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


   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


   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

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**


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.


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**


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.

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**


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. 


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.


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**

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.


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).


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.


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:
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.**

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.


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.


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.


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).

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.


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


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.

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.

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.

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.


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](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**


**News**

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

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