years of life lost to COVID-19 in 81 countries.** Pifarré i Arolas, H., Acosta, E., López-Casasnovas, G. et al. *Sci Rep* 11, 3504 (2021). https://doi.org/10.1038/s41598-021-83040-3
https://www.nature.com/articles/s41598-021-83040-3
Findings: Understanding the mortality impact of COVID-19 requires not only counting the dead, but analyzing how premature the deaths are. We calculate years of life lost (YLL) across 81 countries due to COVID-19 attributable deaths, and also conduct an analysis based on estimated excess deaths. We find that over 20.5 million years of life have been lost to COVID-19 globally. As of January 6, 2021, YLL in heavily affected countries are 2–9 times the average seasonal influenza; three quarters of the YLL result from deaths in ages below 75 and almost a third from deaths below 55; and men have lost 45% more life years than women. The results confirm the large mortality impact of COVID-19 among the elderly. They also call for heightened awareness in devising policies that protect vulnerable demographics losing the largest number of life-years.

10. **Clinical and Laboratory Findings in Patients with Potential SARS-CoV-2 Reinfection, May-July 2020.** Lee JT, Hesse EM, Paulin HN, et al. *Clin Infect Dis.* 2021 Feb 18:ciab148. doi:

10.1093/cid/ciab148. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab148/6142945
Findings: Among 73 potential reinfection patients with available records, 30 patients had recurrent COVID-19 symptoms explained by alternative diagnoses with concurrent SARS-CoV-2 positive RT-PCR, 24 patients remained asymptomatic after recovery but had recurrent or persistent RT-PCR, and 19 patients had recurrent COVID-19 symptoms with concurrent SARS-CoV-2 positive RT-PCR but no alternative diagnoses. These 19 patients had symptom recurrence a median of 57 days after initial symptom onset (interquartile range: 47 - 76). Six of these patients had paired specimens available for further testing, but none had laboratory findings confirming reinfections. Testing of an additional three patients with recurrent symptoms and alternative diagnoses also did not confirm reinfection. CONCLUSIONS: We did not confirm SARS-CoV-2 reinfection within 90 days of the initial infection based on the clinical and laboratory characteristics of cases in this investigation. Our findings support current CDC guidance around quarantine and testing for patients who have recovered from COVID-19.

11. **Early introductions and community transmission of SARS-CoV-2 variant B.1.1.7 in the United States.** Alpert T, Lasek-Nesselquist E, Brito AF, et al. *medRxiv. PREPRINT.* 2021 Feb 12:2021.02.10.21251540. doi: 10.1101/2021.02.10.21251540. https://www.medrxiv.org/content/10.1101/2021.02.10.21251540v2
Findings: The emergence and spread of SARS-CoV-2 lineage B.1.1.7, first detected in the United Kingdom, has become a national public health concern in the United States because of its increased transmissibility. Over 500 COVID-19 cases associated with this variant have been detected since December 2020, but its local establishment and pathways of spread are relatively unknown. Using travel, genomic, and diagnostic testing data, we highlight the primary ports of entry for B.1.1.7 in the US and locations of possible underreporting of B.1.1.7 cases. New York, which receives the most international travel from the UK, is likely one of the key hubs for introductions and domestic spread. Finally, we provide evidence for increased community transmission in several states. Thus, genomic surveillance for B.1.1.7 and other variants urgently needs to be enhanced to better inform the public health response.

12. **SARS-CoV-2 Positivity on or After 9 Days among Quarantined Student Contacts of Confirmed Cases.** Nelson EJ, McKune SL, Ryan KA, et al. *JAMA*. 2021 Feb 19. doi: 10.1001/jama.2021.2392. https://jamanetwork.com/journals/jama/fullarticle/2776857
Findings: Schools reopened during the fall of 2020 with various approaches to mitigate SARS-CoV-2 infection. At that time, the US Centers for Disease Control and Prevention (CDC) recommended a 14-day quarantine without testing for close contacts of anyone diagnosed with COVID-19. However, data indicated that the incubation period for SARS-CoV-2 infection is 4 to 5 days from exposure in adults and is 6 to 7 days from exposure in children suggesting that most infected students should test positive by day 9. Therefore, Alachua County, Florida, implemented SARS-CoV-2 testing on day 9 and return to school on day 10 for student contacts of confirmed COVID-19 cases. We evaluated test positivity rates for SARS-CoV-2 infection among these student contacts.

13. **Trends in Risk-Adjusted 28-Day Mortality Rates for Patients Hospitalized with COVID-19 in England.** Jones S, Mason N, Palser T, et al. *J Hosp Med*. 2021 Feb 5. doi: 10.12788/jhm.3599. https://www.journalofhospitalmedicine.com/jhospmed/article/235557/hospital-medicine/trends-risk-adjusted-28-day-mortality-rates-patients
Findings: Early reports showed high mortality from coronavirus disease 2019 (COVID-19). Mortality rates have recently been lower; however, patients are also now younger, with fewer comorbidities. We explored 28-day mortality for patients hospitalized for COVID-19 in England over a 5-month period, adjusting for a range of potentially mitigating variables, including sociodemographics and comorbidities. Among 102,610 hospitalizations, crude mortality decreased from 33.4% (95% CI, 32.9-34.0) in March 2020 to 15.5% (95% CI, 14.1-17.0) in July. Adjusted mortality decreased from 33.4% (95% CI, 32.8-34.1) in March to 17.4% (95% CI, 11.3-26.9) in July. The relative risk of mortality decreased from a reference of 1 in March to 0.52 (95% CI, 0.34-0.80) in July. This demonstrates that the reduction in mortality is not solely due to changes in the demographics of those with COVID-19.

14. **Clusters of SARS-CoV-2 Infection among Elementary School Educators and Students in One School District — Georgia, December 2020–January 2021.** Gold JA, Gettings JR, Kimball A, et al. *MMWR Morb Mortal Wkly Rep*. ePub: 22 February 2021. DOI: http://dx.doi.org/10.15585/mmwr.mm7008e4
What is already known about this topic? In-person learning provides important benefits to children and communities. Understanding SARS-CoV-2 transmission in schools is critical to improving the safety of in-person learning. An investigation of SARS-CoV-2 transmission in a Georgia school district during December 1, 2020–January 22, 2021, identified nine clusters of COVID-19 cases involving 13 educators and 32 students at six elementary schools. Two clusters involved probable educator-to-educator transmission that was followed by educator-to-student transmission in classrooms and resulted in approximately one half (15 of 31) of school-associated cases. Educators might play a central role in in-school transmission networks. Preventing SARS-CoV-2 infections through multifaceted school mitigation measures and COVID-19 vaccination of educators is a critical component of preventing in-school transmission.

Healthcare Delivery & Healthcare Workers

15. **Surge effects and survival to hospital discharge in critical care patients with COVID-19 during the early pandemic: a cohort study.** Dale CR, Starcher RW, Chang SC, Robicsek A, Parsons G, Goldman JD, Vovan A, Hotchkin D, Gluckman TJ. [**Providence authors]** *Crit Care*. 2021 Feb 17;25(1):70. doi: 10.1186/s13054-021-03504-w.
https://ccforum.biomedcentral.com/articles/10.1186/s13054-021-03504-w
Findings: The early months of the COVID-19 pandemic were fraught with much uncertainty and some resource constraint. We assessed the change in survival to hospital discharge over time for intensive care unit patients with COVID-19 during the first 3 months of the pandemic and the presence of any surge effects on patient outcomes. RESULTS: Of 620 patients with COVID-19 admitted to the ICU [mean age 63.5 years (SD 15.7) and 69% male], 403 (65%) survived to hospital discharge and 217 (35%) died in the hospital. Survival to hospital discharge increased over time, from 60.0% in the first 2 weeks of the study period to 67.6% in the last 2 weeks. In a

multivariable logistic regression analysis, the risk-adjusted odds of survival to hospital discharge increased over time (biweekly change, adjusted odds ratio [aOR] 1.22, 95% CI 1.04-1.40, P = 0.02). Additionally, an a priori-defined explanatory model showed that after adjusting for both hospital occupancy and percent hospital capacity by COVID-19-positive individuals and persons under investigation (PUI), the temporal trend in risk-adjusted patient survival to hospital discharge remained the same (biweekly change, aOR 1.18, 95% CI 1.00-1.38, P = 0.04). The presence of greater rates of COVID-19 positive/PUI as a percentage of hospital capacity was, however, significantly and inversely associated with survival to hospital discharge (aOR 0.95, 95% CI 0.92-0.98, P < 0.01). CONCLUSIONS: During the early COVID-19 pandemic, risk-adjusted survival to hospital discharge increased over time for critical care patients. An association was also seen between a greater COVID-19-positive/PUI percentage of hospital capacity and a lower survival rate to hospital discharge.

Prognosis

16. **D-dimer and Death in Critically Ill Patients with Coronavirus Disease 2019.** STOP-COVID Investigators. *Crit Care Med.* 2021 Feb 12. doi: 10.1097/CCM.0000000000004917. https://journals.lww.com/ccmjournal/Abstract/9000/D_dimer_and_Death_in_Critically_Ill_Patients_With.95357.aspx
Findings: Critically ill adults with coronavirus disease 2019 admitted to ICUs between March 4, 2020, and May 25, 2020, with a measured D-dimer concentration on ICU day 1 or 2. The primary exposure was the highest normalized D-dimer level (assessed in four categories: < 2×, 2-3.9×, 4-7.9×, and ≥ 8× the upper limit of normal) on ICU day 1 or 2. The primary endpoint was 28-day mortality. Multivariable logistic regression was used to adjust for confounders. Among 3,418 patients (63.1% male; median age 62 yr [interquartile range, 52-71 yr]), 3,352 (93.6%) had a D-dimer concentration above the upper limit of normal. A total of 1,180 patients (34.5%) died within 28 days. Patients in the highest compared with lowest D-dimer category had a 3.11-fold higher odds of death (95% CI, 2.56-3.77) in univariate analyses, decreasing to a 1.81-fold increased odds of death (95% CI, 1.43-2.28) after multivariable adjustment for demographics, comorbidities, and illness severity. Further adjustment for therapeutic anticoagulation did not meaningfully attenuate this relationship (odds ratio, 1.73; 95% CI, 1.36-2.19). CONCLUSIONS: In a large multicenter cohort study of critically ill patients with coronavirus disease 2019, higher D-dimer levels were independently associated with a greater risk of death.

17. **von Willebrand Factor Multimer Formation Contributes to Immunothrombosis in Coronavirus Disease 2019.** Doevelaar AAN, Bachmann M, Hölzer B, et al. *Crit Care Med.* 2021 Feb 15. doi: 10.1097/CCM.0000000000004918. https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=ovft&AN=00003246-900000000-95344&PDF=y
Findings: von Willebrand factor antigen, ADAMTS13, and von Willebrand factor multimer formation were analyzed. von Willebrand factor antigen was 4.1 times higher in COVID-19 patients compared with healthy controls (p < 0.0001), whereas ADAMTS13 activities were not significantly different (p = 0.18). The ADAMTS13/von Willebrand factor antigen ratio was significantly lower in COVID-19 than in the control group (24.4 ± 20.5 vs 82.0 ± 30.7; p <

0.0001). Fourteen patients (18.7%) undercut a critical ratio of 10 as described in thrombotic thrombocytopenic purpura. Gel analysis of multimers resembled a thrombotic thrombocytopenic purpura pattern with loss of the largest multimers in 75% and a smeary triplet pattern in 39% of the patients. The ADAMTS13/von Willebrand factor antigen ratio decreased continuously from mild to critical disease (analysis of variance p = 0.026). Furthermore, it differed significantly between surviving patients and those who died from COVID-19 (p = 0.001) yielding an area under the curve of 0.232 in receiver operating characteristic curve curve analysis. COVID-19 is associated with a substantial increase in von Willebrand factor levels, which can exceed the ADAMTS13 processing capacity resulting in the formation of large von Willebrand factor multimers indistinguishable from thrombotic thrombocytopenic purpura. The ADAMTS13/von Willebrand factor antigen ratio is an independent predictor of severity of disease and mortality. These findings provide a rationale to consider plasma exchange as a therapeutic option in COVID-19 and to include von Willebrand factor and ADAMTS13 in the diagnostic workup.

18. **Predictors of hospital discharge and mortality in patients with diabetes and COVID-19: updated results from the nationwide CORONADO study.** CORONADO investigators. *Diabetologia.* 2021 Feb 17. doi: 10.1007/s00125-020-05351-w.
https://link.springer.com/article/10.1007/s00125-020-05351-w
Findings: We included 2796 participants: 63.7% men, mean age 69.7 ± 13.2 years, median BMI (25th-75th percentile) 28.4 (25.0-32.4) kg/m2. Microvascular and macrovascular diabetic complications were found in 44.2% and 38.6% of participants, respectively. Within 28 days, 1404 (50.2%; 95% CI 48.3%, 52.1%) were discharged from hospital with a median duration of hospital stay of 9 (5-14) days, while 577 participants died (20.6%; 95% CI 19.2%, 22.2%). In multivariable models, younger age, routine metformin therapy and longer symptom duration on admission were positively associated with discharge. History of microvascular complications, anticoagulant routine therapy, dyspnoea on admission, and higher aspartate aminotransferase, white cell count and C-reactive protein levels were associated with a reduced chance of discharge. Factors associated with death within 28 days mirrored those associated with discharge, and also included routine treatment by insulin and statin as deleterious factors. CONCLUSIONS/INTERPRETATION: In patients with diabetes hospitalised for COVID-19, we established prognostic factors for hospital discharge and death that could help clinicians in this pandemic period.

19. **Prognostic Accuracy of Early Warning Scores for Clinical Deterioration in Patients With COVID-19.** Su Y, Ju MJ, et al. *Front Med (Lausanne)*. 2021 Feb 1;7:624255. doi: 10.3389/fmed.2020.624255. eCollection 2020.
https://www.frontiersin.org/articles/10.3389/fmed.2020.624255/full
Findings: Between February 7, 2020 and February 17, 2020, patients confirmed with COVID-19 were screened for this study. The outcomes were early deterioration of respiratory function (EDRF) and need for intensive respiratory support (IRS) during the treatment process. The EDRF was defined as changes in the respiratory component of the sequential organ failure assessment (SOFA) score at day 3 (ΔSOFAresp = SOFA resp at day 3-SOFAresp on admission), in which the positive value reflects clinical deterioration. The IRS was defined as the use of high

flow nasal cannula oxygen therapy, noninvasive or invasive mechanical ventilation. The performances of EWS including NEWS, NEWS 2, NEWS-C, Modified Early Warning Scores (MEWS), Hamilton Early Warning Scores (HEWS), and quick sepsis-related organ failure assessment (qSOFA) for predicting EDRF and IRS were compared using the area under the receiver operating characteristic curve (AUROC). Results: A total of 116 patients were included in this study. Of them, 27 patients (23.3%) developed EDRF and 24 patients (20.7%) required IRS. Among these EWS, NEWS-C was the most accurate scoring system for predicting EDRF [AUROC 0.79 (95% CI, 0.69-0.89)] and IRS [AUROC 0.89 (95% CI, 0.82-0.96)], while NEWS 2 had the lowest accuracy in predicting EDRF [AUROC 0.59 (95% CI, 0.46-0.720)] and IRS [AUROC 0.69 (95% CI, 0.57-0.81)]. A NEWS-C ≥ 9 had a sensitivity of 59.3% and a specificity of 85.4% for predicting EDRF. For predicting IRS, a NEWS-C ≥ 9 had a sensitivity of 75% and a specificity of 88%. Conclusions: The NEWS-C was the most accurate scoring system among common EWS to identify patients with COVID-19 at risk for EDRF and need for IRS. The NEWS-C could be recommended as an early triage tool for patients with COVID-19.

20. **Discriminant Accuracy of the SOFA Score for Determining the Probable Mortality of Patients With COVID-19 Pneumonia Requiring Mechanical Ventilation.** Raschke RA, Agarwal S, Rangan P, Heise CW, Curry SC. *JAMA.* 2021 Feb 17. doi: 10.1001/jama.2021.1545.
https://jamanetwork.com/journals/jama/fullarticle/2776737
Findings: The coronavirus disease 2019 (COVID-19) pandemic has raised concern regarding the capacity to provide care for a surge of critically ill patients that might require excluding patients with a low probability of short-term survival from receiving mechanical ventilation. A survey identified 26 unique COVID-19 triage policies, of which 20 used some form of the Sequential Organ Failure Assessment (SOFA) score. However, studies performed in 2016 and 2017 have shown only moderate discriminant accuracy of the SOFA score for predicting survival in intensive care unit (ICU) patients with sepsis and an area under the receiver operating characteristic curve (AUROC) of 0.74 to 0.75. We hypothesized that the SOFA score might be less accurate in patients requiring mechanical ventilation for COVID-19 pneumonia because such patients generally have severe single-organ dysfunction and less variation in SOFA scores.

21. **SARS-CoV-2 infection and COVID-19 severity in individuals with prior seasonal coronavirus infection.** Gombar S, Bergquist T, Pejaver V, et al. *Diagn Microbiol Infect Dis*. 2021 Feb 9;100(2):115338. doi: 10.1016/j.diagmicrobio.2021.115338.
https://www.sciencedirect.com/science/article/pii/S0732889321000316
Findings: We show that individuals with documented history of seasonal coronavirus have a similar SARS-CoV-2 infection rate and COVID-19 severity as those with no prior history of seasonal coronavirus. Our findings suggest prior infection with seasonal coronavirus does not provide immunity to subsequent infection with SARS-CoV-2.

22. **Asthma in patients with coronavirus disease 2019: a systematic review and meta-analysis.** Shi L, Xu J, Xiao W, et al. *Ann Allergy Asthma Immunol*. 2021 Feb 17:S1081-1206(21)00130-7. doi: 10.1016/j.anai.2021.02.013.
https://www.sciencedirect.com/science/article/pii/S1081120621001307

Findings: The pooled prevalence of asthma in COVID-19 patients worldwide was 8.3% (95% CI 7.6-9.0%) based on 116 articles (119 studies) with 403,392 cases. The pooled ES based on unadjusted effect estimates showed that asthma was not associated with the reduced risk of poor outcomes in COVID-19 patients (ES 0.91, 95% CI 0.78-1.06). Similarly, the pooled ES based on unadjusted effect estimates revealed that asthma was not associated with the reduced risk of mortality in COVID19 patients (ES 0.88, 95% CI 0.73-1.05). However, the pooled ES based on adjusted effect estimates indicated that asthma was significantly associated with the reduced risk of mortality in COVID-19 patients (ES 0.80, 95% CI 0.74-0.86). CONCLUSION: The pooled prevalence of asthma in COVID-19 patients was similar to that in the general population, and asthma might be an independent protective factor for the death of COVID-19 patients, which suggests that we should pay high attention to COVID-19 patients with asthma and take locally tailored interventions and treatment. Further well-designed studies with large sample sizes are required to verify our findings.

23. **Impact of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers in Hypertensive Patients with COVID-19 (COVIDECA Study).** Mustafic H, Fayssoil A, Josseran L, et al. *Am J Cardiol*. 2021 Feb 19:S0002-9149(21)00153-3. doi: 10.1016/j.amjcard.2021.02.009. https://www.ajconline.org/article/S0002-9149(21)00153-3/fulltext
Findings: Effect of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) among hypertensive patients with coronavirus disease 2019 (COVID-19) is debated. The aim of the COVIDECA study was to assess the outcome of ACEI and ARB among hypertensive patients presenting with COVID-19. We reviewed from the Assistance Publique-Hôpitaux de Parishealthcare record database all patients presenting with confirmed COVID-19 by RT-PCR. We compared hypertensive patients with ACEI or ARB and hypertensive patients without ACEI and ARB. Among 13,521 patients presenting with confirmed COVID-19 by RT-PCR, 2981 hypertensive patients (mean age: 78.4 ± 13.6 years, 1464 men) were included. Outcome of hypertensive patients was similar whatever the use or non-use of ACEI or ARB: admission in ICU (13.4% in patients with ACEI or ARB versus 14.8% in patients without ACEI/ARB, p = 0.35), need of mechanical ventilation (5.5% in patients with ACEI or ARB versus 6.3% in patients without ACEI/ARB, p = 0.45), in-hospital mortality (27.5% in patients with ACEI or ARB versus 26.7% in patients without ACEI/ARB, p = 0.70). In conclusion, the use of ACEI and ARB remains safe and can be maintained in hypertensive patients presenting with COVID-19.

24. **Impact and Determinants of High-Sensitivity Cardiac Troponin-T Concentration in Patients With COVID-19 Admitted to Critical Care.** Demir OM, Ryan M, Cirillo C, et al. *Am J Cardiol.* 2021 Feb 19:S0002-9149(21)00148-X. doi: 10.1016/j.amjcard.2021.01.037. https://www.ajconline.org/article/S0002-9149(21)00148-X/fulltext
Findings: Cardiac Troponin (hs-TnT) elevation has been reported in unselected patients hospitalised with COVID-19 however the mechanism and relationship with mortality remain unclear. Consecutive patients admitted to a high-volume intensive care unit (ICU) in London with severe COVID-19 pneumonitis were included if hs-TnT concentration at admission was known. Kaplan-Meier survival analysis performed, with cohorts classified a priori by multiples of the upper limit of normal (ULN). 277 patients were admitted during a 7-week period in 2020; 176 were included (90% received invasive ventilation). hs-TnT at admission was 16.5 (9.0-49.3)

ng/L, 56% had concentrations >ULN. 56 patients (31.8%) died during the index admission. Admission hs-TnT level was lower in survivors (12.0 (8.0-27.8) vs 28.5 (14.0-81.0) ng/L, p=0.001). Univariate predictors of mortality were age, APACHE-II Score and admission hs-TnT (HR 1.73, p=0.007). By multivariate regression, only age (HR 1.33, CI: 1.16.-1.51, p<0.01) and admission hs-TnT (HR 1.94, CI: 1.22-3.10, p=0.006) remained predictive. Survival was significantly lower when admission hs-TnT was >ULN (log-rank p-value<0.001). Peak hs-TnT was higher in those who died but was not predictive of death after adjustment for other factors. In conclusion, In critically ill patients with COVID-19 pneumonitis, the hs-TnT level at admission is a powerful independent predictor of the likelihood of surviving to discharge from ICU. In most cases, hs-TnT elevation does not represent major myocardial injury but acts as a sensitive integrated biomarker of global stress. Whether stratification based on admission Troponin level could be used to guide prognostication and management warrants further evaluation.

Survivorship & Rehabilitation

25. **Posttraumatic Stress Disorder in Patients after Severe COVID-19 Infection.** Gemelli Against COVID-19 Post-Acute Care Study Group. *JAMA Psychiatry*. 2021 Feb 18. doi: 10.1001/jamapsychiatry.2021.0109.
https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2776722
Findings: Posttraumatic stress disorder (PTSD) may occur in individuals who have experienced a traumatic event. Previous coronavirus epidemics were associated with PTSD diagnoses in post-illness stages, with meta-analytic findings indicating a prevalence of 32.2% (95% CI, 23.7-42.0). However, information after (SARS-CoV-2 is piecemeal. We aimed at filling this gap by studying a group of patients with coronavirus disease 2019 (COVID-19) who sought treatment at the emergency department, most of whom required hospitalization, eventually recovered, and were subsequently referred to a post-acute care service for multidisciplinary assessment.

26. **Plasma metabolomic profiling of patients recovered from COVID-19 with pulmonary sequelae 3 months after discharge.** Xu J, Zhou M, Luo P, et al. *Clin Infect Dis*. 2021 Feb 17:ciab147. doi: 10.1093/cid/ciab147. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab147/6141511
Findings: To determine the metabolomic profile of circulating plasma from COVID-19 survivors with pulmonary sequelae 3 months after discharge, a random, outcome-stratified case-control sample was analyzed. We enrolled 103 recovered COVID-19 patients as well as 27 healthy donors, and performed pulmonary function tests, computerized tomography (CT) scans, laboratory examinations, and liquid chromatography-mass spectrometry. RESULTS: Plasma metabolite profiles of COVID-19 survivors with abnormal pulmonary function were evidently different from those of healthy donors or subjects with normal pulmonary function. These alterations were associated with disease severity and mainly involved amino acid, and glycerophospholipid metabolic pathways. Furthermore, increased levels of triacylglycerols, phosphatidylcholines, prostaglandin E2, arginine, and decreased levels of betain and adenosine were associated with pulmonary CO diffusing capacity and total lung capacity. The global plasma metabolomic profile differed between subjects with abnormal and normal pulmonary function. CONCLUSIONS: Further metabolite-based analysis may help to identify the

mechanisms underlying pulmonary dysfunction in COVID-19 survivors, and provide potential therapeutic targets in the future.

27. **Sequelae in Adults at 6 Months after COVID-19 Infection.** Logue JK, Franko NM, McCulloch DJ, et al. *JAMA Netw Open.* 2021 Feb 1;4(2):e210830. doi: 10.1001/jamanetworkopen.2021.0830. https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2776560
Findings: In this cohort of individuals with COVID-19 who were followed up for as long as 9 months after illness, approximately 30% reported persistent symptoms. A unique aspect of our cohort is the high proportion of outpatients with mild disease. Persistent symptoms were reported by one-third of outpatients in our study, consistent with a previously reported study, in which 36% of outpatients had not returned to baseline health by 14 to 21 days following infection. However, this has not been previously described 9 months after infection. Consistent with existing literature, fatigue was the most commonly reported symptom.2-4 This occurred in 14% of individuals in this study, lower than the 53% to 71%2-4 reported in cohorts of hospitalized patients, likely reflecting the lower acuity of illness in our cohort. Furthermore, impairment in HRQoL has previously been reported among hospitalized patients who have recovered from COVID-19; we found 29% of outpatients reported worsened HRQoL.

28. **Delayed-onset myocarditis following COVID-19.** Bajaj R, Sinclair HC, Patel K, et al. *Lancet Respir Med*. 2021 Feb 19:S2213-2600(21)00085-0. doi: 10.1016/S2213-2600(21)00085-0. https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00085-0/fulltext
Findings: A multisystem inflammatory syndrome occurring several weeks after SARS-CoV-2 infection and that can include severe acute heart failure has been reported in children (MIS-C). In adults with acute severe heart failure, we have identified a similar syndrome (MIS-A) and describe presenting characteristics, diagnostic features, and early outcomes. Our data also complement reports of MIS-A.

Therapeutics

29. **Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients with Moderate to Severe COVID-19: A Randomized Clinical Trial.** Murai IH, Fernandes AL, Sales LP, et al. *JAMA.* February 17, 2021. doi:10.1001/jama.2020.26848 https://jamanetwork.com/journals/jama/fullarticle/2776738
Findings: In this randomized clinical trial that involved 240 hospitalized patients with moderate to severe COVID-19, a single dose of 200 000 IU of vitamin D3, compared with placebo, did not significantly reduce hospital length of stay (median of 7.0 vs 7.0 days; unadjusted hazard ratio for hospital discharge, 1.07). The study does not support the use of a high dose of vitamin D3 for treatment of moderate to severe COVID-19 in hospitalized patients.

30. **Assessment of narcotic, sedative, and neuromuscular blocker needs of patients with COVID-19 requiring invasive mechanical ventilation.** Spangler J, Martley TJ, Schieber T, Mohamed A, Woods M. *Am J Health Syst Pharm*. 2021 Feb 18:zxab055. doi: 10.1093/ajhp/zxab055. https://academic.oup.com/ajhp/advance-article/doi/10.1093/ajhp/zxab055/6144082

Findings: Fifty-three patients were included in the review. The mean age was 65.5 years, and 36 (67.9%) patients were male. The median (IQR) intubation duration and hospital length of stay were 14.8 (7, 22) days and 21 (14.5, 33) days, respectively. The mean (SD) total daily opioid dose, in morphine milligram equivalents (MME) per 24 hours, was 965 (753) MME. Mean (SD) daily propofol, midazolam (continuous infusion [CI]), lorazepam, diazepam, and dexmedetomidine doses were 3,040 (2,240) mg, 79 (75.7) mg, 2 (1.8) mg, 15 (12.8) mg, and 492 (845) mcg, respectively. Twenty-six (49%) patients received NMBAs through CI. The mean (SD) daily cisatracurium and rocuronium CI amounts were 237 (138) mg and 618 (349) mg, respectively. Younger age and male gender were associated with statistically significant higher opioid and sedative requirements ($P < 0.05$).

31. **Ivermectin shows clinical benefits in mild to moderate COVID19: A randomised controlled double-blind, dose-response study in Lagos.** Babalola OE, Bode CO, Ajayi AA, et al. *QJM.* 2021 Feb 18:hcab035. doi: 10.1093/qjmed/hcab035. https://academic.oup.com/qjmed/advance-article/doi/10.1093/qjmed/hcab035/6143037
Findings: The Days to COVID negativity [DTN] was significantly and dose dependently reduced by IV ($p = 0.0066$). The DTN for Control were, = 9.1+/-5.2, for A 6.0 +/- 2.9, and for B 4.6 +/-3.2 . 2 Way repeated measures ANOVA of ranked COVID 19 +/- scores at 0, 84, 168, 232 hours showed a significant IV treatment effect ($p = 0.035$) and time effect ($p < 0.0001$). IV also tended to increase SPO2% compared to controls, $p = 0.073$, 95% CI - 0.39 to 2.59 and increased platelet count compared to C ($p = 0.037$) 95%CI 5.55 - 162.55 × 103/ml. The platelet count increase was inversely correlated to DTN ($r = -0.52$, $p = 0.005$). No SAE was reported. CONCLUSIONS: 12 mg IV regime may have superior efficacy. IV should be considered for use in clinical management of SARS-Cov-2, and may find applications in community prophylaxis in high-risk areas.

32. **Patient-Directed Prone Positioning in Awake Patients with COVID-19 Requiring Hospitalization (PAPR).** Johnson SA, Horton DJ, Fuller MJ, et al. *Ann Am Thorac Soc.* 2021 Feb 17. doi: 10.1513/AnnalsATS.202011-1466RL.
https://www.atsjournals.org/doi/10.1513/AnnalsATS.202011-1466RL
Findings: In this pragmatic randomized controlled trial, we investigated the feasibility and efficacy of patient-directed prone positioning among non-intubated, spontaneously breathing patients hospitalized with COVID-19. We found that adherence to our prone positioning protocol was very low suggesting a patient-directed approach is not feasible. Our protocol appeared safe, although it did not improve oxygenation, an unexpected finding.

33. **Prone Positioning and Survival in Mechanically Ventilated Patients with Coronavirus Disease 2019-Related Respiratory Failure.** Study of the Treatment and Outcomes in Critically Ill Patients with Coronavirus Disease (STOP-COVID) Investigators. *Crit Care Med.* 2021 Feb 17. doi: 10.1097/CCM.0000000000004938.
https://ovidsp.ovid.com/ovidweb.cgi?T=JS&CSC=Y&NEWS=N&PAGE=fulltext&D=ovft&AN=00003246-900000000-95335&PDF=y
Findings: Among 2,338 eligible patients, 702 (30.0%) were proned within the first 2 days of ICU admission. After inverse probability weighting, baseline and severity of illness characteristics were well-balanced between groups. A total of 1,017 (43.5%) of the 2,338 patients were

discharged alive, 1,101 (47.1%) died, and 220 (9.4%) were still hospitalized at last follow-up. Patients proned within the first 2 days of ICU admission had a lower adjusted risk of death compared with nonproned patients (hazard ratio, 0.84; 95% CI, 0.73-0.97). CONCLUSIONS: In-hospital mortality was lower in mechanically ventilated hypoxemic patients with coronavirus disease 2019 treated with early proning compared with patients whose treatment did not include early proning.

34. **Meta-Analysis of the Effect of Colchicine on Mortality and Mechanical Ventilation in COVID-19.** Salah HM, Mehta JL. *Am J Cardiol.* 2021 Feb 19:S0002-9149(21)00142-9. doi: 10.1016/j.amjcard.2021.02.005. https://www.ajconline.org/article/S0002-9149(21)00142-9/fulltext
Due to the significant healthcare and economic burdens of the COVID-19 and the lack of effective treatment, repurposing of existing medications based on plausible mechanism of action have been used. Colchicine, an anti-inflammatory medication, has been proposed as a possible treatment option for COVID-19. Colchicine exerts its anti-inflammatory effects via inhibition of neutrophil chemotaxis, adhesion, and mobilization; suppression of superoxide production; and reduction of tumor necrosis factor (TNF)-α generation and activity. Additionally, it is proposed that colchicine may have some anti-viral properties via inhibition of microtubule polymerization and regulation of production of anti-oxidative factor. Early reports suggested possible benefits for colchicine in patients with COVID-19. Further, a recent meta-analysis showed mortality benefit associated with the use of colchicine in patients with COVID-19. However, since then, more observational studies were published, and the results of the Colchicine Coronavirus SARS-CoV2 Trial (COLCORONA; NCT04322682), the largest clinical trial to date investigating the use of colchicine in non-hospitalized patients with COVID-19 infection, were reported. In this report, we sought to examine the association between colchicine use and severity of COVID-19 infection in the light of the recent evidence.

35. **Early and Significant Reduction in C-Reactive Protein Levels After Corticosteroid Therapy Is Associated with Reduced Mortality in Patients With COVID-19.** Cui Z, Merritt Z, Assa A, et al. *J Hosp Med.* 2021 Feb 17. doi: 10.12788/jhm.3560.
https://www.journalofhospitalmedicine.com/jhospmed/article/235876/hospital-medicine/early-and-significant-reduction-c-reactive-protein-levels
Findings: Of 2,707 patients admitted during the study period, 324 received corticosteroid treatment. Of patients who received corticosteroid treatment, CRP responders had reduced risk of death compared with risk among CRP nonresponders (25.2% vs 47.8%; unadjusted odds ratio [OR], 0.37; 95% CI, 0.21-0.65; P < .001). This effect remained strong and significant after adjustment for potential confounders (adjusted OR, 0.27; 95% CI, 0.14-0.54; P < .001). CONCLUSION: Reduction in CRP by 50% or more within 72 hours of initiating corticosteroid therapy potentially predicts inpatient mortality. This may serve as an early biomarker of response to corticosteroid therapy in patients with COVID-19.

Transmission / Infection Control

36. **Evidence of SARS-CoV-2 reinfection without mutations in Spike protein.** Kulkarni O, Narreddy S, Zaveri L, et al. *Clin Infect Dis*. 2021 Feb 16:ciab136. doi: 10.1093/cid/ciab136. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab136/6137553
Several cases of SARS-CoV-2 reinfection have now been documented across the globe. Recently, Selhorst et al reported a case of reinfection despite the presence of neutralizing antibodies. Their study showed the presence of S477N, an immune escape mutation, in the Spike protein of the virus from the second episode. This conforms to the fact that most reported reinfections show the presence of at least one unique variation in structural proteins between episodes, particularly the Spike protein. Here, we report two cases– one clear case and one possible case, of SARS-CoV-2 reinfection that were detected during routine surveillance. Of note, there was no difference in the Spike protein of the virus between episodes.

37. **Maximizing Fit for Cloth and Medical Procedure Masks to Improve Performance and Reduce SARS-CoV-2 Transmission and Exposure, 2021.** Brooks JT, Beezhold DH, Noti JD, et al. *MMWR Morb Mortal Wkly Rep*. 2021 Feb 19;70(7):254-257. doi: 10.15585/mmwr.mm7007e1. https://www.cdc.gov/mmwr/volumes/70/wr/mm7007e1.htm
Findings: The effectiveness of cloth and medical procedure masks can be improved by ensuring that they are well fitted to the contours of the face to prevent leakage of air around the masks' edges. During January 2021, CDC conducted experimental simulations using pliable elastomeric source and receiver headforms to assess the extent to which two modifications to medical procedure masks, 1) wearing a cloth mask over a medical procedure mask (double masking) and 2) knotting the ear loops of a medical procedure mask where they attach to the mask's edges and then tucking in and flattening the extra material close to the face (knotted and tucked masks), could improve the fit of these masks and reduce the receiver's exposure to an aerosol of simulated respiratory droplet particles of the size considered most important for transmitting SARS-CoV-2. The receiver's exposure was maximally reduced (>95%) when the source and receiver were fitted with modified medical procedure masks. These laboratory-based experiments highlight the importance of good fit to optimize mask performance. Until vaccine-induced population immunity is achieved, universal masking is a highly effective means to slow the spread of SARS-CoV-2 when combined with other protective measures, such as physical distancing, avoiding crowds and poorly ventilated indoor spaces, and good hand hygiene. Innovative efforts to improve the fit of cloth and medical procedure masks to enhance their performance merit attention.

38. **Analysis of Asymptomatic and Presymptomatic Transmission in SARS-CoV-2 Outbreak, Germany, 2020.** Bender JK, Brandl M, Höhle M, et al. *Emerg Infect Dis.* 2021 Feb 18;27(4). doi: 10.3201/eid2704.204576. https://wwwnc.cdc.gov/eid/article/27/4/20-4576_article
Findings: We determined secondary attack rates (SAR) among close contacts of 59 asymptomatic and symptomatic coronavirus disease case-patients by presymptomatic and symptomatic exposure. We observed no transmission from asymptomatic case-patients and

highest SAR through presymptomatic exposure. Rapid quarantine of close contacts with or without symptoms is needed to prevent presymptomatic transmission.

39. **Genomic Evidence of SARS-CoV-2 Reinfection Involving E484K Spike Mutation, Brazil.** Nonaka CKV, Franco MM, Gräf T, et al. *Emerg Infect Dis.* 2021 Feb 19;27(5). doi: 10.3201/eid2705.210191. https://wwwnc.cdc.gov/eid/article/27/5/21-0191_article
Uncertainty remains about how long the protective immune responses against severe acute respiratory syndrome coronavirus 2 persists, and suspected reinfection in recovered patients has been reported. We describe a case of reinfection from distinct virus lineages in Brazil harboring the E484K mutation, a variant associated with escape from neutralizing antibodies.

Vaccine

40. **Effectiveness of BNT162b2 mRNA Vaccine against Infection and COVID-19 Vaccine Coverage in Healthcare Workers in England, Multicentre Prospective Cohort Study (the SIREN Study).** Hall VJ, Foulkes S, Saei A, et al. *Lancet PREPRINT*. February 22, 2021. Available at SSRN: https://ssrn.com/abstract=3790399
Findings: The SIREN study is a prospective cohort study among staff working in publicly funded hospitals. Baseline risk factors, vaccination status (from 8/12/2020-5/2/2021), and symptoms are recorded at 2 weekly intervals and all SARS-CoV-2 PCR and antibody test results documented. Vaccine coverage was 89% on 5/2/2021. Significantly lower coverage was associated with prior infection (aOR 0.59 95% confidence interval [CI] 0.54-0.64), female (aOR 0.72, 95% CI 0.63-0.82), aged under 35 years, being from minority ethnic groups (especially Black, aOR 0.26, 95% CI 0.21-0.32), porters/security guards (aOR 0.61, 95% CI 0.42-0.90),or midwife (aOR 0.74, 95% CI 0.57-0.97), and living in more deprived neighbourhoods (IMD 1 (most) vs. 5 (least) (aOR 0.75, 95% CI 0.65-0.87). A single dose of BNT162b2 vaccine demonstrated vaccine effectiveness of 72% (95% CI 58-86) 21 days after first dose and 86% (95% CI 76-97) seven days after two doses in the antibody negative cohort. Our study demonstrates that the BNT162b2 vaccine effectively prevents both symptomatic and asymptomatic infection in working age adults; this cohort was vaccinated when the dominant variant in circulation was B1.1.7 and demonstrates effectiveness against this variant.

41. **Prioritizing between second-generation SARS-CoV-2 vaccines through low-dosage challenge studies.** Steuwer B, Jamrozik E, Eyal N. *Int J Infect Dis.* 2021 Feb 13;S1201-9712(21)00124-7. doi: 10.1016/j.ijid.2021.02.038.
https://www.sciencedirect.com/science/article/pii/S1201971221001247?via%3Dihub
This Perspective explores some advantages and disadvantages of "low-dosage" challenge studies, in the setting of testing second-generation vaccines against COVID-19. Compared to a conventional vaccine challenge, a low-dosage vaccine challenge would be likelier to start and start earlier. A low-dosage challenge would also be less likely to rule out a vaccine candidate which would have been potentially effective in target usage. A key ethical advantage of a low-dosage challenge over conventional challenge is that both it and its dose escalation process are safer for each participant. Low-dosage studies usually require larger numbers of participants than conventional challenges, but this and other potential disadvantages are less serious than

they may initially appear. Overall, low-dosage challenges should be considered for certain roles, such as prioritizing between second-generation vaccines against COVID-19.

42. **Serum Neutralizing Activity Elicited by mRNA-1273 Vaccine - Preliminary Report.** Wu K, Werner AP, Koch M, et al. *N Engl J Med*. 2021 Feb 17. doi: 10.1056/NEJMc2102179. https://www.nejm.org/doi/full/10.1056/NEJMc2102179
Findings: The mRNA-1273 vaccine against SARS-CoV-2 elicited high neutralizing-antibody titers in phase 1 trial participants and has been shown to be highly efficacious in preventing symptomatic Covid-19 disease and severe disease. The recent emergence of SARS-CoV-2 variants in the United Kingdom (the B.1.1.7 lineage) and in South Africa (the B.1.351 lineage) has led to concerns about increased transmission and the potential of these variants to circumvent immunity elicited by natural infection or vaccination. We assayed the serum neutralizing activity against recombinant vesicular stomatitis virus (rVSV)–based SARS-CoV-2 (a pseudovirus-based model) in specimens obtained from participants in the phase 1 trial of the mRNA-1273 vaccine. We tested pseudoviruses bearing the spike protein from the original Wuhan-Hu-1 isolate, the D614G variant, the B.1.1.7 and B.1.351 variants, and other variants (20E [EU1], 20A.EU2, N439K-D614G, and the mink cluster 5 variant that was first identified in Denmark).

43. **Neutralizing Activity of BNT162b2-Elicited Serum - Preliminary Report.** Liu Y, Liu J, Xia H, et al. *N Engl J Med*. 2021 Feb 17. doi: 10.1056/NEJMc2102017. https://www.nejm.org/doi/full/10.1056/NEJMc2102017
Findings: New, highly transmissible SARS-CoV-2 variants that were first detected in the United Kingdom (B.1.1.7 lineage), South Africa (B.1.351 lineage), and Brazil (P.1 lineage) with mutations in the S gene are spreading globally. To analyze effects on neutralization elicited by BNT162b2, we engineered S mutations from the B.1.351 lineage into USA-WA1/2020, a relatively early isolate of the virus (in January 2020). We subsequently produced three recombinant viruses. The first had an N-terminal domain deletion and the globally dominant D614G substitution (Δ242-244+D614G) the second had mutations affecting three amino acids at the receptor-binding site (K417N, E484K, and N501Y) and a D614G substitution (B.1.351-RBD+D614G), and the third had all the mutations found in the S gene in the B.1.351 lineage (B.1.351-spike). All the mutant viruses yielded infectious titers exceeding 107 plaque-forming units per milliliter. The B.1.351-spike virus formed plaques that were smaller than those of the other viruses.

44. **Early rate reductions of SARS-CoV-2 infection and COVID-19 in BNT162b2 vaccine recipients.** Amit S, Regev-Yochay G, Afek A, Kreiss Y, Leshem E. *Lancet* 2021 Feb 18. DOI:https://doi.org/10.1016/S0140-6736(21)00448-7 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00448-7/fulltext
Findings: In December, 2020, the Israeli Government approved the BNT162b2 COVID-19 vaccine and initiated a national immunisation campaign prioritising health-care workers (HCWs), as in other countries. This campaign coincided with a third wave of COVID-19, peaking at 10 116 daily new cases by mid-January, 2021. The Sheba Medical Centre, Israel's largest hospital with 9647 HCWs, began staff vaccination on Dec 19, 2020. All HCWs, excluding those with previous

SARS-CoV-2 infection, were eligible for vaccination. Clinical trial data of BNT162b2 vaccine estimated an early vaccine efficacy in preventing COVID-19 of 52·4% before dose two, and 90.5% on days 2–7 after dose two. A recent analysis of BNT162b2 vaccine data estimated vaccine efficacy of 89–91% during days 15–28 after the first dose. We examined early reductions in SARS-CoV-2 infection and COVID-19 rates in vaccinated HCWs.

45. **Evolution of immune responses to SARS-CoV-2 in mild-moderate COVID-19.** Wheatley AK, Juno JA, Wang JJ, et al. *Nat Commun*. 2021 Feb 19;12(1):1162. doi: 10.1038/s41467-021-21444-5. https://www.nature.com/articles/s41467-021-21444-5
Findings: The durability of infection-induced SARS-CoV-2 immunity has major implications for reinfection and vaccine development. Here, we show a comprehensive profile of antibody, B cell and T cell dynamics over time in a cohort of patients who have recovered from mild-moderate COVID-19. Binding and neutralising antibody responses, together with individual serum clonotypes, decay over the first 4 months post-infection. A similar decline in Spike-specific CD4+ and circulating T follicular helper frequencies occurs. By contrast, S-specific IgG+ memory B cells consistently accumulate over time, eventually comprising a substantial fraction of circulating the memory B cell pool. Modelling of the concomitant immune kinetics predicts maintenance of serological neutralising activity above a titre of 1:40 in 50% of convalescent participants to 74 days, although there is probably additive protection from B cell and T cell immunity. This study indicates that SARS-CoV-2 immunity after infection might be transiently protective at a population level. Therefore, SARS-CoV-2 vaccines might require greater immunogenicity and durability than natural infection to drive long-term protection.

46. **Thrombocytopenia following Pfizer and Moderna SARS/CoV-2 vaccination.** Lee EJ, Cines DB, Gernsheimer T, et al. *Am J Hematol*. 2021 Feb 19. doi: 10.1002/ajh.26132. https://onlinelibrary.wiley.com/doi/10.1002/ajh.26132
Cases of apparent secondary immune thrombocytopenia (ITP) after SARS/CoV-2 vaccination with both the Pfizer and Moderna versions have been reported and reached public attention. Public alarm was heightened following the death of the first identified patient from an intracranial hemorrhage, which was reported on the Internet, then in USA Today and then in The New York Times. Described below, we have collected a series of cases of very low platelet counts occurring within 2 weeks of vaccination in order to enhance our understanding of the possible relationship, if any, between SARS/CoV-2 vaccination and development of ITP with implications for surveillance and management.

47. **Do Corticosteroid Injections for the Treatment of Pain Influence the Efficacy of mRNA COVID-19 Vaccines?** Spine Intervention Society's Patient Safety Committee. *Pain Med*. 2021 Feb 19:pnab063. doi: 10.1093/pm/pnab063. https://academic.oup.com/painmedicine/advance-article/doi/10.1093/pm/pnab063/6144926
Myth: Corticosteroid injection for the treatment of pain and inflammation is known to decrease the efficacy of the messenger ribonucleic acid (mRNA)-vaccines for COVID-19.
Fact: There is currently no direct evidence to suggest that a corticosteroid injection before or after the administration of an mRNA COVID-19 vaccine decreases the efficacy of the vaccine. However, based on the known timeline of hypothalamic-pituitary-adrenal (HPA) axis

suppression following epidural and intraarticular corticosteroid injections, and the timeline of the reported peak efficacy of the Pfizer-BioNTech and Moderna vaccines, physicians should consider timing an elective corticosteroid injection such that it is administered no less than two weeks prior to a COVID-19 mRNA vaccine dose and no less than one week following a COVID-19 mRNA vaccine dose, whenever possible.

48. **First Month of COVID-19 Vaccine Safety Monitoring — United States, December 14, 2020–January 13, 2021.** Gee J, Marquez P, Su J, et al. *MMWR Morb Mortal Wkly Rep*. ePub: 19 February 2021. DOI: http://dx.doi.org/10.15585/mmwr.mm7008e3
What is added by this report? Monitoring, conducted as part of the U.S. vaccination program, indicates reassuring safety profiles for COVID-19 vaccines. Local and systemic reactions were common; rare reports of anaphylaxis were received. No unusual or unexpected reporting patterns were detected. Health care providers and vaccine recipients can be reassured about the safety of Pfizer BioNTech and Moderna COVID-19 vaccines. Counseling vaccine recipients to expect transient local and systemic reactions might ease concerns and encourage completion of the 2-dose vaccination series.

49. **Poor antigen-specific responses to the second BNT162b2 mRNA vaccine dose in SARS-CoV-2-experienced individuals.** Samanovic MI, Cornelius AR, Wilson JP, et al. *medRxiv PREPRINT*. 2021.02.07.21251311; doi: https://doi.org/10.1101/2021.02.07.21251311
FINDINGS: The advent of COVID-19 vaccines will play a major role in helping to end the pandemic that has killed millions worldwide. Vaccine candidates have demonstrated robust humoral responses and have protected against infection. However, efficacy trials were focused on individuals with no prior exposure to SARS-CoV-2, and, as a result, little is known about immune responses induced by these mRNA vaccines in individuals who recovered from COVID-19. Here, we evaluated immune responses in 32 subjects who received two-dose BNT162b2 mRNA vaccination. In individuals naive to SARS-CoV-2, we observed robust increases in humoral and antigen-specific antibody-secreting cell (ASC) responses following each dose of vaccine, whereas individuals with prior exposure to SARS-CoV-2 demonstrated strong humoral and antigen-specific ASC responses to the first dose but muted responses to the second dose of the vaccine for the time points studied. These data highlight an important gap in our knowledge and may have major implications for how these vaccines should be used to prevent COVID-19.

50. **Antibodies elicited by SARS-CoV-2 infection and boosted by vaccination neutralize an emerging variant and SARS-CoV-1.** Stamatatos L, Czartoski J, Wan Y-H, et al. *medRxiv PREPRINT.* 2021.02.05.21251182; doi: https://doi.org/10.1101/2021.02.05.21251182
Findings: The emergence of SARS-CoV-2 variants raises concerns about their resistance to neutralizing antibodies elicited from previous infection, or from vaccination. Here we examined whether sera and monoclonal antibodies from convalescent donors, prior to and following a single immunization with the Pfizer or Moderna mRNA vaccines, neutralize the Wuhan-Hu-1 strain and a variant, B.1.351 from South Africa. Pre-vaccination sera weakly neutralized Wuhan-Hu-1 and sporadically neutralized B.1.351. Immunization with either vaccine generated anamnestic B and CD4+ T cell responses and a 1000-fold increase in neutralizing antibody titers against both strains and SARS-CoV-1. Neutralization was likely due to anti-RBD and anti-S2

antibodies. Our study highlights the importance of vaccination of both uninfected and of previously infected subjects, as the elicited immune response will neutralize distinct viral strains.

51. **Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials.** Voysey M et al. *Lancet* 2021 Feb 19. doi: https://doi.org/10.1016/S0140-6736(21)00432-3
Findings: We present data from three single-blind randomised controlled trials—one phase 1/2 study in the UK (COV001), one phase 2/3 study in the UK (COV002), and a phase 3 study in Brazil (COV003)—and one double-blind phase 1/2 study in South Africa (COV005). As previously described, individuals 18 years and older were randomly assigned 1:1 to receive two standard doses of ChAdOx1 nCoV-19 (5 × 1010 viral particles) or a control vaccine or saline placebo. Between April 23 and Dec 6, 2020, 24 422 participants were recruited and vaccinated across the four studies, of whom 17 178 were included in the primary analysis (8597 receiving ChAdOx1 nCoV-19 and 8581 receiving control vaccine). There were no hospital admissions for COVID-19 in the ChAdOx1 nCoV-19 group after the initial 21-day exclusion period, and 15 in the control group. 108 (0·9%) of 12 282 participants in the ChAdOx1 nCoV-19 group and 127 (1·1%) of 11 962 participants in the control group had serious adverse events. There were seven deaths considered unrelated to vaccination (two in the ChAdOx1 nCov-19 group and five in the control group), including one COVID-19-related death in one participant in the control group. Exploratory analyses showed that vaccine efficacy after a single standard dose of vaccine from day 22 to day 90 after vaccination was 76·0% (59·3–85·9). Our modelling analysis indicated that protection did not wane during this initial 3-month period. Similarly, antibody levels were maintained during this period with minimal waning by day 90 (geometric mean ratio [GMR] 0·66 [95% CI 0·59–0·74]). In the participants who received two standard doses, after the second dose, efficacy was higher in those with a longer prime-boost interval (vaccine efficacy 81·3% [95% CI 60·3–91·2] at ≥12 weeks) than in those with a short interval (vaccine efficacy 55·1% [33·0–69·9] at <6 weeks). These observations are supported by immunogenicity data that showed binding antibody responses more than two-fold higher after an interval of 12 or more weeks compared with an interval of less than 6 weeks in those who were aged 18–55 years (GMR 2·32 [2·01–2·68]). Interpretation: The results of this primary analysis of two doses of ChAdOx1 nCoV-19 were consistent with those seen in the interim analysis of the trials and confirm that the vaccine is efficacious, with results varying by dose interval in exploratory analyses. A 3-month dose interval might have advantages over a programme with a short dose interval for roll-out of a pandemic vaccine to protect the largest number of individuals in the population as early as possible when supplies are scarce, while also improving protection after receiving a second dose.

Whole Person Care

52. **Follow-up Survey of US Adult Reports of Mental Health, Substance Use, and Suicidal Ideation During the COVID-19 Pandemic, September 2020.** Czeisler MÉ, Lane RI, Wiley JF, et al. *JAMA*

Netw Open. 2021 Feb 1;4(2):e2037665. doi: 10.1001/jamanetworkopen.2020.37665. https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2776559
Findings: Adverse mental health symptoms among US adults were more prevalent during the early phase (April-June 2020) of the coronavirus disease 2019 (COVID-19) pandemic compared with prepandemic estimates (eg, 3-fold increased prevalences of anxiety and depression symptoms, 2-fold increased prevalence of suicidal ideation). In June 2020, 2238 (40.9%) of 5470 US adults reported adverse mental or behavioral health symptoms. During this time, the prevalence of symptoms was lower in adults aged 65 years or older (141 of 933 [15.1%]) than in young adults aged 18 to 24 years (547 of 731 [74.9%]; P < .001). Given suggestions that acute increases in the prevalence of adverse mental health symptoms may represent a transient response to mass trauma, we sought to determine whether these patterns persisted in September 2020 and to examine disproportionately affected demographic groups.

Women & Children

53. **Higher SARS-CoV-2 Infection Rate in Pregnant Patients.** Lokken EM, Taylor GG, Huebner EM, Vanderhoeven J, et al. **[Providence author]**. *Am J Obstet Gynecol*. 2021 Feb 11:S0002-9378(21)00098-3. doi: 10.1016/j.ajog.2021.02.011. https://www.ajog.org/action/showPdf?pii=S0002-9378%2821%2900098-3
Findings: Pregnant patients with a PCR-confirmed SARS-CoV-2 infection diagnosed between March 1-June 30, 2020 were identified within 35 hospitals/clinic systems capturing 61% of annual deliveries in Washington State. A total of 240 pregnant patients with SARS-CoV-2 infections were identified during the study period with 70.7% from minority racial and ethnic groups. CONCLUSIONS: The SARS-CoV-2 infection rate in pregnant people was 70% higher than similarly aged adults in Washington State, which could not be completely explained by universal screening at delivery. Pregnant patients from nearly all racial/ethnic minority groups and patients receiving medical care in a non-English language were overrepresented. Pregnant women were not protected from COVID-19 in the early months of the pandemic with the greatest burden of infections occurring in nearly all racial/ethnic minority groups. This data coupled with a broader recognition that pregnancy is a risk factor for severe illness and maternal mortality strongly suggests that pregnant people should be broadly prioritized for COVID-19 vaccine allocation in the U.S. similar to some states.

GUIDELINES & CONSENSUS STATEMENTS

Surgical site infections - guidance for elective surgery during the SARS-CoV-2 pandemic - international recommendations and clinical experience. Ojan A, Markus G, Colin M K, et al. *J Hosp Infect*. 2021 Feb 15:S0195-6701(21)00070-0. doi: 10.1016/j.jhin.2021.02.011.

FDA / CDC / NIH / WHO Updates

CDC - Vital Statistics Rapid Release: Provisional Life Expectancy Estimates for January through June, 2020

FDA - Pulse Oximeter Accuracy and Limitations: FDA Safety Communication

FDA - Coronavirus (COVID-19) Update: FDA Issues Policies to Guide Medical Product Developers Addressing Virus Variants

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Commentary / News

Modify Centers for Medicare & Medicaid Services' Sepsis Core Measure (SEP-1) Now to Optimize Care for COVID-19. Peled H, Dau NQ, Sanders SS. **[Providence authors]**. *Ann Intern Med*. 2021 Feb 16. doi: 10.7326/M20-8266.
In the commentary, the authors urge the Centers for Medicare & Medicaid Services to remove lactate measurement from the national Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) during the COVID-19 crisis.

Covid-19: World's first human challenge trials to start in UK

The Price of Success-How to Evaluate COVID-19 Vaccines When They're Available Outside of Clinical Trials. Rubin R. *JAMA*. 2021 Feb 18. doi: 10.1001/jama.2021.0641.

SARS-CoV-2 Variants of Concern in the United States-Challenges and Opportunities. Walensky RP, Walke HT, Fauci AS. *JAMA*. 2021 Feb 17. doi: 10.1001/jama.2021.2294.

Why Are COVID-19 Case Numbers Dropping?

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