Providence

COVID-19 Resource Desk

#98 | 3.13.2022 to 3.19.2022

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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. **KIR+CD8+ T cells suppress pathogenic T cells and are active in autoimmune diseases and COVID-19.** Su Yapeng, Heath James R, et al. **[Providence authors].** *Science.* 2022 Mar 8:eabi9591. doi: 10.1126/science.abi9591. https://www.science.org/doi/10.1126/science.abi9591

Here we find that CD8+ T cells expressing inhibitory killer cell immunoglobulin-like receptors (KIRs) are the human equivalent of Ly49+CD8+ regulatory T cells in mice and are increased in the blood and inflamed tissues of patients with a variety of autoimmune diseases. Moreover, these CD8+ T cells efficiently eliminated pathogenic gliadin-specific CD4+ T cells from celiac disease patients' leukocytes in vitro. We also find elevated levels of KIR+CD8+ T cells, but not CD4+ regulatory T cells, in COVID-19 patients, which correlated with disease severity and vasculitis. Selective ablation of Ly49+CD8+ T cells in virus-infected mice led to autoimmunity post infection. Our results indicate that in both species, these regulatory CD8+ T cells act uniquely to suppress pathogenic T cells in autoimmune and infectious diseases.

Clinical Syndrome

2. **Comparison of Patients Infected with Delta Versus Omicron COVID-19 Variants Presenting to Paris Emergency Departments: A Retrospective Cohort Study.** Bouzid D et al. *Ann Intern Med*. 2022 Mar 15. doi: 10.7326/M22-0308. https://www.acpjournals.org/doi/10.7326/M22-0308

Compared with the Delta variant, infection with the Omicron variant in patients in the ED had different clinical and biological patterns and was associated with better in-hospital outcomes, including higher survival.

Diagnostics & Screening

3. **Comparison of SARS-CoV-2 Reverse Transcriptase Polymerase Chain Reaction and BinaxNOW Rapid Antigen Tests at a Community Site During an Omicron Surge : A Cross-Sectional Study.** Schrom J et al. *Ann Intern Med*. 2022 Mar 15. doi: 10.7326/M22-0202. https://www.acpjournals.org/doi/10.7326/M22-0202

BinaxNOW detected persons with high SARS-CoV-2 levels during the Omicron surge, enabling rapid responses to positive test results. Cheek or throat swabs should not replace nasal swabs. As currently recommended, high-risk persons with an initial negative BinaxNOW result should have repeated testing.

Epidemiology & Public Health

4. **Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020-21.** COVID-19 Excess Mortality Collaborators. *Lancet.* 2022 Mar 10:S0140-6736(21)02796-3. doi: 10.1016/S0140-6736(21)02796-3. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)02796-3/fulltext

The full impact of the pandemic has been much greater than what is indicated by reported deaths due to COVID-19 alone. Strengthening death registration systems around the world, long understood to be crucial to global public health strategy, is necessary for improved monitoring of this pandemic and future pandemics. In addition, further research is warranted to help distinguish the proportion of excess mortality that was directly caused by SARS-CoV-2 infection and the changes in causes of death as an indirect consequence of the pandemic.

5. **SARS-CoV-2 incidence, transmission, and reinfection in a rural and an urban setting: results of the PHIRST-C cohort study, South Africa, 2020-21.** Cohen C et al. *Lancet Infect Dis*. 2022 Mar 14:S1473-3099(22)00069-X. doi: 10.1016/S1473-3099(22)00069-X. https://www.sciencedirect.com/science/article/pii/S147330992200069X

In this study, 565 (85·3%) SARS-CoV-2 infections were asymptomatic and index case symptom status did not affect HCIR, suggesting a limited role for control measures targeting symptomatic individuals. Increased household transmission of beta and delta variants was likely to have contributed to successive waves of SARS-CoV-2 infection, with more than 60% of individuals infected by the end of follow-up.

Healthcare Delivery & Healthcare Workers

6. **Effects of Safety Zone Implementation on Perceptions of Safety and Well-being When Caring for COVID-19 Patients.** Skinner Claudia, Ablir Lilian, Bloom Todd, Fujimoto Stacie, Rozenfeld Yelena, Leung Peggy. **[Providence authors].** *Am J Crit Care.* 2022 Mar 1;31(2):104-110. doi: 10.4037/ajcc2022633. https://aacnjournals.org/ajcconline/article/31/2/104/31661/Effects-of-Safety-Zone-Implementation-on

To determine if implementing safety zones improves the perceptions of safety, well-being, workflow, and teamwork among hospital staff caring for patients during a pandemic. Safety zone implementation improved caregivers' perceptions of their safety, their well-being, and collaboration within the multidisciplinary staff but did not improve their perceptions of teamwork or workflow.

7. **Out-of-Pocket Spending for Health Care After COVID-19 Hospitalization.** Kao-Ping Chua et al. *Am J Manag Care*. 2022;28(8):In Press https://www.ajmc.com/view/out-of-pocket-spending-for-health-care-after-covid-19-hospitalization

For most patients hospitalized for COVID-19, postdischarge care may not be a major source of financial stress. Although this is reassuring, our findings also suggest that a sizable minority of COVID-19 survivors have substantial out-of-pocket spending after discharge. These survivors could be particularly vulnerable to financial toxicity if they also receive bills for the hospitalization owing to the expiration of insurer cost-sharing waivers. Insurers should consider this possibility when deciding whether to reinstate cost-sharing waivers for COVID-19 hospitalizations.

Therapeutics

8. **Efficacy and safety of CD24Fc in hospitalised patients with COVID-19: a randomised, double-blind, placebo-controlled, phase 3 study.** Welker J et al. *Lancet Infect Dis*. 2022 Mar 11:S1473-3099(22)00058-5. doi: 10.1016/S1473-3099(22)00058-5. https://www.sciencedirect.com/science/article/pii/S1473309922000585

CD24Fc is generally well tolerated and accelerates clinical improvement of hospitalised patients with COVID-19 who are receiving oxygen support. These data suggest that targeting inflammation in response to tissue injuries might provide a therapeutic option for patients hospitalised with COVID-19.

See also: CD24Fc: an emerging COVID-19 therapy. Eckhardt CM, O'Donnell MR. *Lancet Infect Dis.* 2022 Mar 11:S1473-3099(22)00125-6. doi: 10.1016/S1473-3099(22)00125-6.

9. **Effect of Sotrovimab on Hospitalization or Death Among High-risk Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial.** Gupta A et al. *JAMA.* 2022 Mar 14. doi: 10.1001/jama.2022.2832. https://jamanetwork.com/journals/jama/fullarticle/2790246

Among nonhospitalized patients with mild to moderate COVID-19 and at risk of disease progression, a single intravenous dose of sotrovimab, compared with placebo, significantly reduced the risk of a composite end point of all-cause hospitalization or death through day 29. The findings support sotrovimab as a treatment option for nonhospitalized, high-risk patients with mild to moderate COVID-19, although efficacy against SARS-CoV-2 variants that have emerged since the study was completed is unknown.

10. **One-Year Outcomes with Venovenous Extracorporeal Membrane Oxygenation Support for Severe COVID-19.** Smith DE et al. *Ann Thorac Surg*. 2022 Feb 20:S0003-4975(22)00064-9. doi: 10.1016/j.athoracsur.2022.01.003. https://www.sciencedirect.com/science/article/pii/S0003497522000649

A well-defined patient selection and management strategy of VV-ECMO support in patients with severe COVID-19 resulted in exceptional survival to discharge that was sustained at 1-year after ECMO cannulation.

Vaccines / Immunology

11. **Antibody-mediated Immunogenicity against SARS-CoV-2 following priming, boosting and hybrid immunity: insights from 11 months of follow-up of a healthcare worker cohort in Israel, December 2020-October 2021.** Edelstein M, et al. *Clin Infect Dis.* 2022 Mar 12:ciac212. doi: 10.1093/cid/ciac212. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciac212/6547893

Immunity waned in all age groups and previously infected individuals, reversed by boosting. IgG titres decrease and reinfections in individuals with hybrid immunity (infection+vaccination) suggests they may also require further doses. Our study also highlights the difficulty in determining protective IgG levels.

12. **Emerging evidence on heterologous COVID-19 vaccine schedules-To mix or not to mix?** Parker EPK, et al. *Lancet Infect Dis.* 2022 Mar 9:S1473-3099(22)00178-5. doi: 10.1016/S1473-3099(22)00178-5. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(22)00178-5/fulltext

We did a comprehensive review of available data on the safety, immunogenicity, and effectiveness of heterologous vaccine schedules (for methods, see appendix pp 1–3). We identified 48 studies that tested a combination of WHO EUL COVID-19 vaccines from different platforms. These included seven controlled trials and 41 observational studies. Schedules involved a combination (in any order) of vectored–mRNA vaccines (36 studies), vectored–inactivated vaccines (eight studies), and inactivated–mRNA vaccines (eight studies). No protein-based vaccines had received a WHO EUL at the time of the review. A total of 37 studies considered heterologous primary schedules (involving more than one product during a two-dose primary series), whereas 13 considered heterologous boosting (among individuals who have previously received a complete homologous primary series). Most studies considered humoral immune response endpoints (38 studies), with a subset reporting on safety (23 studies) and vaccine effectiveness (VE; 11 studies).

13. **COVID-19 vaccines in patients with cancer: immunogenicity, efficacy and safety.** Fendler A, et al. *Nat Rev Clin Oncol.* 2022 Mar 11. doi: 10.1038/s41571-022-00610-8. https://www.nature.com/articles/s41571-022-00610-8

Patients with cancer have a higher risk of severe coronavirus disease (COVID-19) and associated mortality than the general population. Owing to this increased risk, patients with cancer have been prioritized for COVID-19 vaccination globally, for both primary and booster vaccinations. However, given that these patients were not included in the pivotal clinical trials, considerable uncertainty remains regarding vaccine efficacy, and the extent of humoral and cellular immune responses in these patients, as well as the risks of vaccine-related adverse events. In this Review, we summarize the current knowledge generated in studies conducted since COVID-19 vaccines first became available. We also highlight critical points that might affect vaccine efficacy in patients with cancer in the future.

14. **Stroke Among SARS-CoV-2 Vaccine Recipients in Mexico: A Nationwide Descriptive Study.** López-Mena D et al. *Neurology.* 2022 Mar 11:10.1212/WNL.0000000000200388. doi: 10.1212/WNL.0000000000200388. https://n.neurology.org/content/early/2022/03/11/WNL.0000000000200388

Stroke is an exceedingly rare AEFI against SARS-CoV-2. Pre-existing stroke risk factors were identified in most patients. Further research is needed to evaluate causal associations between SARS-COV-2 vaccines and stroke.

15. **Safety and immunogenicity of an inactivated recombinant Newcastle disease virus vaccine expressing SARS-CoV-2 spike: Interim results of a randomised, placebo-controlled, phase 1 trial.** Pitisuttithum P et al. *EClinicalMedicine.* 2022 Mar 8;45:101323. doi:

10.1016/j.eclinm.2022.101323. eCollection 2022 Mar. https://www.sciencedirect.com/science/article/pii/S2589537022000530

NDV-HXP-S had an acceptable safety profile and potent immunogenicity. The 3 µg and 3 µg+CpG1018 formulations advanced to phase 2.

16. **Characteristics Associated with Serological Covid-19 Vaccine Response and Durability in an Older Population with Significant Comorbidity: The Danish Nationwide ENFORCE Study.** Søgaard OS et al. *Clin Microbiol Infect.* 2022 Mar 10:S1198-743X(22)00142-2. doi: 10.1016/j.cmi.2022.03.003.https://www.sciencedirect.com/science/article/pii/S1198743X22001422

Comorbidity, male sex and vaccine type were risk factors for hypo-responsiveness and non-durable response to COVID-19 vaccination. The functional activity of vaccine-induced antibodies declined with increasing age and had waned to pre-2nd vaccination levels for most individuals after 6 months.

17. **Persistent Antibody Responses up to 18 Months after Mild SARS-CoV-2 Infection.** Choe PG, et al. *J Infect Dis.* 2022 Mar 17:jiac099. doi: 10.1093/infdis/jiac099. https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiac099/6550287

Serum IgA and IgG antibodies against spike or receptor-binding domain (RBD) protein of wild-type SARS-CoV-2 were detected for up to 18 months, and neutralizing antibodies persisted for 8 to 18 months after infection. However, any significant antibody responses against RBD proteins of SARS-CoV-2 variants were not observed, and median neutralizing antibody titers against the Delta variant at 8, 12, and 18 months were 8-11 fold lower than against wild-type viruses ($P < .001$). Humoral immunity persisted for up to 18 months after SARS-CoV-2 infection in patients with mild COVID-19. Humoral immune activity against more recently circulating variants, however, was reduced in this population.

18. **Durability of the Single-Dose Ad26.COV2.S Vaccine in the Prevention of COVID-19 Infections and Hospitalizations in the US Before and During the Delta Variant Surge.** Polinski JM, et al. *JAMA Netw Open.* 2022 Mar 1;5(3):e222959. doi: 10.1001/jamanetworkopen.2022.2959. https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2790204

This cohort study in US clinical practice showed stable VE of Ad26.COV2.S for at least 6 months before as well as during the time the Delta variant emerged and became dominant.

19. **Efficacy of a Fourth Dose of Covid-19 mRNA Vaccine against Omicron.** Regev-Yochay G et al. *N Engl J Med.* 2022 Mar 16. doi: 10.1056/NEJMc2202542. https://www.nejm.org/doi/10.1056/NEJMc2202542

In this open-label, nonrandomized clinical study, we assessed the immunogenicity and safety of a fourth dose of either BNT162b2 (Pfizer–BioNTech) or mRNA-1273 (Moderna) administered 4 months after the third dose in a series of three BNT162b2 doses (ClinicalTrials.gov numbers, NCT05231005. opens in new tab and NCT05230953. opens in new tab; the protocol is available with the full text of this letter at NEJM.org). Of the 1050 eligible health care workers enrolled in the Sheba HCW COVID-19 Cohort,1,2 154 received the fourth dose of BNT162b2 and, 1 week later, 120 received mRNA-1273. For each participant, two age-matched controls were selected from the remaining eligible participants (Fig. S1 in the Supplementary Appendix, available at NEJM.org).

20. **Association between covid-19 vaccination, SARS-CoV-2 infection, and risk of immune mediated neurological events: population based cohort and self-controlled case series analysis.** Li X, et al. *BMJ.* 2022 Mar 16;376:e068373. doi: 10.1136/bmj-2021-068373. https://www.bmj.com/content/376/bmj-2021-068373

No safety signal was observed between covid-19 vaccines and the immune mediated neurological events of Bell's palsy, encephalomyelitis, Guillain-Barré syndrome, and transverse myelitis. An increased risk of Bell's palsy, encephalomyelitis, and Guillain-Barré syndrome was, however, observed for people with SARS-CoV-2 infection.

21. **Effectiveness of mRNA Vaccination in Preventing COVID-19–Associated Invasive Mechanical Ventilation and Death — United States, March 2021–January 2022.** Tenforde MW, et al. *MMWR Morb Mortal Wkly Rep*. ePub: 18 March 2022. DOI: http://dx.doi.org/10.15585/mmwr.mm7112e1

Using a case-control design, mRNA vaccine effectiveness (VE) against COVID-19–associated IMV and in-hospital death was evaluated among adults aged ≥18 years hospitalized at 21 U.S. medical centers during March 11, 2021–January 24, 2022. During this period, the most commonly circulating variants of SARS-CoV-2, the virus that causes COVID-19, were B.1.1.7 (Alpha), B.1.617.2 (Delta), and B.1.1.529 (Omicron). Previous vaccination (2 or 3 versus 0 vaccine doses before illness onset) in prospectively enrolled COVID-19 case-patients who received IMV or died within 28 days of hospitalization was compared with that among hospitalized control patients without COVID-19. Among 1,440 COVID-19 case-patients who received IMV or died, 307 (21%) had received 2 or 3 vaccine doses before illness onset. Among 6,104 control-patients, 4,020 (66%) had received 2 or 3 vaccine doses. Among the 1,440 case-patients who received IMV or died, those who were vaccinated were older (median age = 69 years), more likely to be immunocompromised (40%), and had more chronic medical conditions compared with unvaccinated case-patients (median age = 55 years; immunocompromised = 10%; $p<0.001$ for both). VE against IMV or in-hospital death was 90% (95% CI = 88%–91%) overall, including 88% (95% CI = 86%–90%) for 2 doses and 94% (95% CI = 91%–96%) for 3 doses, and 94% (95% CI = 88%–97%) for 3 doses during the Omicron-predominant period. COVID-19 mRNA vaccines are highly effective in preventing COVID-19–associated death and respiratory failure treated with IMV. CDC recommends that all persons eligible for vaccination get vaccinated and stay up to date with COVID-19 vaccination.

Women & Children

22. **Comparing Human Milk Antibody Response After 4 Different Vaccines for COVID-19.** Juncker HG, et al. *JAMA Pediatr*. 2022 Mar 14. doi: 10.1001/jamapediatrics.2022.0084. https://jamanetwork.com/journals/jamapediatrics/fullarticle/2789947

COVID-19 usually has a mild course in children; however, newborns and infants are more susceptible to severe disease. Human milk is suggested to play an important role to protect against infections, mostly owing to disease-specific antibodies. Antibodies against SARS-CoV-2 are present in the human milk of previously infected women, as well as following vaccination with a SARS-CoV-2 vaccine, and are capable of neutralizing the virus. Because maternal vaccination during lactation may protect not only the mother but also her breastfed infant, knowledge of its effect is important to guide health care workers and lactating women in decision-making regarding SARS-CoV-2 vaccination. Therefore, this

study aims to compare the antibody response in human milk after vaccination with mRNA-based and vector-based vaccines.

23. **Effectiveness of 2-Dose BNT162b2 (Pfizer BioNTech) mRNA Vaccine in Preventing SARS-CoV-2 Infection Among Children Aged 5-11 Years and Adolescents Aged 12-15 Years - PROTECT Cohort, July 2021-February 2022.** Fowlkes AL et al. *MMWR Morb Mortal Wkly Rep*. 2022 Mar 18;71(11):422-428. doi: 10.15585/mmwr.mm7111e1. https://www.cdc.gov/mmwr/volumes/71/wr/mm7111e1.htm?s_cid=mm7111e1_w

The PROTECT prospective cohort of 1,364 children and adolescents aged 5-15 years was tested weekly for SARS-CoV-2, irrespective of symptoms, and upon COVID-19-associated illness during July 25, 2021-February 12, 2022. Among unvaccinated participants with any laboratory-confirmed SARS-CoV-2 infection, those with B.1.617.2 (Delta) variant infections were more likely to report COVID-19 symptoms (66%) than were those with Omicron infections (49%). Among fully vaccinated children aged 5-11 years, VE against any symptomatic and asymptomatic Omicron infection 14-82 days after receipt of dose 2 of the Pfizer-BioNTech vaccine was 31%, adjusted for sociodemographic characteristics, health information, frequency of social contact, mask use, location, and local virus circulation. Among adolescents aged 12-15 years, adjusted VE 14-149 days after dose 2 was 87% against symptomatic and asymptomatic Delta infection and 59% (95% CI = 22%-79%) against Omicron infection. Fully vaccinated participants with Omicron infection spent an average of one half day less sick in bed than did unvaccinated participants with Omicron infection. All eligible children and adolescents should remain up to date with recommended COVID-19 vaccinations.

24. **Hospitalization of Infants and Children Aged 0-4 Years with Laboratory-Confirmed COVID-19 - COVID-NET, 14 States, March 2020-February 2022.** Marks KJ et al. *MMWR Morb Mortal Wkly Rep*. 2022 Mar 18;71(11):429-436. doi: 10.15585/mmwr.mm7111e2. https://www.cdc.gov/mmwr/volumes/71/wr/mm7111e2.htm?s_cid=mm7111e2_w

Coinciding with increased Omicron circulation, COVID-19-associated hospitalization rates increased rapidly among infants and children aged 0-4 years, a group not yet eligible for vaccination. Coronavirus Disease 19-Associated Hospitalization Surveillance Network (COVID-NET) data were analyzed to describe COVID-19-associated hospitalizations among U.S. infants and children aged 0-4 years since March 2020. During the period of Omicron predominance (December 19, 2021-February 19, 2022), weekly COVID-19-associated hospitalization rates per 100,000 infants and children aged 0-4 years peaked at 14.5 (week ending January 8, 2022); this Omicron-predominant period peak was approximately five times that during the period of SARS-CoV-2 B.1.617.2 (Delta) predominance (June 27-December 18, 2021, which peaked the week ending September 11, 2021). During Omicron predominance, 63% of hospitalized infants and children had no underlying medical conditions; infants aged <6 months accounted for 44% of hospitalizations, although no differences were observed in indicators of severity by age. Strategies to prevent COVID-19 among infants and young children are important and include vaccination among currently eligible populations such as pregnant women (3), family members, and caregivers of infants and young children.

25. **Persistent cough and asthma-like symptoms post COVID-19 hospitalization in children.** Esmaeilzadeh H, et al. *BMC Infect Dis*. 2022 Mar 12;22(1):244. doi: 10.1186/s12879-022-07252-2. https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-022-07252-2

We found an asthma-like prevalence of 41.5% in the cohort of COVID-19 hospitalized children. Family history of asthma and previous history of asthma and allergic rhinitis are risk factors for asthma-like after COVID-19 hospitalization. COVID-19 presentations are more severe in the asthma-like group.

26. **Management and outcome of critically ill pregnant women with COVID-19.** COVPREG study group. *Intensive Care Med.* 2022 Mar 14. doi: 10.1007/s00134-022-06653-w. https://link.springer.com/article/10.1007/s00134-022-06653-w

Coronavirus disease 2019 (COVID-19)-infected pregnant women are at higher risk of intensive care unit (ICU) admission and mechanical ventilation. Because reports describing the clinical course and management of critically ill COVID-19 pregnant women remain scarce, it is important to better grasp the trajectory and management of these women to improve decision making and allocation of resources. We therefore describe the trajectory, the ICU treatment adapted to pregnancy, and maternal outcomes among critically ill COVID-19 pregnant women admitted to the ICU of a larger tertiary referral center in the Netherlands.

27. **SARS-CoV-2 positivity in offspring and timing of mother-to-child transmission: living systematic review and meta-analysis.** Allotey J et al. *BMJ.* 2022 Mar 16;376:e067696. doi: 10.1136/bmj-2021-067696. https://www.bmj.com/content/376/bmj-2021-067696

SARS-CoV-2 positivity rates were found to be low in babies born to mothers with SARS-CoV-2 infection. Evidence suggests confirmed vertical transmission of SARS-CoV-2, although this is likely to be rare. Severity of maternal covid-19 appears to be associated with SARS-CoV-2 positivity in offspring. READERS' NOTE: This article is a living systematic review that will be updated to reflect emerging evidence. Updates may occur for up to two years from the date of original publication.

FDA / CDC / NIH / WHO Updates

CDC - The Advisory Committee on Immunization Practices' Recommendation for Use of Moderna COVID-19 Vaccine in Adults Aged ≥18 Years and Considerations for Extended Intervals for Administration of Primary Series Doses of mRNA COVID-19 Vaccines - United States, February 2022. Wallace M et al. MMWR Morb Mortal Wkly Rep. 2022 Mar 18;71(11):416-421. doi: 10.15585/mmwr.mm7111a4.

News

Moderna seeks FDA authorization for a 4th COVID vaccine shot for all adults

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