

COVID-19 Resource Desk

#86 | 12.12.2021 to 12.18.2021

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New Research

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

COVID-19 related publications by Providence caregivers – see [Digital Commons](#)

Epidemiology & Public Health

- 1. Global Percentage of Asymptomatic SARS-CoV-2 Infections Among the Tested Population and Individuals with Confirmed COVID-19 Diagnosis: A Systematic Review and Meta-analysis.** Ma Q, Liu J, Liu Q, et al. *JAMA Netw Open*. 2021;4(12):e2137257. doi:10.1001/jamanetworkopen.2021.37257
<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2787098>
In this systematic review and meta-analysis of 95 unique studies with 29 776 306 individuals undergoing testing, the pooled percentage of asymptomatic infections was 0.25% among the tested population and 40.50% among the population with confirmed COVID-19.
- 2. SARS-CoV-2 B.1.1.529 (Omicron) Variant — United States, December 1–8, 2021.** *MMWR Morb Mortal Wkly Rep*. ePub: 10 December 2021. DOI: <http://dx.doi.org/10.15585/mmwr.mm7050e1>
A new variant of SARS-CoV-2 (the virus that causes COVID-19), B.1.1.529 (Omicron), was first reported to the World Health Organization (WHO) by South Africa on November 24, 2021. Omicron has numerous mutations with potential to increase transmissibility, confer resistance to therapeutics, or partially escape infection- or vaccine-induced immunity. On November 26, WHO designated B.1.1.529 as a variant of concern, as did the U.S. SARS-CoV-2 Interagency Group (SIG)* on November 30. On December 1, the first case of COVID-19 attributed to the Omicron variant was reported in the United States. As of December 8, a total of 22 states had identified at least one Omicron variant case, including some that indicate community transmission. Among 43 cases with initial follow-up, one hospitalization and no deaths were reported. This report summarizes U.S. surveillance for SARS-CoV-2 variants, characteristics of the initial persons investigated with COVID-19 attributed to the Omicron variant and public health measures implemented to slow the spread of Omicron in the United States. Implementation of concurrent prevention strategies, including vaccination, masking, increasing ventilation, testing, quarantine, and isolation, are recommended to slow transmission of SARS-CoV-2, including variants such as Omicron, and to protect against severe illness and death from COVID-19.

3. **An open repository of real-time COVID-19 indicators.** Reinhart A et al. *Proc Natl Acad Sci U S A*. 2021 Dec 21;118(51):e2111452118. doi: 10.1073/pnas.2111452118.
<https://www.pnas.org/content/118/51/e2111452118.long>

The COVID-19 pandemic presented enormous data challenges in the United States. Policy makers, epidemiological modelers, and health researchers all require up-to-date data on the pandemic and relevant public behavior, ideally at fine spatial and temporal resolution. The COVIDcast API is our attempt to fill this need: Operational since April 2020, it provides open access to both traditional public health surveillance signals (cases, deaths, and hospitalizations) and many auxiliary indicators of COVID-19 activity, such as signals extracted from deidentified medical claims data, massive online surveys, cell phone mobility data, and internet search trends. These are available at a fine geographic resolution (mostly at the county level) and are updated daily. The COVIDcast API also tracks all revisions to historical data, allowing modelers to account for the frequent revisions and backfill that are common for many public health data sources. All of the data are available in a common format through the API and accompanying R and Python software packages. This paper describes the data sources and signals, and provides examples demonstrating that the auxiliary signals in the COVIDcast API present information relevant to tracking COVID activity, augmenting traditional public health reporting and empowering research and decision-making.

Healthcare Delivery & Healthcare Workers

4. **Adherence of Clinical Practice Guidelines for Pharmacologic Treatments of Hospitalized Patients with COVID-19 to Trustworthy Standards: A Systematic Review.** Burns KEA et al. *JAMA Netw Open*. 2021 Dec 1;4(12):e2136263. doi: 10.1001/jamanetworkopen.2021.36263.
<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2787001>
- Thirty-two CPGs were included in the review. Of these, 25 (78.1%) were developed by professional societies and emanated from a single World Health Organization (WHO) region. Overall, the CPGs were of low quality. Only 7 CPGs (21.9%) reported funding sources, and 12 (37.5%) reported conflicts of interest. Only 5 CPGs (15.6%) included a methodologist, described a search strategy or study selection process, or synthesized the evidence. Although 14 CPGs (43.8%) made recommendations or suggestions for or against treatments, they infrequently rated confidence in the quality of the evidence (6 of 32 [18.8%]), described potential benefits and harms (6 of 32 [18.8%]), or graded the strength of the recommendations (5 of 32 [15.6%]). External review, patient or public perspectives, or a process for updating were rare. High-quality CPGs included a methodologist and multidisciplinary collaborations involving investigators from 2 or more WHO regions. In this review, few COVID-19 CPGs met NAM standards for trustworthy guidelines. Approaches that prioritize engagement of a methodologist and multidisciplinary collaborators from at least 2 WHO regions may lead to the production of fewer, high-quality CPGs that are poised for updates as new evidence emerges.

Therapeutics

5. **Angiotensin-Converting Enzyme Inhibitors, Angiotensin II Receptor Blockers, and Outcomes in Patients Hospitalized for COVID-19.** Pan M et al. *J Am Heart Assoc.* 2021 Dec 10:e023535. doi: 10.1161/JAHA.121.023535. <https://www.ahajournals.org/doi/10.1161/JAHA.121.023535>
We leveraged the ISIC (International Study of Inflammation in COVID-19), identified patients admitted for symptomatic COVID-19 between February 1, 2020 and June 1, 2021 for COVID-19, and examined the association between in-hospital ACEi/ARB use and all-cause death, need for ventilation, and need for dialysis. We estimated the causal effect of ACEi/ARB on the composite outcomes using marginal structural models accounting for serial blood pressure and serum creatinine measures. Of 2044 patients in ISIC, 1686 patients met inclusion criteria, of whom 398 (23.6%) patients who were previously on ACEi/ARB received at least 1 dose during their hospitalization for COVID-19. There were 215 deaths, 407 patients requiring mechanical ventilation, and 124 patients who required dialysis during their hospitalization. Prior ACEi/ARB use was associated with lower levels of soluble urokinase plasminogen activator receptor and C-reactive protein. In multivariable analysis, in-hospital ACEi/ARB use was associated with a lower risk of the composite outcome of in-hospital death, mechanical ventilation, or dialysis. In patients hospitalized for COVID-19, ACEi/ARB use was associated with lower levels of inflammation and lower risk of in-hospital outcomes. Clinical trials will define the role of ACEi/ARB in the treatment of COVID-19.
6. **Efficacy and Safety of COVID-19 Convalescent Plasma in Hospitalized Patients: A Randomized Clinical Trial.** Ortigoza MB et al. *JAMA Intern Med.* 2021 Dec 13. doi: 10.1001/jamainternmed.2021.6850. <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2787090>
In this trial, CCP did not meet the prespecified primary and secondary outcomes for CCP efficacy. However, high-titer CCP may have benefited participants early in the pandemic when remdesivir and corticosteroids were not in use.
7. **Rehabilitation needs following COVID-19: Five-month post-discharge clinical follow-up of individuals with concerning self-reported symptoms.** Wahlgren C et al. *EClinicalMedicine.* 2022 Jan;43:101219. doi: 10.1016/j.eclinm.2021.101219. Epub 2021 Dec 5. [https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370\(21\)00500-9/fulltext](https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00500-9/fulltext)
INTERPRETATION: Our study underscores the importance of providing extensive examination of cases with persisting problems after COVID-19, especially since symptoms such as fatigue and breathlessness are highly nonspecific, but may represent significant underlying functional impairments. Robust neurocognitive testing should be performed, as cognitive problems may easily be overlooked during routine medical consultation. In the Swedish context, most rehabilitative interventions could be provided in a primary care setting. A substantial minority of patients should be triaged to specialized rehabilitation services.
8. **Namilumab or infliximab compared with standard of care in hospitalised patients with COVID-19 (CATALYST): a randomised, multicentre, multi-arm, multistage, open-label, adaptive, phase 2, proof-of-concept trial.** Fisher BA, *Lancet Respiratory Medicine* December 16,

2021 DOI:[https://doi.org/10.1016/S2213-2600\(21\)00460-4](https://doi.org/10.1016/S2213-2600(21)00460-4)

[https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(21\)00460-4/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00460-4/fulltext)

Namilumab, but not infliximab, showed proof-of-concept evidence for reduction in inflammation—as measured by CRP concentration—in hospitalised patients with COVID-19 pneumonia. Namilumab should be prioritised for further investigation in COVID-19.

Vaccines / Immunology

9. **Neutralization of SARS-CoV-2 Omicron variant by sera from BNT162b2 or Coronavac vaccine recipients.** Lu L, et al. *Clin Infect Dis*. 2021 Dec 16:ciab1041. doi: 10.1093/cid/ciab1041. <https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab1041/6463504>
Omicron variant escapes neutralizing antibodies elicited by BNT162b2 or Coronavac. The additional R346K mutation did not affect the neutralization susceptibility. Our data suggest that the Omicron variant may be associated with lower COVID-19 vaccine effectiveness.
10. **Rate and Risk Factors for Severe/Critical Disease among Fully Vaccinated Persons with Breakthrough SARS-CoV-2 Infection in a High-risk National Population.** Butt AA, et al. *Clin Infect Dis*. 2021 Dec 10:ciab1023. doi: 10.1093/cid/ciab1023. <https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab1023/6459161>
Among 502,780 vaccinated and 599,974 unvaccinated persons, there were 2,332 (0.5%) breakthrough infections in the vaccinated group and 40,540 (6.8%) infections in the unvaccinated group over a follow up period of 69,083 person-days in each group. Among these groups, we identified 1,728 vaccinated persons with breakthrough infection (cases) and 1,728 propensity-score matched unvaccinated controls with infection. Among the former, 95 (5.5%) persons met the criteria for severe/critical disease, while 200 (11.6%) persons met the criteria among the latter group. Incidence rate for severe/critical disease per 1,000 person-days (95% CI) was 0.55 (0.45-0.68) among the former and 1.22 (1.07-1.41) among the latter group ($P < 0.0001$). Risk was higher (HR, 95% CI) with increasing age (per 10-year increase 1.25; 1.11-1.41), and those with >4 comorbidities (2.85; 1.49-5.43), while being vaccinated was associated with strong protection against severe/critical disease (HR 0.41; 0.32-0.52). Rate of severe/critical disease is higher among older persons and those with >4 comorbidities, but lower among fully vaccinated persons with breakthrough infection compared with unvaccinated controls who develop infection.
11. **Serological responses and vaccine effectiveness for extended COVID-19 vaccine schedules in England.** Amirthalingam G et al. *Nat Commun*. 2021 Dec 10;12(1):7217. doi: 10.1038/s41467-021-27410-5. <https://www.nature.com/articles/s41467-021-27410-5>
The UK prioritised delivery of the first dose of BNT162b2 (Pfizer/BioNTech) and AZD1222 (AstraZeneca) vaccines by extending the interval between doses up to 12 weeks. In 750 participants aged 50-89 years, we here compare serological responses after BNT162b2 and AZD1222 vaccination with varying dose intervals, and evaluate these against real-world national vaccine effectiveness (VE) estimates against COVID-19 in England. We show that antibody levels 14-35 days after dose two are higher in BNT162b2 recipients with an extended vaccine interval (65-84 days) compared with those vaccinated with a standard (19-29 days) interval. Following

the extended schedule, antibody levels were 6-fold higher at 14-35 days post dose 2 for BNT162b2 than AZD1222. For both vaccines, VE was higher across all age-groups from 14 days after dose two compared to one dose, but the magnitude varied with dose interval. Higher dose two VE was observed with >6 week interval between BNT162b2 doses compared to the standard schedule. Our findings suggest higher effectiveness against infection using an extended vaccine schedule. Given global vaccine constraints these results are relevant to policymakers.

12. **Reduced magnitude and durability of humoral immune responses to COVID-19 mRNA vaccines among older adults.** Brockman MA et al. *J Infect Dis.* 2021 Dec 9:jjab592. doi: 10.1093/infdis/jiab592. <https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiab592/6458430>

Humoral responses to COVID-19 mRNA vaccines are significantly weaker in older adults, and antibody-mediated activities in plasma decline universally over time. Older adults may thus remain at elevated risk of infection despite vaccination.

13. **Comparative immunogenicity and effectiveness of mRNA-1273, BNT162b2 and Ad26.COV2.S COVID-19 vaccines.** Naranbhai V et al. *J Infect Dis.* 2021 Dec 9:jjab593. doi: 10.1093/infdis/jiab593. <https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiab593/6458467>

A single dose of either mRNA vaccine yielded comparable antibody and neutralization titers to convalescent individuals. Ad26.COV2.S yielded lower antibody concentrations and frequently undetectable neutralization titers. Bulk and cytotoxic T-cell responses were higher in mRNA1273 and BNT162b2 than Ad26.COV2.S recipients. Regardless of vaccine, <50% of vaccinees demonstrated CD8+ T-cell responses. Antibody concentrations and neutralization titers increased comparably after the first dose of either vaccine, and further in recipients of a second dose. Prior infection was associated with high antibody concentrations and neutralization even after a single dose and regardless of vaccine. Neutralization of beta, gamma and delta strains were poorer regardless of vaccine. In meta-analysis, relative to mRNA1273 the effectiveness of BNT162b2 was lower against infection and hospitalization; and Ad26COV2.S was lower against infection, hospitalization and death. Variation in the immunogenicity correlates with variable effectiveness of the three FDA EUA vaccines deployed in the USA.

14. **WHO international standard for SARS-CoV-2 antibodies to determine markers of protection.** Zhu F et al. *Lancet Microbe.* 2021 Dec 3. doi: 10.1016/S2666-5247(21)00307-4. [https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247\(21\)00307-4/fulltext](https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00307-4/fulltext)

Several studies have shown that neutralising antibody level is a good biomarker for the correlate of protection against SARS-CoV-2 infection. However, results from these studies are presented using assays that have not been calibrated using a common reference standard, making it difficult to define the exact level of neutralising antibodies required for protection and to compare with current and future studies. The most recent study⁴ is the only one we have identified that reports the neutralising antibody level using WHO international units by calibrating their neutralisation assays against the WHO international standard for SARS-CoV-2 immunoglobulin; the international standard was established by the WHO Expert Committee on

Biological Standardization as a primary calibrant to harmonise the measurement of anti-SARS-CoV-2 antibodies and was made available in December, 2020 from the WHO Collaborative centre, the National Institute for Biological Standards and Control (NIBSC), UK.

15. **Severe breakthrough COVID-19 cases in the SARS-CoV-2 delta (B.1.617.2) variant era.** Wang SY, et al. *Lancet Microbe*. 2021 Dec 3. doi: 10.1016/S2666-5247(21)00306-2.

[https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247\(21\)00306-2/fulltext](https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00306-2/fulltext)

We conducted a systematic review of patients with SARS-CoV-2 infection confirmed by PCR test, who were hospitalised at the Yale New Haven Health System (New Haven, CT, USA) between Aug 4 and Oct 12, 2021, during which time the SARS-CoV-2 delta (B.1.617.2) variant accounted for over 95% of COVID-19 cases in the region.⁵ Among 371 patients admitted with a positive SARS-CoV-2 PCR test, 129 (35%) were fully vaccinated at the time of hospitalisation. 222 (60%) patients met the criteria for being severely or critically ill with COVID-19 during their hospitalisation, among whom 82 (37%) were fully vaccinated. Overall, a much larger proportion of patients hospitalised with a positive SARS-CoV-2 test had severe or critical breakthrough COVID-19 during this period (82 [22%] of 371 patients) than was reported in the same health-care system between March 23 to July 1, 2021 (14 [1%] of 969 patients), when the delta variant accounted for less than 20% of COVID-19 cases in the region.^{5, 6} Additionally, evaluation of time to COVID-19 from the date of final vaccine dose showed a marked rise in the frequency of severe breakthrough cases with an increasing number of days since completed vaccination.

16. **Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection.** Patone, M., Mei, X.W., Handunnetthi, L. et al. *Nat Med* (2021). <https://doi.org/10.1038/s41591-021-01630-0>

Although myocarditis and pericarditis were not observed as adverse events in coronavirus disease 2019 (COVID-19) vaccine trials, there have been numerous reports of suspected cases following vaccination in the general population. We undertook a self-controlled case series study of people aged 16 or older vaccinated for COVID-19 in England between 1 December 2020 and 24 August 2021 to investigate hospital admission or death from myocarditis, pericarditis and cardiac arrhythmias in the 1–28 days following adenovirus (ChAdOx1, n = 20,615,911) or messenger RNA-based (BNT162b2, n = 16,993,389; mRNA-1273, n = 1,006,191) vaccines or a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive test (n = 3,028,867). We found increased risks of myocarditis associated with the first dose of ChAdOx1 and BNT162b2 vaccines and the first and second doses of the mRNA-1273 vaccine over the 1–28 days postvaccination period, and after a SARS-CoV-2 positive test. We estimated an extra two (95% confidence interval (CI) 0, 3), one (95% CI 0, 2) and six (95% CI 2, 8) myocarditis events per 1 million people vaccinated with ChAdOx1, BNT162b2 and mRNA-1273, respectively, in the 28 days following a first dose and an extra ten (95% CI 7, 11) myocarditis events per 1 million vaccinated in the 28 days after a second dose of mRNA-1273. This compares with an extra 40 (95% CI 38, 41) myocarditis events per 1 million patients in the 28 days following a SARS-CoV-2 positive test. We also observed increased risks of pericarditis and cardiac arrhythmias following a positive SARS-CoV-2 test. Similar associations were not observed with any of the COVID-19 vaccines, apart from an increased risk of arrhythmia

following a second dose of mRNA-1273. Subgroup analyses by age showed the increased risk of myocarditis associated with the two mRNA vaccines was present only in those younger than 40.

17. Effectiveness of mRNA BNT162b2 Vaccine 6 Months after Vaccination among Patients in Large Health Maintenance Organization, Israel. Kertes J, et al. *Emerg Infect Dis.* 2021 Dec 14;28(2). doi: 10.3201/eid2802.211834. https://wwwnc.cdc.gov/eid/article/28/2/21-1834_article

Israel experienced a new wave of coronavirus disease during June 2021, six months after implementing a national vaccination campaign. We conducted 3 discrete analyses using data from a large health maintenance organization in Israel to determine whether IgG levels of fully vaccinated persons decrease over time, describe the relationship between IgG titer and subsequent PCR-confirmed infection, and compare PCR-confirmed infection rates by period of vaccination. Mean IgG levels steadily decreased over the 6-month period in the total tested population and in all age groups. An inverse relationship was found between IgG titer and subsequent PCR-positive infection. Persons vaccinated during the first 2 months of the campaign were more likely to become infected than those subsequently vaccinated. The vaccinated group >60 years of age had lower initial IgG levels and were at greater risk for infection. The findings support the decision to add a booster vaccine for persons >60 years of age.

FDA / CDC / NIH / WHO Updates

[CDC advisors recommend mRNA COVID vaccines over J&J.](#)

[WHO lists 9th COVID-19 vaccine for emergency use with aim to increase access to vaccination in lower-income countries.](#)

Commentary / News / Press Releases

[PFIZER AND BIONTECH PROVIDE UPDATE ON ONGOING STUDIES OF COVID-19 VACCINE](#), low dose may not provide adequate response in 2-5 year olds.

[Discovery Health, South Africa's largest private health insurance administrator, releases at-scale, real-world analysis of Omicron outbreak based on 211 000 COVID-19 test results in South Africa, including collaboration with the South Africa](#)

[The U.S. COVID-19 Vaccination Program at One Year: How Many Deaths and Hospitalizations Were Averted?](#) Schneider EC et al. (Commonwealth Fund, December 2021).

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