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

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

Clinical Syndrome

   Olfactory dysfunction is a common symptom of COVID-19, with reported rates as high as 70%. This symptom can be associated with mild COVID-19, mostly occurs within 5 days after symptom onset, and can persist for a few days to several months after infection resolution. The mechanism of SARS-CoV-2–related olfactory dysfunction is not completely understood.

Epidemiology & Public Health

   The SARS-CoV-2 Omicron variant is thought to cause less severe disease among the general population, but disease severity among at-risk populations is unknown. We performed a retrospective analysis using a matched cohort of United States veterans to compare the disease severity of subjects infected during Omicron and Delta predominant periods within 14 days of initial diagnosis. We identified 22,841 matched pairs for both periods. During the Omicron period, 20,681 (90.5%) veterans had mild, 1308 (5.7%) moderate, and 852 (3.7%) severe disease. During the Delta predominant period, 19,356 (84.7%) had mild, 1467 (6.4%) moderate, and 2018 (8.8%) severe disease. Moderate or severe disease was less likely during the Omicron period and more common among older subjects and those with more comorbidities. Here we show that infection with the Omicron variant is associated with less severe disease than the Delta variant in a high-risk older veteran population, and vaccinations provide protection against severe or critical disease.

COVID-19 vaccination has substantially altered the course of the pandemic, saving tens of millions of lives globally. However, inadequate access to vaccines in low-income countries has limited the impact in these settings, reinforcing the need for global vaccine equity and coverage.

**FUNDING:** Schmidt Science Fellowship in partnership with the Rhodes Trust; WHO; UK Medical Research Council; Gavi, the Vaccine Alliance; Bill & Melinda Gates Foundation; National Institute for Health Research; and Community Jameel.


Our cohort included 2,541 individuals with DS and 10,164 without DS matched on age, sex, and race/ethnicity (51.6% female, 53.3% Hispanic, median age 25 years). While the rate of COVID-19 infection in individuals with DS was 32% lower than their matched counterparts, the rate of severe COVID-19 disease was 6-fold higher. Although the risk of COVID-19 infection is lower, the risk of severe disease is higher in individuals with DS compared to their matched counterparts. Better infection monitoring, early treatment, and promotion of vaccine for COVID-19 are warranted for DS populations.

**5. Emergence of SARS-CoV-2 Omicron lineages BA.4 and BA.5 in South Africa.** Tegally H et al. *Nat Med.* 2022 Jun 27. doi: 10.1038/s41591-022-01911-2.  [https://www.nature.com/articles/s41591-022-01911-2](https://www.nature.com/articles/s41591-022-01911-2)

Three lineages (BA.1, BA.2 and BA.3) of the SARS-CoV-2 Omicron variant of concern predominantly drove South Africa's fourth COVID-19 wave. We have now identified two new lineages, BA.4 and BA.5, responsible for a fifth wave of infections. The spike proteins of BA.4 and BA.5 are identical, and comparable to BA.2 except for the addition of 69-70del (present in the Alpha variant and the BA.1 lineage), L452R (present in the Delta variant), F486V and the wild type amino acid at Q493. The two lineages only differ outside of the spike region. The 69-70 deletion in spike allows these lineages to be identified by the proxy marker of S-gene target failure, on the background of variants not possessing this feature. BA.4 and BA.5 have rapidly replaced BA.2, reaching more than 50% of sequenced cases in South Africa by the first week of April 2022. Using a multinomial logistic regression model, we estimate growth advantages for BA.4 and BA.5 of 0.08 (95% CI: 0.08 - 0.09) and 0.10 (95% CI: 0.09 - 0.11) per day respectively over BA.2 in South Africa. The continued discovery of genetically diverse Omicron lineages points to the hypothesis that a discrete reservoir, such as human chronic infections and/or animal hosts, is potentially contributing to further evolution and dispersal of the virus.

**Prognosis**


This is the first report of mid-term outcomes among COVID-19 patients undergoing surgery. COVID-19 is associated with decreased overall and complication-free survival primarily in the early postoperative
period, delaying surgery by 5 weeks or more reduces risk of complications. Case urgency has a multiplicative effect on short- and long-term risk of postoperative mortality and complications.

**Survivorship & Rehabilitation**


The frequency of, and risk factors for, long COVID are unclear among community-based individuals with a history of COVID-19. To elucidate the burden and possible causes of long COVID in the community, we coordinated analyses of survey data from 6907 individuals with self-reported COVID-19 from 10 UK longitudinal study (LS) samples and 1.1 million individuals with COVID-19 diagnostic codes in electronic healthcare records (EHR) collected by spring 2021. Proportions of presumed COVID-19 cases in LS reporting any symptoms for 12+ weeks ranged from 7.8% and 17% (with 1.2 to 4.8% reporting debilitating symptoms). Increasing age, female sex, white ethnicity, poor pre-pandemic general and mental health, overweight/obesity, and asthma were associated with prolonged symptoms in both LS and EHR data, but findings for other factors, such as cardio-metabolic parameters, were inconclusive.


129Xe MRI measurements were lower in ever-hospitalized participants with post-acute COVID-19 syndrome, 34±25 weeks post-infection compared to controls. 129Xe MRI measures were associated with CT pulmonary vascular density, DLco, exercise capacity, and dyspnea. ClinicalTrials.gov: NCT04584671 See also the editorial by Wild and Collier.

**Therapeutics**


Early treatment with interferon beta-1b and remdesivir was safe and better than remdesivir only in alleviating symptoms, shorten viral shedding and hospitalization with earlier seropositivity in high-risk COVID-19 patients.

CP was not associated with viral load reduction, despite the early increase in IgG anti-SARS-CoV-2 antibodies. However, CP is safe and could be a therapeutic option to reduce the hospital length of stay. Trial registration NCT04332835.


AUTHORS’ CONCLUSIONS: We found no direct evidence on whether early spontaneous breathing in SARS-CoV-2-induced ARDS is beneficial or detrimental to this particular group of patients. RCTs comparing early spontaneous breathing with ventilatory strategies not allowing for spontaneous breathing in SARS-CoV-2-induced ARDS are necessary to determine its value within the treatment of severely ill people with COVID-19. Additionally, studies should aim to clarify whether treatment effects differ between people with SARS-CoV-2-induced ARDS and people with non-SARS-CoV-2-induced ARDS.

Transmission / Infection Control


This rapid systematic review found evidence suggesting that long distance airborne transmission of SARS-CoV-2 might occur in indoor settings such as restaurants, workplaces, and venues for choirs, and identified factors such as insufficient air replacement that probably contributed to transmission. These results strengthen the need for mitigation measures in indoor settings, particularly the use of adequate ventilation.


The B.1.1.529 (omicron) variant of SARS-CoV-2 has a shorter incubation period and a higher transmission rate than previous variants. Recently, the Centers for Disease Control and Prevention recommended shortening the strict isolation period for infected persons in non–health care settings from 10 days to 5 days after symptom onset or after the initial positive test, followed by 5 days of masking. However, the viral decay kinetics of the omicron variant and the duration of shedding of culturable virus have not been well characterized.

Vaccines / Immunology

The omicron variant of SARS-CoV-2 comprises several sublineages (BA.1, BA.1.1, BA.2, and BA.3, etc) with an increasing prevalence of the sublineage BA.2.1. Although the receipt of a third (booster) dose of an mRNA-based SARS-CoV-2 vaccine is associated with improved protection against the omicron variant, many breakthrough infections occurred during the initial omicron surge, and it is unknown whether a breakthrough infection with BA.1 in an individual who had received a booster vaccine would provide protection from infection from another sublineage.

15. **Duration of effectiveness of vaccination against COVID-19 caused by the omicron variant.**


We recently conducted a systematic review and meta-regression of the duration of effectiveness of primary series COVID-19 vaccination against clinical outcomes before the predominance of the omicron (B.1.1.529) SARS-CoV-2 variant. Here we assess the duration of vaccine protection, after a primary vaccine series and after the first booster dose, against omicron, the current predominant variant, using the same methods.

16. **Epidemiology of Myocarditis and Pericarditis Following mRNA Vaccination by Vaccine Product, Schedule, and Interdose Interval Among Adolescents and Adults in Ontario, Canada.**


The findings of this population-based cohort study of Ontario adolescents and adults with myocarditis or pericarditis following mRNA COVID-19 vaccination suggest that vaccine products and interdose intervals, in addition to age and sex, may be associated with the risk of myocarditis or pericarditis after receipt of these vaccines. Vaccination program strategies, such as age-based product considerations and longer interdose intervals, may reduce the risk of myocarditis or pericarditis following receipt of mRNA vaccines.

17. **Safety and immunogenicity of a hybrid-type vaccine booster in BBIBP-CorV recipients in a randomized phase 2 trial.**

Kaabi NA et al. *Nat Commun.* 2022 Jun 27;13(1):3654. doi: 10.1038/s41467-022-31379-0. [https://www.nature.com/articles/s41467-022-31379-0](https://www.nature.com/articles/s41467-022-31379-0)

Both Neutralizing and IgG antibodies elicited by NVSI-06-08 booster are significantly higher than those by BBIBP-CorV booster against not only SARS-CoV-2 prototype strain but also multiple variants of concerns (VOCs). Especially, the neutralizing antibody GMT against Omicron variant induced by heterologous NVSI-06-08 booster reaches 367.67, which is substantially greater than that boosted by BBIBP-CorV (GMT: 45.03). In summary, NVSI-06-08 is safe and immunogenic as a booster dose following two doses of BBIBP-CorV, which is immunogenically superior to the homologous boost with another dose of BBIBP-CorV.

18. **SARS-CoV-2 Infection in Patients with a History of VITT.**


Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a prothrombotic adverse effect of vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an important
measure in the prevention of severe coronavirus disease 2019 (Covid-19). VITT is caused by platelet-activating antiplatelet factor 4 (PF4) antibodies of immunoglobulin G class that have been rarely induced by two adenovirus vector–based Covid-19 vaccines, ChAdOx1 nCoV-19 (AstraZeneca) and Ad26.COV2.S (Johnson & Johnson/Janssen).


Previous reports demonstrated that SARS-CoV-2 binding IgG did not increase significantly between first and second doses of the BNT162b2 vaccine in previously-infected individuals. We tested neutralizing antibodies (nAb) against SARS-CoV-2 Delta and Omicron variants post first and second doses of BNT162b2 in infection-naïve and previously-infected individuals. Delta, but not Omicron, nAb significantly increased from first to second dose in both groups of individuals. Importantly, we found Omicron nAb titers were much lower than Delta nAb titers and that even after two doses of vaccine, 17 of 29 individuals in the infection-naïve group and 2 of 27 individuals in the previously-infected group did not have detectable Omicron nAb titers. Infection history alone did not adequately predict if a second dose resulted in adequate nAb. For future variants of concern, the discussion on the optimal number of vaccine doses should be based on studies testing for nAb against the specific variant.


We present an interim analysis of a registered clinical study (NCT04800133) to establish immunobridging with various antibody and cellular immunity markers and to compare the immunogenicity and reactogenicity of 2-dose BNT162b2 and CoronaVac in healthy adolescents as primary objectives. One-dose BNT162b2, recommended in some localities for risk reduction of myocarditis, is also assessed. Antibodies and T cell immune responses are non-inferior or similar in adolescents receiving 2 doses of BNT162b2 (BB, N = 116) and CoronaVac (CC, N = 123) versus adults after 2 doses of the same vaccine (BB, N = 147; CC, N = 141) but not in adolescents after 1-dose BNT162b2 (B, N = 116). CC induces SARS-CoV-2 N and N C-terminal domain seropositivity in a higher proportion of adolescents than adults. Adverse reactions are mostly mild for both vaccines and more frequent for BNT162b2. We find higher S, neutralising, avidity and Fc receptor-binding antibody responses in adolescents receiving BB than CC, and a similar induction of strong S-specific T cells by the 2 vaccines, in addition to N- and M-specific T cells induced by CoronaVac but not BNT162b2, possibly implying differential durability and cross-variant protection by BNT162b2 and CoronaVac, the 2 most used SARS-CoV-2 vaccines worldwide. Our results support the use of both vaccines in adolescents.

Women & Children

Compared with controls, children aged 0-14 years who had a SARS-CoV-2 infection had more prevalent long-lasting symptoms. There was a tendency towards better quality-of-life scores related to emotional and social functioning in cases than in controls in older children. The burden of symptoms among children in the control group requires attention. Long COVID must be recognised and multi-disciplinary long COVID clinics for children might be beneficial.

**FUNDING:** A P Møller and Chastine Mc-Kinney Møller Foundation.


Here, we characterize the antibody profile after Ad26.COV2.S, mRNA-1273 or BNT162b2 vaccination in 158 pregnant individuals and evaluate transplacental antibody transfer by profiling maternal and umbilical cord blood in 175 maternal-neonatal dyads. These analyses reveal lower vaccine-induced functions and Fc receptor-binding after Ad26.COV2.S compared to mRNA vaccination and subtle advantages in titer and function with mRNA-1273 versus BN162b2. mRNA vaccines have higher titers and functions against SARS-CoV-2 variants of concern. First and third trimester vaccination results in enhanced maternal antibody-dependent NK-cell activation, cellular and neutrophil phagocytosis, and complement deposition relative to second trimester. Higher transplacental transfer ratios following first and second trimester vaccination may reflect placental compensation for waning maternal titers. These results provide novel insight into the impact of platform and trimester of vaccination on maternal humoral immune response and transplacental antibody transfer.


The National Center for Health Statistics (NCHS) reported an 18.4% increase in US maternal mortality (ie, death during pregnancy or within 42 days of pregnancy) between 2019 and 2020. The relative increase was 44.4% among Hispanic, 25.7% among non-Hispanic Black, and 6.1% among non-Hispanic White women.1 Given a 16.8% increase in overall US mortality in 2020, largely attributed to the COVID-19 pandemic,2 we examined the pandemic’s role in 2020 maternal death rates.


Our findings suggest that as omicron was becoming the dominant variant, two doses of the BNT162b2 messenger RNA vaccine provided moderate protection against documented SARS-CoV-2 infection and symptomatic Covid-19 in children 5 to 11 years of age. (Funded by the European Union through the VERDI project and others.).

Over one in four children hospitalized with acute COVID-19 or MIS-C experienced persistent symptoms or activity impairment for at least 2 months. Patients with MIS-C and respiratory conditions or obesity are at higher risk of prolonged recovery.


On April 21, 2022, CDC issued a health advisory† encouraging U.S. clinicians to report all patients aged <10 years with hepatitis of unknown etiology to public health authorities, after identification of similar cases in both the United States (1) and Europe.§ A high proportion of initially reported patients had adenovirus detected in whole blood specimens, thus the health advisory encouraged clinicians to consider requesting adenovirus testing, preferentially on whole blood specimens. For patients meeting the criteria in the health advisory (patients under investigation [PUIs]), jurisdictional public health authorities abstracted medical charts and interviewed patient caregivers. As of June 15, 2022, a total of 296 PUIs with hepatitis onset on or after October 1, 2021, were reported from 42 U.S. jurisdictions. The median age of PUIs was 2 years, 2 months. Most PUIs were hospitalized (89.9%); 18 (6.1%) required a liver transplant, and 11 (3.7%) died. Adenovirus was detected in a respiratory, blood, or stool specimen of 100 (44.6%) of 224 patients.¶ Current or past infection with SARS-CoV-2 (the virus that causes COVID-19) was reported in 10 of 98 (10.2%) and 32 of 123 (26.0%) patients, respectively. No common exposures (e.g., travel, food, or toxicants) were identified. This nationwide investigation is ongoing. Further clinical data are needed to understand the cause of hepatitis in these patients and to assess the potential association with adenovirus.


On June 17, 2022, the Food and Drug Administration (FDA) issued Emergency Use Authorization (EUA) amendments for the mRNA-1273 (Moderna) COVID-19 vaccine for use in children aged 6 months-5 years, administered as 2 doses (25 µg [0.25 mL] each), 4 weeks apart, and BNT162b2 (Pfizer-BioNTech) COVID-19 vaccine for use in children aged 6 months-4 years, administered as 3 doses (3 µg [0.2 mL] each), at intervals of 3 weeks between doses 1 and 2 and ≥8 weeks between doses 2 and 3. On June 18, 2022, the Advisory Committee on Immunization Practices (ACIP) issued separate interim recommendations for use of the Moderna COVID-19 vaccine in children aged 6 months-5 years and the Pfizer-BioNTech COVID-19 vaccine in children aged 6 months-4 years for the prevention of COVID-19.* Both the Moderna and Pfizer-BioNTech COVID-19 vaccines met the criteria for immunobridging, which is the comparison of neutralizing antibody levels postvaccination in young children with those in young adults in whom efficacy had been demonstrated. Descriptive efficacy analyses were also conducted for both Moderna and Pfizer-BioNTech COVID-19 vaccines during the period when the Omicron variant of SARS-CoV-2 (the virus that causes COVID-19) predominated. No specific safety concerns were
identified among recipients of either vaccine. ACIP recommendations for the use of the Moderna COVID-19 vaccine and the Pfizer-BioNTech COVID-19 vaccine in children aged 6 months-5 years and 6 months-4 years, respectively, are interim and will be updated as additional information becomes available. Vaccination is important for protecting children aged 6 months-5 years against COVID-19.


COVID-19 can lead to severe outcomes in children, including multisystem inflammatory syndrome, hospitalization, and death (1,2). On November 2, 2021, the Advisory Committee on Immunization Practices issued an interim recommendation for use of the BNT162b2 (Pfizer-BioNTech) vaccine in children aged 5-11 years for the prevention of COVID-19; however, vaccination coverage in this age group remains low (3). As of June 7, 2022, 36.0% of children aged 5-11 years in the United States had received ≥1 of COVID-19 vaccine (3). Among factors that might influence vaccination coverage is the availability of vaccine providers (4). To better understand how provider availability has affected COVID-19 vaccination coverage among children aged 5-11 years, CDC analyzed data on active COVID-19 vaccine providers and county-level vaccine administration data during November 1, 2021-April 25, 2022. Among 2,586 U.S. counties included in the analysis, 87.5% had at least one active COVID-19 vaccine provider serving children aged 5-11 years. Among the five assessed active provider types, most counties had at least one pharmacy (69.1%) or public health clinic (61.3%), whereas fewer counties had at least one pediatric clinic (29.7%), family medicine clinic (29.0%), or federally qualified health center (FQHC)* (22.8%). Median county-level vaccination coverage was 14.5% (IQR = 8.9%-23.6%). After adjusting for social vulnerability index (SVI)† and urbanicity, the analysis found that vaccination coverage among children aged 5-11 years was higher in counties with at least one active COVID-19 vaccine provider than in counties with no active providers (adjusted rate ratio [aRR] = 1.66). For each provider type, presence of at least one provider in the county was associated with higher coverage; the largest difference in vaccination coverage was observed between counties with and without pediatric clinics (aRR = 1.37). Ensuring broad access to COVID-19 vaccines, in addition to other strategies to address vaccination barriers, could help increase vaccination coverage among children aged 5-11 years.

GUIDELINES & CONSENSUS STATEMENTS


FDA / CDC / NIH / WHO Updates

Pfizer and BioNTech Announce Omicron-Adapted COVID-19 Vaccine Candidates Demonstrate High Immune Response Against Omicron

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