Providence

COVID-19 Resource Desk

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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

Clinical Syndrome

1. **Lung epithelial and endothelial damage, loss of tissue repair, inhibition of fibrinolysis, and cellular senescence in fatal COVID-19.** D'Agnillo F, Walters Kathie-Anne, et al. **[Providence authors].** *Sci Transl Med.* 2021 Oct 14:eabj7790. doi: 10.1126/scitranslmed.abj7790. https://www.science.org/doi/epdf/10.1126/scitranslmed.abj7790
The pathological mechanisms underlying COVID-19 respiratory distress and the interplay with aggravating risk factors have not been fully defined. Lung autopsy samples from 18 patients with fatal COVID-19, with symptom onset-to-death times ranging from 3 to 47 days, and antemortem plasma samples from 6 of these cases were evaluated using deep sequencing of SARS-CoV-2 RNA, multiplex plasma protein measurements, and pulmonary gene expression and imaging analyses. Prominent histopathological features in this case series included progressive diffuse alveolar damage with excessive thrombosis and late onset pulmonary tissue and vascular remodeling. Acute damage at the alveolar-capillary barrier was characterized by the loss of surfactant protein expression with injury to alveolar epithelial cells, endothelial cells, respiratory epithelial basal cells, and defective tissue repair processes. Other key findings included impaired clot fibrinolysis with increased concentrations of plasma and lung plasminogen activator inhibitor-1, and modulation of cellular senescence markers, including p21 and sirtuin-1, in both lung epithelial and endothelial cells. Together, these findings further define the molecular pathological features underlying the pulmonary response to SARS-CoV-2 infection and provide important insights into signaling pathways that may be amenable to therapeutic intervention.

Epidemiology & Public Health

2. **Severity of Disease among Adults Hospitalized with Laboratory-Confirmed COVID-19 before and During the Period of SARS-CoV-2 B.1.617.2 (Delta) Predominance — COVID-NET, 14 States, January–August 2021.** Taylor CA, et al. *MMWR Morb Mortal Wkly Rep.* ePub: 22 October 2021. DOI: http://dx.doi.org/10.15585/mmwr.mm7043e1
The SARS-CoV-2 B.1.617.2 (Delta) variant is highly transmissible; however, whether it causes more severe disease in adults has been uncertain. Analysis of COVID-NET data from 14 states found no significant increases in the proportion of hospitalized COVID-19 patients with severe

outcomes during the Delta period. The proportion of hospitalized unvaccinated COVID-19 patients aged 18–49 years significantly increased during the Delta period. Lower vaccination coverage in adults aged 18–49 years likely contributed to the increase in hospitalized patients during the Delta period. COVID-19 vaccination is critical for all eligible adults, including adults aged <50 years who have relatively low vaccination rates compared with older adults.

3. **Effect of Delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK.** Pouwels KB et al. *Nat Med*. 2021 Oct 14. doi: 10.1038/s41591-021-01548-7. https://www.nature.com/articles/s41591-021-01548-7
We found that the effectiveness of BNT162b2 and ChAdOx1 against infections with symptoms or high viral burden is reduced with the B.1.617.2 variant (absolute difference of 10-13% for BNT162b2 and 16% for ChAdOx1) compared to the B.1.1.7 (Alpha) variant. The effectiveness of two doses remains at least as great as protection afforded by prior natural infection. The dynamics of immunity after second doses differed significantly between BNT162b2 and ChAdOx1, with greater initial effectiveness against new PCR-positive cases but faster declines in protection against high viral burden and symptomatic infection with BNT162b2. There was no evidence that effectiveness varied by dosing interval, but protection was higher in vaccinated individuals after a prior infection and in younger adults. With B.1.617.2, infections occurring after two vaccinations had similar peak viral burden as those in unvaccinated individuals. SARS-CoV-2 vaccination still reduces new infections, but effectiveness and attenuation of peak viral burden are reduced with B.1.617.2.

4. **Associations between HIV infection and clinical spectrum of COVID-19: a population level analysis based on US National COVID Cohort Collaborative (N3C) data.** Yang X et al. *Lancet HIV*. 2021 Oct 13:S2352-3018(21)00239-3. doi: 10.1016/S2352-3018(21)00239-3. https://www.thelancet.com/journals/lanhiv/article/PIIS2352-3018(21)00239-3/fulltext
Given the COVID-19 pandemic's exacerbating effects on health inequities, public health and clinical communities must strengthen services and support to prevent aggravated COVID-19 outcomes among people with HIV, particularly for those with pronounced immunodeficiency.

Healthcare Delivery & Healthcare Workers

5. **SARS-CoV-2 vaccine breakthrough infections with the alpha variant are asymptomatic or mildly symptomatic among health care workers.** Rovida F et al. *Nat Commun.* 2021 Oct 15;12(1):6032. doi: 10.1038/s41467-021-26154-6. https://www.nature.com/articles/s41467-021-26154-6
Vaccine breakthrough SARS-CoV-2 infection has been monitored in 3720 healthcare workers receiving 2 doses of BNT162b2. SARS-CoV-2 infection is detected in 33 subjects, with a 100-day cumulative incidence of 0.93%. Vaccine protection against acquisition of SARS-CoV-2 infection is 83% in the overall population and 93% in SARS-CoV-2-experienced subjects, when compared with a non-vaccinated control group from the same Institution, in which SARS-CoV-2 infection occurs in 20/346 subjects (100-day cumulative incidence: 5.78%). The infection is symptomatic in 16 (48%) vaccinated subjects vs 17 (85%) controls. All analyzed patients, in whom the amount of viral RNA was sufficient for genome sequencing, results infected by the alpha variant.

Antibody and T-cell responses are not reduced in subjects with breakthrough infection. Evidence of virus transmission, determined by contact tracing, is observed in two (6.1%) cases. This real-world data support the protective effect of BNT162b2 vaccine. A triple antigenic exposure, such as two-dose vaccine schedule in experienced subjects, may confer a higher protection.

6. **Risk factors for breakthrough SARS-CoV-2 infection in vaccinated healthcare workers.** Alishaq M et al. *PLoS One.* 2021 Oct 15;16(10):e0258820. doi: 10.1371/journal.pone.0258820. eCollection 2021. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0258820
Presence of symptoms and contact with a confirmed case are major risk factors for breakthrough SARS-CoV-2 infection after vaccination, and these groups should be prioritized for screening even after full vaccination.

Prognosis

7. **Proton-pump inhibitor use is not associated with severe COVID-19-related outcomes: a propensity score-weighted analysis of a national veteran cohort.** Shah S et al. *Gut*. 2021 Oct 18:gutjnl-2021-325701. doi: 10.1136/gutjnl-2021-325701.
https://gut.bmj.com/content/early/2021/10/17/gutjnl-2021-325701
We assembled a national retrospective cohort of US veterans who tested positive for SARS-CoV-2 (index date). Current outpatient PPI use up to and including the index date (primary exposure) was compared with non-use, defined as no PPI prescription fill in the 365 days prior to the index date. The primary composite outcome was mechanical ventilation use or death within 60 days; the secondary composite outcome also included hospital or ICU admission. In contrast to PS matching, PS weighting allowed inclusion of all patients. Weighted logistic regression models evaluated severe COVID-19 outcomes between current PPI users versus non-users.

Survivorship & Rehabilitation

8. **Inpatient Rehabilitation Outcomes Following Severe COVID-19 Infections: A Retrospective Cohort Study.** Abramoff BA, et al. *Am J Phys Med Rehabil.* 2021 Oct 14. doi: 10.1097/PHM.0000000000001885.
https://journals.lww.com/ajpmr/Abstract/9000/Inpatient_Rehabilitation_Outcomes_Following_Severe.97562.aspx
While patients with a history of COVID-19 had worse function at time of admission to acute rehabilitation, inpatient rehabilitation significantly improved their function to comparable levels as patients who did not have COVID-19.

Therapeutics

9. **Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial.** Rosas IO, Diaz George, Robinson Philip, et al. **[Providence authors].** *Intensive Care Med.* 2021 Oct 5:1-13. doi: 10.1007/s00134-021-06507-x.

This randomized, double-blind, placebo-controlled, multicenter trial included patients hospitalized with severe COVID-19 pneumonia requiring > 6 L/min supplemental oxygen. Patients were randomly assigned (2:1 ratio) to receive tocilizumab 8 mg/kg or placebo intravenously plus ≤ 10 days of remdesivir. Among 649 enrolled patients, 434 were randomly assigned to tocilizumab plus remdesivir and 215 to placebo plus remdesivir. 566 patients (88.2%) received corticosteroids during the trial to day 28. Tocilizumab plus remdesivir did not shorten time to hospital discharge or "ready for discharge" to day 28 compared with placebo plus remdesivir in patients with severe COVID-19 pneumonia.

10. **Investigating Lipid-Modulating Agents for Prevention or Treatment of COVID-19: JACC State-of-the-Art Review.** Talasaz AH et al. *J Am Coll Cardiol.* 2021 Oct 19;78(16):1635-1654. doi:10.1016/j.jacc.2021.08.021.
https://www.sciencedirect.com/science/article/pii/S0735109721059702
Coronavirus disease-2019 (COVID-19) is associated with systemic inflammation, endothelial activation, and multiorgan manifestations. Lipid-modulating agents may be useful in treating patients with COVID-19. These agents may inhibit viral entry by lipid raft disruption or ameliorate the inflammatory response and endothelial activation. In addition, dyslipidemia with lower high-density lipoprotein cholesterol and higher triglyceride levels portend worse outcomes in patients with COVID-19. Upon a systematic search, 40 randomized controlled trials (RCTs) with lipid-modulating agents were identified, including 17 statin trials, 14 omega-3 fatty acids RCTs, 3 fibrate RCTs, 5 niacin RCTs, and 1 dalcetrapib RCT for the management or prevention of COVID-19. From these 40 RCTs, only 2 have reported preliminary results, and most others are ongoing. This paper summarizes the ongoing or completed RCTs of lipid-modulating agents in COVID-19 and the implications of these trials for patient management.

11. **Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with covid-19 admitted to hospital: RAPID randomised clinical trial.** Sholzberg M et al. *BMJ*. 2021 Oct 14;375:n2400. doi: 10.1136/bmj.n2400. https://www.bmj.com/content/375/bmj.n2400
In moderately ill patients with covid-19 and increased D-dimer levels admitted to hospital wards, therapeutic heparin was not significantly associated with a reduction in the primary outcome but the odds of death at 28 days was decreased. The risk of major bleeding appeared low in this trial.

12. **Toxic Effects from Ivermectin Use Associated with Prevention and Treatment of Covid-19.** Temple C, et al. *N Engl J Med.* 2021 Oct 20. doi: 10.1056/NEJMc2114907.
https://www.nejm.org/doi/full/10.1056/NEJMc2114907
The Oregon Poison Center is a telephone consultative center staffed by specialty-trained nurses, pharmacists, and physicians who provide treatment advice for the public and comprehensive treatment consultation for health care workers caring for patients in Oregon, Alaska, and Guam. The center has recently received an increasing number of calls regarding ivermectin exposure related to Covid-19. The rate of calls regarding ivermectin had been 0.25 calls per month in 2020 and had increased to 0.86 calls per month from January through July 2021; in August 2021, the center received 21 calls. Six of the 21 persons were hospitalized for

toxic effects from ivermectin use; all 6 reported preventive use, including the 3 who had obtained the drug by prescription. Four received care in an intensive care unit, and none died. Symptoms were gastrointestinal distress in 4 persons, confusion in 3, ataxia and weakness in 2, hypotension in 2, and seizures in 1. Of the persons who were not admitted to a hospital, most had gastrointestinal distress, dizziness, confusion, vision symptoms, or rash.

13. **Lessons learned from COVID-19 therapies: Critical perspectives from the IDSA COVID-19 treatment guideline panel.** Bhimraj A et al. *Clin Infect Dis.* 2021 Oct 20:ciab882. doi: 10.1093/cid/ciab882. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab882/6398589
Despite the challenges of the pandemic, there has been substantial progress with COVID-19 therapies. Pivotal COVID-19 trials like SOLIDARITY, RECOVERY and ACCT-1 were rapidly conducted and data disseminated to support effective therapies. However, critical shortcomings remain on trial conduct, dissemination and interpretation of study results, and regulatory guidance in pandemic settings. The lessons we learned have implications for both the current pandemic and future emerging infectious diseases. There is a need for establishing and standardizing clinical meaningful outcomes in therapeutic trials and for targeting defined populations and phenotypes that will most benefit from specific therapies. Standardized processes should be established for rapid and critical data review and dissemination to ensure scientific integrity. Clarity around the evidence standards needed for issuance of both Emergency Use Authorization (EUA) and Biologic License Application (BLA) should be established and an infrastructure for executing rapid trials in epidemic settings maintained.

14. **Association between glucocorticoids treatment and viral clearance delay in patients with COVID-19: a systematic review and meta-analysis.** Li J, et al. *BMC Infect Dis*. 2021 Oct 14;21(1):1063. doi: 10.1186/s12879-021-06548-z.
https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-021-06548-z
Glucocorticoids treatment delayed viral clearance in COVID-19 patients of taking high doses or medium doses, rather in those of taking low doses of glucocorticoids.

15. **Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial.** RECOVERY Collaborative Group. *Lancet Respir Med* 2021 Oct 18. doi: https://doi.org/10.1016/S2213-2600(21)00435-5
https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00435-5/fulltext
In adults hospitalised with COVID-19, colchicine was not associated with reductions in 28-day mortality, duration of hospital stay, or risk of progressing to invasive mechanical ventilation or death.

16. **Efficacy of interferon beta-1a plus remdesivir compared with remdesivir alone in hospitalised adults with COVID-19: a double-bind, randomised, placebo-controlled, phase 3 trial.** Kalil AC et al. *Lancet Respir Med* 2021 Oct 18. doi: https://doi.org/10.1016/S2213-2600(21)00384-2
https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00384-2/fulltext

Interferon beta-1a plus remdesivir was not superior to remdesivir alone in hospitalised patients with COVID-19 pneumonia. Patients who required high-flow oxygen at baseline had worse outcomes after treatment with interferon beta-1a compared with those given placebo.

Vaccines / Immunology

17. **COVID-19 Vaccination and Non–COVID-19 Mortality Risk — Seven Integrated Health Care Organizations, United States, December 14, 2020–July 31, 2021.** Xu S, et al. *MMWR Morb Mortal Wkly Rep.* ePub: 22 October 2021. DOI: http://dx.doi.org/10.15585/mmwr.mm7043e2
Although deaths after COVID-19 vaccination have been reported to the Vaccine Adverse Events Reporting System, few studies have been conducted to evaluate mortality not associated with COVID-19 among vaccinated and unvaccinated groups. During December 2020–July 2021, COVID-19 vaccine recipients had lower rates of non–COVID-19 mortality than did unvaccinated persons after adjusting for age, sex, race and ethnicity, and study site. There is no increased risk for mortality among COVID-19 vaccine recipients. This finding reinforces the safety profile of currently approved COVID-19 vaccines in the United States. All persons aged ≥12 years should receive a COVID-19 vaccine.

18. **Effectiveness of the mRNA-1273 Vaccine during a SARS-CoV-2 Delta Outbreak in a Prison.** Chin ET, et al. *N Engl J Med.* 2021 Oct 20. doi: 10.1056/NEJMc2114089.
https://www.nejm.org/doi/full/10.1056/NEJMc2114089
Our results indicate that the mRNA-1273 vaccine was quite effective against SARS-CoV-2 infection during a delta variant–driven outbreak in this high-risk, congregate setting. Although the effectiveness against infection was substantially lower than that estimated in studies conducted before the emergence of the delta variant, protection against symptomatic illness remained robust — an outcome consistent with other recent reports. Notably, full vaccination also conferred additional substantial protection against infection in men with previous confirmed infections.

19. **BNT162b2 and ChAdOx1 nCoV-19 Vaccine Effectiveness against Death from the Delta Variant.** Sheikh A, et al. *N Engl J Med.* 2021 Oct 20. doi: 10.1056/NEJMc2113864.
https://www.nejm.org/doi/full/10.1056/NEJMc2113864
We used a Scotland-wide surveillance platform (Early Pandemic Evaluation and Enhanced Surveillance of COVID-19 [EAVE II]) that includes individual-level linked data on vaccination, testing, viral sequencing, primary care, hospital admissions, and mortality among 5.4 million people (approximately 99% of the Scottish population). We conducted a cohort study and used Cox regression to estimate vaccine effectiveness against death from delta variant infection from April 1 to August 16, 2021, among adults 18 years of age or older, who were followed up to September 27, 2021.

20. **COVID-19 mRNA vaccines drive differential antibody Fc-functional profiles in pregnant, lactating, and non-pregnant women.** Atyeo C et al. *Sci Transl Med* 2021 Oct 19. doi: 10.1126/scitranslmed.abi8631 https://www.science.org/doi/10.1126/scitranslmed.abi8631

To define potential changes in vaccine response during pregnancy and lactation, we undertook deep sequencing of the humoral vaccine response in a group of pregnant and lactating women and non-pregnant age-matched controls. Vaccine-specific titers were comparable between pregnant women, lactating women, and non-pregnant controls. However, Fc receptor (FcR)-binding and antibody effector functions were induced with delayed kinetics in both pregnant and lactating women compared to non-pregnant women after the first vaccine dose, which normalized after the second dose. Vaccine boosting resulted in high FcR-binding titers in breastmilk. These data suggest that pregnancy promotes resistance to generating pro-inflammatory antibodies and indicates that there is a critical need to follow prime-boost timelines in this vulnerable population to ensure full immunity is attained.

Women & Children

21. **COVID-19 and Novel mRNA Vaccines in Pregnancy: An Updated Literature Review.** Joubert E, et al. *BJOG.* 2021 Oct 15. doi: 10.1111/1471-0528.16973.
https://obgyn.onlinelibrary.wiley.com/doi/abs/10.1111/1471-0528.16973
The novel coronavirus, SARS-CoV-2, or COVID-19, has affected the world on a pandemic scale resulting in catastrophic outcomes and deaths. Currently, there is limited safety data specific to mRNA vaccine use in pregnant or lactating individuals and the potential risks to a pregnant individual and the fetus are unknown. We report an updated literature review of current information and evidence available to aid in the decision whether to vaccinate against COVID-19 currently being made by pregnant individuals and their healthcare providers so that they are able to make a well-informed recommendation and decision.

22. **Changes in Adverse Pregnancy Outcomes Associated With the COVID-19 Pandemic in the United States.** Sun S, et al. *JAMA Netw Open.* 2021 Oct 1;4(10):e2129560. doi: 10.1001/jamanetworkopen.2021.29560.
https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2785014
The COVID-19 pandemic and ensuing government response has led to profound changes in lifestyle, physical and mental health, and health care access and delivery. The cumulative impact of these stressors on the risk of adverse pregnancy outcomes has not been examined in detail, and initial evidence has been inconsistent. Accordingly, we evaluated the change in rates of pregnancy complications associated with the pandemic period among pregnant women with commercial health insurance across the US.

23. **Covid-19 Vaccination during Pregnancy and First-Trimester Miscarriage.** Magnus MC, et al. *N Engl J Med.* 2021 Oct 20. doi: 10.1056/NEJMc2114466.
https://www.nejm.org/doi/full/10.1056/NEJMc2114466
Our study found no evidence of an increased risk for early pregnancy loss after Covid-19 vaccination and adds to the findings from other reports supporting Covid-19 vaccination during pregnancy.

GUIDELINES & CONSENSUS STATEMENTS

2021 Interim Guidance to Health Care Providers for Basic and Advanced Cardiac Life Support in Adults, Children, and Neonates with Suspected or Confirmed COVID-19. Carl Hinkson, et al; Emergency Cardiovascular Care Committee and Get with the Guidelines-Resuscitation Adult and Pediatric Task Forces of the American Heart Association in Collaboration with the American Academy of Pediatrics, American Association for Respiratory Care, American College of Emergency Physicians, American Society of Anesthesiologists, and the Society of Critical Care Anesthesiologists. **{Providence collaborator]**. *Circ Cardiovasc Qual Outcomes.* 2021 Oct 13:CIRCOUTCOMES121008396. doi: 10.1161/CIRCOUTCOMES.121.008396.

FDA / CDC / NIH / WHO Updates

CDC Expands Eligibility for COVID-19 Booster Shots, Oct 21, 2021

FDA Takes Additional Actions on the Use of a Booster Dose for COVID-19 Vaccines Oct 20, 2021

NIH – Covid-19 Treatment Guidelines, update Prevention of SARS-CoV-2 Infection.

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