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

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

**Basic Science / Virology / Pre-clinical**


   **Findings:** We report the preclinical development of two BNT162b vaccine candidates, which contain lipid-nanoparticle (LNP) formulated nucleoside-modified mRNA encoding SARS-CoV-2 spike glycoprotein-derived immunogens. BNT162b1 encodes a soluble, secreted, trimerised receptor-binding domain (RBD-foldon). BNT162b2 encodes the full-length transmembrane spike glycoprotein, locked in its prefusion conformation (P2 S). The flexibly tethered RBDs of the RBD-foldon bind ACE2 with high avidity. Approximately 20% of the P2S trimers are in the two-RBD 'down,' one-RBD 'up' state. In mice, one intramuscular dose of either candidate elicits a dose-dependent antibody response with high virus-entry inhibition titres and strong TH1 CD4+ and IFNγ+ CD8+ T-cell responses. Prime/boost vaccination of rhesus macaques with BNT162b candidates elicits SARS-CoV-2 neutralising geometric mean titres 8.2 to 18.2 times that of a SARS-CoV-2 convalescent human serum panel. The vaccine candidates protect macaques from SARS-CoV-2 challenge, with BNT162b2 protecting the lower respiratory tract from the presence of viral RNA and with no evidence of disease enhancement. Both candidates are being evaluated in phase 1 trials in Germany and the United States1-3. BNT162b2 is being evaluated in an ongoing global, pivotal Phase 2/3 trial.


   **Findings:** Mass vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is ongoing amidst widespread transmission during the Coronavirus Disease 2019 (COVID-19) pandemic. Disease phenotypes of SARS-CoV-2 exposure occurring around the time of vaccine administration have not been described. Two-dose (14 days apart) vaccination regimen with a formalin-inactivated whole virion SARS-CoV-2 in golden Syrian hamster model was established. To investigate the disease phenotypes of a one-dose regimen given 3 days prior, 1 or 2 days after, or on the day of virus challenge, we monitored the serial clinical severity, tissue
histopathology, virus burden, and antibody response of the vaccinated hamsters. The one-dose vaccinated hamsters had significantly lower clinical disease severity score. Vaccination just before or soon after exposure to SARS-CoV-2 does not worsen disease phenotypes and may even ameliorate infection.


Antibodies are a potential therapy for SARS-CoV-2, but the risk of the virus evolving to escape them remains unclear. Here we map how all mutations to SARS-CoV-2's receptor-binding domain (RBD) affect binding by the antibodies in the REGN-COV2 cocktail and the antibody LY-CoV016. These complete maps uncover a single amino-acid mutation that fully escapes the REGN-COV2 cocktail, which consists of two antibodies targeting distinct structural epitopes. The maps also identify viral mutations that are selected in a persistently infected patient treated with REGN-COV2, as well as during in vitro viral escape selections. Finally, the maps reveal that mutations escaping the individual antibodies are already present in circulating SARS-CoV-2 strains. Overall, these complete escape maps enable interpretation of the consequences of mutations observed during viral surveillance.

4. **Broad and potent activity against SARS-like viruses by an engineered human monoclonal antibody.** Rappazzo CG, et al. *Science* 2021 Jan 25;eabf4830. doi: 10.1126/science.abf4830. [https://science.sciencemag.org/content/early/2021/01/22/science.abf4830](https://science.sciencemag.org/content/early/2021/01/22/science.abf4830)

Findings: We employed a directed evolution approach to engineer three SARS-CoV-2 antibodies for enhanced neutralization breadth and potency. One of the affinity-matured variants, ADG-2, displays strong binding activity to a large panel of sarbecovirus receptor binding domains (RBDs) and neutralizes representative epidemic sarbecoviruses with high potency. Structural and biochemical studies demonstrate that ADG-2 employs a distinct angle of approach to recognize a highly conserved epitope overlapping the receptor binding site. In immunocompetent mouse models of SARS and COVID-19, prophylactic administration of ADG-2 provided complete protection against respiratory burden, viral replication in the lungs, and lung pathology. Altogether, ADG-2 represents a promising broad-spectrum therapeutic candidate against clade 1 sarbecoviruses.

Clinical Syndrome


Findings: A number of published papers have investigated the relation between atrial fibrillation (AF) and clinical outcomes of patients with coronavirus disease 2019 (COVID-19). However, the conclusions drawn from previous studies are not consistent. 23 studies with 108,745 COVID-19 patients were eligibly included in the present quantitative meta-analysis. Our study demonstrates that AF was significantly associated with an increased risk of unfavorable outcomes among COVID-19 patients, especially for death.

**Findings:** We identified 18 studies from 7 countries; all were case reports and case series from autopsies. All the patients were over 15 years old, and 67.2% were male. We performed a meta-analysis of 5 studies, including 116 patients. Pooled prevalence estimates of liver histopathological findings were hepatic steatosis 55.1%, congestion of hepatic sinuses 34.7%, vascular thrombosis 29.4%, fibrosis 20.5%, Kupffer cell hyperplasia 13.5%, portal inflammation 13.2%, and lobular inflammation 11.6%. We also identified the presence of venous outflow obstruction, phlebosclerosis of the portal vein, herniated portal vein, periportal abnormal vessels, hemophagocytosis, and necrosis. We found a high prevalence of hepatic steatosis and vascular thrombosis as major histological liver features. Other frequent findings included portal and lobular inflammation and Kupffer cell hyperplasia or proliferation. Further studies are needed to establish the mechanisms and implications of these findings.


**Findings:** Of the 14,483 laboratory-confirmed patients with COVID-19, 156 (1.1%) were diagnosed with AIS. Sixty-one (39.4%) were female, 84 (67.2%) white, and 88 (61.5%) were between 60 and 79 years of age. The most frequently reported etiology of AIS was cryptogenic (55/129, 42.6%), which was associated with significantly higher white blood cell count, c-reactive protein, and D-dimer levels than non-cryptogenic AIS patients. In a multivariable backward stepwise regression model estimating the odds of in-hospital mortality, cryptogenic stroke mechanism was associated with a fivefold greater odds in-hospital mortality than strokes due to any other mechanism. In that model, older age and higher baseline NIHSS were also independently predictive of mortality. Our findings suggest that cryptogenic stroke among COVID-19 patients carries a significant risk of early mortality.


**Findings:** One hundred and seventy-six patients with severe SARS-CoV-2 pneumonia admitted to the ICU between March 1st and 30th June of 2020 were included into the study. Historical control groups comprised 435 patients with bacterial pneumonia and 48 ones with viral pneumonia. ICU-acquired pneumonia occurred in 52% of COVID-19 patients, whereas in 26% and 23% of patients with bacterial or viral pneumonia, respectively. Times from initiation of mechanical ventilation to ICU-acquired pneumonia were similar across the three groups. COVID-19 appears an independent risk factor of ICU-acquired pneumonia in mechanically
ventilated patients with pneumonia. Whether this is driven by immunomodulatory properties by the SARS-CoV-2 or this is related to particular processes of care remains to be investigated.

**Diagnostics & Screening**


**FINDINGS:** Between April 12 and May 4, 2020, we enrolled and collected serological samples from 2345 (53·0%) of 4422 RT-PCR-negative close contacts of cases of RT-PCR-confirmed SARS-CoV-2. 1175 (50·1%) of 2345 were close contacts of cases diagnosed in Shenzhen with contact tracing details, and of these, 880 (74·9%) had serum samples collected more than 2 weeks after exposure to an index case and were included in our analysis. 40 (4·5%) of 880 RT-PCR-negative close contacts were positive on total antibody ELISA. The seropositivity rate with total antibody ELISA among RT-PCR-negative close contacts, adjusted for assay performance, was 4·1% (95% CI 2·9-5·7), which was significantly higher than among individuals residing in neighbourhoods with no reported cases (0·0% [95% CI 0·0-1·1]). RT-PCR-positive individuals were 8·0 times (95% CI 5·3-12·7) more likely to report symptoms than those who were RT-PCR-negative but seropositive, but both groups had a similar distribution of sex, age, contact frequency, and mode of contact. RT-PCR did not detect 48 (36% [95% CI 28-44]) of 134 infected close contacts, and false-negative rates appeared to be associated with stage of infection. Even rigorous RT-PCR testing protocols might miss a substantial proportion of SARS-CoV-2 infections, perhaps in part due to difficulties in determining the timing of testing in asymptomatic individuals for optimal sensitivity. RT-PCR-based surveillance and control protocols that include rapid contact tracing, universal RT-PCR testing, and mandatory 2-week quarantine were, nevertheless, able to contain community spread in Shenzhen, China.


**Findings:** Using data for 20 912 patients from 2 large academic health systems, we analyzed the frequency of severe acute respiratory syndrome coronavirus 2 reverse-transcription polymerase chain reaction test discordance among individuals initially testing negative by nasopharyngeal swab who were retested on clinical grounds within 7 days. The frequency of subsequent positivity within this window was 3.5% and was similar across institutions.


**Findings:** 50 participants (aged 4 to 71 years) were included; of these, 40 had at least one positive sample and were included in the primary sample yield analysis. Saline mouth
rinse/gargle samples had a sensitivity of 98% (39/40) while saliva samples had a sensitivity of 79% (26/33). Both saline mouth rinse/gargle and saliva samples showed stable viral RNA detection after 2 days of room temperature storage. Mouth rinse/gargle samples had the highest (mean 4.9) and HCW-collected NP swabs had the lowest acceptability scores (mean 3.1). Conclusion: Saline mouth rinse/gargle samples demonstrated the highest combined user acceptability ratings and analytical performance when compared with saliva and HCW collected NP swabs. This sample type is a promising swab-independent option, particularly for outpatient self-collection in adults and school aged children.


Findings: Our objective was to create, execute, and appraise whether a focused cardiac ultrasound (FOCUS) curriculum could effectively teach hospital medicine faculty at an 882-bed safety-net academic hospital. Our experience yielded three conclusions: firstly, our learners quickly gained confidence in the acquisition of FOCUS images. Secondly, simulation provided us with a unique environment that made rapid training feasible as well as safe for both the learners and instructors. Lastly, our workshop highlighted the importance of interdisciplinary efforts to overcome the challenges and barriers in clinical care that arise during a crisis which has been highlighted recently.

**Epidemiology & Public Health**


In December 2020, research surveillance detected the B.1.1.7 lineage of severe acute respiratory syndrome coronavirus 2 in São Paulo, Brazil. Rapid genomic sequencing and phylogenetic analysis revealed 2 distinct introductions of the lineage. One patient reported no international travel. There may be more infections with this lineage in Brazil than reported.


Findings: During August 31-November 29, 2020, COVID-19 cases, spread, and compliance with mask use were investigated among 4,876 students and 654 staff members who participated in in-person learning in 17 K-12 schools in rural Wisconsin. School-attributable COVID-19 case rates were compared with rates in the surrounding community. School administration and public health officials provided information on COVID-19 cases within schools. During the study period, widespread community transmission was observed, with 7%-40% of COVID-19 tests having positive results. Masking was required for all students and staff members at all schools, and rate of reported student mask-wearing was high (>92%). COVID-19 case rates among
students and staff members were lower (191 cases among 5,530 persons, or 3,453 cases per 100,000) than were those in the county overall (5,466 per 100,000). Among the 191 cases identified in students and staff members, one in 20 cases among students was linked to in-school transmission; no infections among staff members were found to have been acquired at school. These findings suggest that, with proper mitigation strategies, K-12 schools might be capable of opening for in-person learning with minimal in-school transmission of SARS-CoV-2.


Findings: In Manaus, Brazil, a study of blood donors indicated that 76% of the population had been infected with SARS-CoV-2 by October, 2020. High attack rates of SARS-CoV-2 were also estimated in population-based samples from other locations in the Amazon Basin—eg, Iquitos, Peru 70%. The estimated SARS-CoV-2 attack rate in Manaus would be above the theoretical herd immunity threshold (67%), given a basic case reproduction number of 3.4. In this context, the abrupt increase in the number of COVID-19 hospital admissions in Manaus during January, 2021 (3431 in Jan 1–19, 2021, vs 552 in Dec 1–19, 2020) is unexpected and of concern. There are at least four non-mutually exclusive possible explanations for the resurgence of COVID-19 in Manaus. First, the SARS-CoV-2 attack rate could have been overestimated during the first wave, and the population remained below the herd immunity threshold until the beginning of December, 2020. Second, immunity against infection might have already begun to wane by December, 2020. Third, SARS-CoV-2 lineages might evade immunity generated in response to previous infection. Fourth, SARS-CoV-2 lineages circulating in the second wave might have higher inherent transmissibility than pre-existing lineages circulating in Manaus.


Findings: As of July 29, 2020, there were a total of 4 289 283 COVID-19 cases and 147 074 COVID-19 deaths in the US. In this cross-sectional study, a wide range of sociodemographic risk factors, including socioeconomic status, racial/ethnic minority status, household composition, and environmental factors, were significantly associated with COVID-19 incidence and mortality. To address inequities in the burden of the COVID-19 pandemic, these social vulnerabilities and their root causes must be addressed.


Findings: We used individual-level administrative data on the US population between January 2011 and April 2020 to estimate the geographic variation in excess all-cause mortality by race and Hispanic origin. All-cause mortality allows a better understanding of the overall impact of
During the pandemic, mortality attributable to COVID-19 directly. Nationwide, adjusted excess all-cause mortality during that period was 6.8 per 10,000 for Black people, 4.3 for Hispanic people, 2.7 for Asian people, and 1.5 for White people. Nationwide averages mask substantial geographic variation. For example, despite similar excess White mortality, Michigan and Louisiana had markedly different excess Black mortality, as did Pennsylvania compared with Rhode Island. Wisconsin experienced no significant White excess mortality but had significant Black excess mortality. Further work understanding the causes of geographic variation in racial and ethnic disparities—the relevant roles of social and environmental factors relative to comorbidities and of the direct and indirect health effects of the pandemic—is crucial for effective policy making.

**Healthcare Delivery & Healthcare Workers**


Findings: We screened 8758 French HCW for total serum SARS-CoV-2 anti-spike antibodies between June 10 and July 10, 2020, after the first epidemic wave, and the end of first lockdown. After a median follow-up of 167 days, there were 1028 new infections (12.1%) among the 8482 seronegative HCW and 5 re-infections (1.8%) among the 276 seropositive HCW. The 5 reinfected people included two with very low or undetectable titers of neutralizing antibodies after the first infection, and three with above-median titers. Three re-infected subjects were symptomatic but only one had a significantly increased (> 4-fold) neutralizing antibody titer. The other two re-infections were asymptomatic with no significant change in neutralizing antibodies. Overall, the neutralizing antibody titers of the 276 seropositive HCW increased significantly between June/July and November/December. The increases in neutralizing antibody in the HCW who developed SARS-CoV-2 antibodies after an asymptomatic infection were similar to those who developed symptomatic infections. Similarly, the ELISA indexes of the 276 seropositive HCW increased significantly between June/July and November/December.


Findings: 1790 patients were included, comprising 127 HCWs and 1663 non-HCWs. After 3:1 propensity score matching, 122 HCWs were matched to 366 non-HCWs. Women comprised 71 (58.2%) of matched HCWs and 214 (58.5%) of matched non-HCWs. Matched HCWs had a mean (SD) age of 52 (13) years, whereas matched non-HCWs had a mean age of 57 years. In the matched cohort, the odds of the primary outcome, mechanical ventilation or death, were not significantly different for HCWs compared with non-HCWs. The HCWs were less likely to require admission to an intensive care unit and were also less likely to require an admission of 7 days or longer. There were no differences between matched HCWs and non-HCWs in terms of mechanical ventilation, death, or vasopressor requirements. In this propensity score-matched
multicenter cohort study, HCW status was not associated with poorer outcomes among hospitalized patients with COVID-19 and, in fact, was associated with a shorter length of hospitalization and decreased likelihood of intensive care unit admission. Further research is needed to elucidate the proportion of HCW infections acquired in the workplace and to assess whether HCW type is associated with outcomes.


**Findings:** To quantify demographic, occupational, and community risk factors for SARS-CoV-2 seropositivity among HCWs in a large health care system in the Atlanta, Georgia, metropolitan area. Adjusted SARS-CoV-2 seropositivity was estimated to be 3.8% among the 10,275 HCWs (35% of the Emory Healthcare workforce) who participated in the survey. Demographic and community risk factors, including contact with a COVID-19-positive person and Black race, are more strongly associated with SARS-CoV-2 seropositivity among HCWs than is exposure in the workplace.


**Findings:** We examined the variation in total outpatient visits and telemedicine use across patient demographics, specialties, and conditions in a database of 16.7 million commercially insured and Medicare Advantage enrollees from January to June 2020. During the pandemic, 30.1 percent of all visits were provided via telemedicine, and the weekly number of visits increased twenty-three-fold compared with the prepandemic period. Telemedicine use was lower in communities with higher rates of poverty (31.9 percent versus 27.9 percent for the lowest and highest quartiles of poverty rate, respectively). Across specialties, the use of any telemedicine during the pandemic ranged from 68 percent of endocrinologists to 9 percent of ophthalmologists. Across common conditions, the percentage of visits provided during the pandemic via telemedicine ranged from 53 percent for depression to 3 percent for glaucoma. Higher rates of telemedicine use for common conditions were associated with smaller decreases in total weekly visits during the pandemic.


**Findings:** There is limited understanding of the characteristics and operational burden of persons under investigation and those testing positive for SARS-CoV-2 presenting to EDs. We reviewed all adult ED visits to 5 Johns Hopkins Health System hospitals in the Maryland/District of Columbia (DC) region during the initial coronavirus disease 2019 (COVID-19) surge. Of 27,335
visits, 11,402 (41.7%) were tested and 2484 (21.8%) were SARS-CoV-2 positive. Test-positive rates among Hispanics, Asians, African Americans/Blacks, and Whites were 51.6%, 23.7%, 19.8%, and 12.7% respectively. African American/Blacks infection rates (25.5%-33.8%) were approximately double those of Whites (11.1%-21.1%) in the 3 southern Maryland/DC EDs. Conditions with high test-positive rates were fever (41.9%), constitutional (36.4%), upper respiratory (36.9%), and lower respiratory (31.2%) symptoms. Test-positive rates were similar in all age groups (19.9% to 25.8%), although rates of hospitalization increased successively with age. Almost half, 1103 (44.4%), of test-positive patients required admission, of which 206 (18.7%) were to an ICU. The initial surge of SARS-CoV-2 test-positive patients experienced in a regional hospital system had ≈ 42% of patients meeting testing criteria and nearly one-fifth of those testing positive. The operational burden on ED practice, including intense adherence to infection control precautions, cannot be understated. Disproportionately high rates of infection among underrepresented minorities underscores the vulnerability in this population. The high rate of infection among self-identified Asians was unexpected.

Laboratory Results


Findings: The role of procalcitonin in identifying community-associated bacterial infections among patients with coronavirus disease 2019 is not yet established. In 2443 patients with 148 bacterial co-infections, mean procalcitonin levels were significantly higher with any bacterial infection (13.16 ± 51.19 ng/mL, p=0.0091) and with bacteremia (34.25 ± 85.01 ng/mL, p=0.0125) than without infection (2.00 ±15.26 ng/mL). Procalcitonin (cutoff 0.25 or 0.50 ng/mL) did not reliably identify bacterial co-infections, but may be useful in excluding bacterial infection.


Findings: Sera (n = 533) from patients with real-time polymerase chain reaction-confirmed COVID-19 (n = 94 with acute infections and n = 59 convalescent patients) were tested using a high-throughput quantitative immunoglobulin M (IgM) and immunoglobulin G (IgG) assay that detects antibodies to the spike protein receptor binding domain and nucleocapsid protein. Individual and serial samples covered the time of initial diagnosis, during the disease course, and following recovery. We evaluated antibody kinetics and correlation between magnitude of the response and disease severity. Patterns of SARS-CoV-2 antibody production varied considerably. Among 52 patients with 3 or more serial specimens, 44 (84.6%) and 42 (80.8%) had observed IgM and IgG seroconversion at a median of 8 and 10 days, respectively. Compared to those with milder disease, peak measurements were significantly higher for patients admitted to the intensive care unit for all time intervals between 6 and 20 days for
IgM, and all intervals after 5 days for IgG. High-sensitivity assays with a robust dynamic range provide a comprehensive picture of host antibody response to SARS-CoV-2. IgM and IgG responses were significantly higher in patients with severe than mild disease. These differences may affect strategies for seroprevalence studies, therapeutics, and vaccine development.

**Prognosis**


Findings: We conducted a multicentre retrospective cohort study across 11 academic medical centres in the U.S. Adult patients who received cardiopulmonary resuscitation and/or defibrillation for IHCA between March 1, 2020 and May 31, 2020 who had a documented positive test for Severe Acute Respiratory Syndrome Coronavirus 2 were included. The primary outcome was 30-day survival after IHCA. There were 260 IHCAs among COVID-19 patients during the study period. The median age was 69 years, 71.5% were male, 49.6% were White, 16.9% were Black, and 16.2% were Hispanic. ROSC occurred in 58 patients (22.3%), 32 (12.3%) survived to 30 days, and 31 (11.9%) survived to discharge. Rates of ROSC and 30-day survival in the two hospitals with the highest volume of IHCA over the study period compared to the remaining hospitals were considerably lower (10.8% vs. 64.3% and 5.9% vs. 35.7% respectively). We found rates of ROSC and 30-day survival of 22.3% and 12.3% respectively. There were large variations in centre-level outcomes, which may explain the poor survival in prior studies.


Findings: This study included 8297 adults who have records of COVID-19 test results from UK Biobank (from 16 March 2020 to 29 June 2020). The use of vitamin D supplements, circulating vitamin D levels, and main covariates were measured at baseline. After adjustment for covariates, the habitual use of vitamin D supplements was significantly associated with a 34% lower risk of COVID-19 infection. Circulating vitamin D levels at baseline or genetically predicted vitamin D levels were not associated with the risk of COVID-19 infection. The association between the use of vitamin D supplements and the risk of COVID-19 infection did not vary according to the different levels of circulating or genetically predicted vitamin D.


Findings: In total, 217 patients were included. The male to female ratio was 3:1 and the median age was 63 years. A majority (70%) had one or more co-morbidities, most frequently cardiovascular disease (39%), chronic lung disease (22%), diabetes mellitus (20%), and obesity...
Most patients were admitted for acute hypoxaemic respiratory failure (AHRF) (91%) and invasive mechanical ventilation (MV) was used in 86%, prone ventilation in 38% and 25% of patients received a tracheostomy. Vasoactive drugs were used in 79% and renal replacement therapy in 15%. Median ICU LOS and time of MV was 14.0 and 12.0 days. At end of follow-up 45 patients (21%) were dead. Age, co-morbidities and severity of illness at admission were predictive of death. Severity of AHRF and male gender were associated with LOS. In this national cohort of COVID-19 patients, mortality was low and attributable to known risk factors. Importantly, prolonged length-of-stay must be taken into account when planning for resource allocation for any next surge.


Findings: A total of 1,376 patients were included (median age 78 years, 60% male). In total, 499 (38%) patients died during hospital admission. Parameters indicating presence of frailty (CFS 6-9) were associated with more co-morbidities, shorter symptom duration upon presentation (median 4 vs. 7 days), lower oxygen demand and lower levels of CRP. The in-hospital mortality of older hospitalised COVID-19 patients in the Netherlands was 38%. Frailty was independently associated with higher in-hospital mortality, even though COVID-19 patients with frailty presented earlier to the hospital with less severe symptoms.


Findings: Data of 217 patients without pre-existing liver disease prospectively included in the COVID-19 registry of the LMU university hospital were analysed in order to assess the association of abnormal LFT at admission and course of the disease. Abnormal LFT at baseline was present in 58% of patients, with a predominant elevation of aspartate aminotransferase (AST) (42%), gamma-glutamyltransferase (GGT) (37%) and alanine aminotransferase (ALT) (27%), hypoalbuminaemia was observed in 33%. Elevation of ALT and GGT, as well as hypoalbuminaemia, was associated with higher proportions of patients requiring ICU treatment and mechanical ventilation. After adjusting for age, gender and comorbidities, hypoalbuminaemia combined with abnormal AST or GGT at hospital admission was a highly significant independent risk factor for ICU admission and for a composite endpoint of ICU admission and/or COVID-19-related death. Abnormal LFTs at hospital admission, in particular GGT and albumin, are associated with a severe course of SARS-CoV-2 infection.

Findings: Up to 31 May 2020, mortality in patients admitted to ICU with COVID-19 was 41.6%. Since then, changes in therapeutics and management may have improved outcomes. Also, data from countries affected later in the pandemic are now available. We identified 52 observational studies including 43,128 patients, and first reports from the Middle East, South Asia and Australasia, as well as four national or regional registries. Reported mortality was lower in registries compared with other reports. In two regions, mortality differed significantly from all others, being higher in the Middle East and lower in a single registry study from Australasia. Although ICU mortality (95%CI) was lower than reported in June (35.5% (31.3-39.9%) vs. 41.6% (34.0-49.7%)), the absence of patient-level data prevents a definitive evaluation. A lack of standardisation of reporting prevents comparison of cohorts in terms of underlying risk, severity of illness or outcomes. We found that the decrease in ICU mortality from COVID-19 has reduced or plateaued since May 2020 and note the possibility of some geographical variation.


Findings: This international study is the first to describe risk factors for severe infection and death from COVID-19 in alloHSCT recipients. AlloHSCT recipients are at high risk of COVID-19 severity and mortality, with a fatality rate of 25%. Previous studies of patients with haematological malignancy with COVID-19 reported a fatality rate of 39–61%. The lower mortality rate in our present study might be related to the young age of our patients, as well as the inclusion of non-hospitalised patients with milder forms of COVID-19. In our present study, as previously seen in haematology patients, the risks of severity and death were not associated with the factors seen in the general population (male sex, diabetes and obesity). Probable pneumonia was the only factor associated with severity and death. Immunosuppressive treatment was a risk factor for severity but not for death: the impact of immunosuppression on the course of COVID-19 in alloHSCT recipients is difficult to determine. Recent studies reported the efficacy of steroids and/or tocilizumab in the treatment of severe COVID-19. Immunosuppression may be an aggravating factor (decreasing the ability to control viral replication), but may also be a protective factor (decreasing the inflammatory phase). Unfortunately, we were not able to perform longitudinal cytokines and immunological analyses over the course of COVID-19. Concerning biological data, only a low platelet count, but not a low lymphocyte count, was associated with poorer outcomes in our present population. However, the lymphocyte count was low in the entire population, as expected in alloHSCT recipients.


Findings: In a retrospective study based on a U.S. national registry, we determined the anti-SARS-CoV-2 IgG antibody levels in convalescent plasma used to treat hospitalized adults with Covid-19. Of the 3082 patients included in this analysis, death within 30 days after plasma transfusion occurred in 115 of 515 patients (22.3%) in the high-titer group, 549 of 2006 patients...
(27.4%) in the medium-titer group, and 166 of 561 patients (29.6%) in the low-titer group. The association of anti-SARS-CoV-2 antibody levels with the risk of death from Covid-19 was moderated by mechanical ventilation status. A lower risk of death within 30 days in the high-titer group than in the low-titer group was observed among patients who had not received mechanical ventilation before transfusion (relative risk, 0.66; 95% confidence interval [CI], 0.48 to 0.91), and no effect on the risk of death was observed among patients who had received mechanical ventilation (relative risk, 1.02; 95% CI, 0.78 to 1.32). Among patients hospitalized with Covid-19 who were not receiving mechanical ventilation, transfusion of plasma with higher anti-SARS-CoV-2 IgG antibody levels was associated with a lower risk of death than transfusion of plasma with lower antibody levels.

Survivorship & Rehabilitation


Findings: 114 patients (80[70%] men; mean age, 54±12 years) were studied prospectively. Initial and follow-up CT scans were obtained on 17±11 days and 175±20 days respectively after symptom onset. Lung changes (opacification, consolidation, reticulation, and fibrotic-like changes) and CT extent scores (score per lobe, 0-5; maximum score, 25) were recorded. Six-month follow-up CT showed lung fibrotic-like changes in more than one-third of patients who survived severe COVID-19 pneumonia. These changes were associated with an older age, acute respiratory distress syndrome, longer in-hospital stays, tachycardia, non-invasive mechanical ventilation and higher initial chest CT score.


Findings: A total of 238 patients (31.0%) (median age, 61 years; 142 [59.7%] men) consented to participate to the study. Of these, 219 patients were able to complete both pulmonary function tests and DLco measurement. DLco was reduced to less than 80% of the estimated value in 113 patients (51.6%) and less than 60% in 34 patients (15.5%). The SPPB score was suggested limited mobility (score <11) in 53 patients (22.3%). Patients with SPPB scores within reference range underwent a 2-minute walk test, which was outside reference ranges of expected performance for age and sex in 75 patients (40.5%); thus, a total of 128 patients (53.8%) had functional impairment. Posttraumatic stress symptoms were reported in a total of 41 patients (17.2%). These findings suggest that at 4 months after discharge, respiratory, physical, and psychological sequelae were common among patients who had been hospitalized for COVID-19.

Findings: Increasing evidence suggests that autoimmunity may play a role in the pathophysiology of SARS-CoV-2 infection during both the acute and ‘long COVID’ phases of disease. We compared the levels of 18 different IgG autoantibodies (AABs) between four groups: (1) unexposed pre-pandemic subjects from the general population (n = 29); (2) individuals hospitalized with acute moderate-severe COVID-19 (n = 20); (3) convalescent SARS-CoV-2-infected subjects with asymptomatic to mild viral symptoms during the acute phase with samples obtained between 1.8 and 7.3 months after infection (n = 9); and (4) unexposed pre-pandemic subjects with systemic lupus erythematosus (SLE) (n = 6). Total IgG and IgA levels were also measured from subjects in groups 1-3 to assess non-specific pan-B cell activation. Our findings support existing studies suggesting induction of immune responses to self-epitopes during acute, severe COVID-19 with evidence of general B cell hyperactivation. Also, the preponderance of AAB positivity among convalescent individuals up to seven months after infection indicates potential initiation or proliferation, and then persistence of self-reactive immunity without severe initial disease. These results underscore the importance of further investigation of autoimmunity during SARS-CoV-2 infection and its role in the onset and persistence of post-acute sequelae of COVID-19.

Therapeutics


Findings: Among patients with non-severe COVID-19 and no risk factors for severe disease receiving a single 400 mcg/kg dose of ivermectin within 72 h of fever or cough onset there was no difference in the proportion of PCR positives. There was however a marked reduction of self-reported anosmia/hyposmia, a reduction of cough and a tendency to lower viral loads and lower IgG titers which warrants assessment in larger trials.


Findings: In spontaneously breathing patients with COVID-19, the novel and clinically important findings of this research were that there was no evidence of a consistent response to proning treatment and that the magnitude of any response to proning was not indicative of any subsequent response to another proning treatment. In summary, in spontaneously breathing patients with COVID-19, on an analysis of close to 100 treatments, we found no evidence of reproducible response to proning and no relationship between the effect of proning on first treatment with subsequent treatments. Our findings imply uncertainty about the benefit of this intervention.


Findings: This retrospective, bicentric study done on 96, awake, non-intubated, spontaneously breathing COVID-19 patients with acute hypoxic respiratory failure requiring oxygen supplementation showed that PP for at least three hours a day during three consecutive days prevented the upgrading of oxygen delivery method on D14 after hospital admission compared to no instruction regarding prone positioning or no tolerance of PP during hospitalization. These results are consistent with findings from previous small studies of PP in non-intubated patients with improvement in oxygenation and a trend to improve clinical outcomes.


AUTHORS' CONCLUSIONS: There is currently insufficient evidence to determine the risks and benefits of prophylactic anticoagulants for people hospitalised with COVID-19. Since there are 22 ongoing studies that plan to evaluate more than 15,000 participants in this setting, we will add more robust evidence to this review in future updates.

**Transmission / Infection Control**


Findings: The duration of transmissibility of coronavirus disease 2019 (Covid-19) and the associated level of contagion have been uncertain. We cultured severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in serial respiratory samples obtained from hospitalized patients with Covid-19 to assess the duration of shedding of viable virus. The median time from symptom onset to viral clearance in culture was 7 days, and the median time from symptom onset to viral clearance on real-time RT-PCR was 34 days. The latest positive viral culture was 12 days after symptom onset. Viable virus was identified until 3 days after the resolution in fever. Viral culture was positive only in samples with a cycle-threshold value of 28.4 or less. The incidence of culture positivity decreased with an increasing time from symptom onset and with an increasing cycle-threshold value. Our findings may be useful in guiding isolation periods for patients with Covid-19 and in estimating the risk of secondary transmission among close contacts in contact tracing. Given the small sample size, inconsistent timing of sampling, and relatively mild illness of the enrolled patients, our results should be verified in larger and more diverse groups of patients.

Findings: Forty-eight emergency medical service providers, randomized into teams of two, performed 12 minutes of basic life support (BLS) on a manikin after climbing 3 flights of stairs. Three scenarios were completed in a randomised order: Without personal protective equipment, with personal protective equipment including a filtering face piece (FFP) 2 mask with valve, and with personal protective equipment including an FFP2 mask without valve. The primary outcome was mean depth of chest compressions with a pre-defined non-inferiority margin of 3.5 mm. Secondary outcomes included other measurements of CPR quality, providers' subjective exhaustion levels, and providers' vital signs, including end-tidal CO2. Differences regarding the primary outcome were well below the pre-defined non-inferiority margins for both control vs. personal protective equipment without valve (absolute difference 1 mm, 95% CI [-1, 2]) and control vs. personal protective equipment with valve (absolute difference 1 mm, [-0.2, 2]). This was also true for secondary outcomes regarding quality of chest compressions and providers' vital signs including etCO2. Subjective physical strain after BLS was higher in the personal protective equipment groups (Borg 4 (SD 3) without valve, 4 (SD 2) with valve) than in the control group (Borg 3 (SD 2)). PPE including masks with and without expiration valve is safe for use without concerns regarding the impairment of CPR quality.

Vaccines


Findings: Our study is a phase 1, randomised, double-blind placebo-controlled trial at a specialised clinical trials centre in Australia. We enrolled healthy adult volunteers in two age groups: younger adults (aged 18-54 years) and older adults (aged 55-75 years). Between June 19 and Sept 23, 2020, 151 volunteers were enrolled; three people withdrew, two for personal reasons and one with an unrelated serious adverse event (pituitary adenoma). 148 participants had at least 4 weeks of follow-up after dose two and were included in this analysis (database lock, Oct 23, 2020). Vaccination was well tolerated, with two grade 3 solicited adverse events (pain in 9 μg AS03-adjuvanted and 9 μg CpG/Alum-adjuvanted groups). Most local adverse events were mild injection-site pain, and local events were more frequent with SCB-2019 formulations containing AS03 adjuvant (44-69%) than with those containing CpG/Alum adjuvant (6-44%) or no adjuvant (3-13%). Systemic adverse events were more frequent in younger adults (38%) than in older adults (17%) after the first dose but increased to similar levels in both age groups after the second dose (30% in older and 34% in younger adults). SCB-2019 with no adjuvant elicited minimal immune responses (three seroconversions by day 50), but SCB-2019 with fixed doses of either AS03 or CpG/Alum adjuvants induced high titres and seroconversion rates of binding and neutralising antibodies in both younger and older adults (anti-SCB-2019 IgG antibody geometric mean titres at day 36 were 1567-4452 with AS03 and 174-2440 with CpG/Alum). Titres in all AS03 dose groups and the CpG/Alum 30 μg group were higher than were those recorded in a panel of convalescent serum samples from patients with COVID-19. Both adjuvanted SCB-2019 formulations elicited T-helper-1-biased CD4+ T-cell
responses. The SCB-2019 vaccine, comprising S-Trimer protein formulated with either AS03 or CpG/Alum adjuvants, elicited robust humoral and cellular immune responses against SARS-CoV-2, with high viral neutralising activity. Both adjuvanted vaccine formulations were well tolerated and are suitable for further clinical development.

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00234-8/fulltext
Findings: We did a randomised, double-blind, placebo-controlled, phase 3 trial at 25 hospitals and polyclinics in Moscow, Russia. We included participants aged at least 18 years, with negative SARS-CoV-2 PCR and IgG and IgM tests, no infectious diseases in the 14 days before enrolment, and no other vaccinations in the 30 days before enrolment. Between Sept 7 and Nov 24, 2020, 21 977 adults were randomly assigned to the vaccine group (n=16 501) or the placebo group (n=5476). 19 866 received two doses of vaccine or placebo and were included in the primary outcome analysis. From 21 days after the first dose of vaccine (the day of dose 2), 16 (0·1%) of 14 964 participants in the vaccine group and 62 (1·3%) of 4902 in the placebo group were confirmed to have COVID-19; vaccine efficacy was 91·6% (95% CI 85·6–95·2). Most reported adverse events were grade 1 (7485 [94·0%] of 7966 total events). 45 (0·3%) of 16 427 participants in the vaccine group and 23 (0·4%) of 5435 participants in the placebo group had serious adverse events; none were considered associated with vaccination, with confirmation from the independent data monitoring committee. Four deaths were reported during the study (three [<0·1%] of 16 427 participants in the vaccine group and one [<0·1%] of 5435 participants in the placebo group), none of which were considered related to the vaccine. This interim analysis of the phase 3 trial of Gam-COVID-Vac showed 91·6% efficacy against COVID-19 and was well tolerated in a large cohort.

https://www.clinicalimaging.org/article/S0899-7071(21)00020-6/fulltext
Findings: With the recent U.S. Food and Drug Administration (FDA)-approval and rollout of the Pfizer-BioNTech and Moderna COVID-19 vaccines, it is important for radiologists to consider recent COVID-19 vaccination history as a possible differential diagnosis for patients with unilateral axillary adenopathy. Hyperplastic axillary nodes can be seen on sonography after any vaccination but are more common after a vaccine that evokes a strong immune response, such as the COVID-19 vaccine. As the differential of unilateral axillary adenopathy includes breast malignancy, it is crucial to both thoroughly evaluate the breast for primary malignancy and to elicit history of recent vaccination. As COVID-19 vaccines will soon be available to a larger patient population, radiologists should be familiar with the imaging features of COVID-19 vaccine induced hyperplastic adenopathy and its inclusion in a differential for unilateral axillary adenopathy. Short-term follow-up for unilateral axillary adenopathy in the setting of recent COVID-19 vaccination is an appropriate recommendation, in lieu of immediately performing potentially unnecessary and costly axillary lymph node biopsies.

Findings: As of January 10, 2021, a reported 4,041,396 first doses of Moderna COVID-19 vaccine had been administered in the United States, and reports of 1,266 (0.03%) adverse events after receipt of Moderna COVID-19 vaccine were submitted to the Vaccine Adverse Event Reporting System (VAERS). Among these, 108 case reports were identified for further review as possible cases of severe allergic reaction, including anaphylaxis. Anaphylaxis is a life-threatening allergic reaction that occurs rarely after vaccination, with onset typically within minutes to hours. Among these case reports, 10 cases were determined to be anaphylaxis (a rate of 2.5 anaphylaxis cases per million Moderna COVID-19 vaccine doses administered), including nine in persons with a documented history of allergies or allergic reactions, five of whom had a previous history of anaphylaxis. The median interval from vaccine receipt to symptom onset was 7.5 minutes (range = 1-45 minutes). Among eight persons with follow-up information available, all had recovered or been discharged home. Among the remaining case reports that were determined not to be anaphylaxis, 47 were assessed to be nonanaphylaxis allergic reactions, and 47 were considered nonallergic adverse events. For four case reports, investigators have been unable to obtain sufficient information to assess the likelihood of anaphylaxis. This report summarizes the clinical and epidemiologic characteristics of case reports of allergic reactions, including anaphylaxis and nonanaphylaxis allergic reactions, after receipt of the first dose of Moderna COVID-19 vaccine during December 21, 2020-January 10, 2021, in the United States. CDC has issued updated interim clinical considerations for use of mRNA COVID-19 vaccines currently authorized in the United States (3) and interim considerations for preparing for the potential management of anaphylaxis (4).


Findings: Recently, a new SARS-CoV-2 lineage called B.1.1.7 (variant of concern: VOC 202012/01) emerged in the United Kingdom that was reported to spread more efficiently and faster than other strains. This variant has an unusually large number of mutations with 10 amino acid changes in the spike protein, raising concerns that its recognition by neutralizing antibodies may be affected. Here, we tested SARS-CoV-2-S pseudoviruses bearing either the Wuhan reference strain or the B.1.1.7 lineage spike protein with sera of 40 participants who were vaccinated in a previously reported trial with the mRNA-based COVID-19 vaccine BNT162b2. The immune sera had slightly reduced but overall largely preserved neutralizing titers against the B.1.1.7 lineage pseudovirus. These data indicate that the B.1.1.7 lineage will not escape BNT162b2-mediated protection.

Findings: Coronavirus disease (COVID-19) symptoms can be mistaken for vaccine-related side effects during initial days after immunization. Among 4,081 vaccinated healthcare workers in Israel, 22 (0.54%) developed COVID-19 from 1-10 days (median 3.5 days) after immunization. Clinicians should not dismiss postvaccination symptoms as vaccine-related and should promptly test for COVID-19.

Women & Children


Findings: The principal study findings were: 1) among 240 pregnant patients in Washington State with SARS-CoV-2 infections, 1 in 11 developed severe or critical disease, 1 in 10 were hospitalized for COVID-19, and 1 in 80 died; 2) the COVID-19-associated hospitalization rate was 3.5-fold higher than in similarly-aged adults in Washington State [10.0% vs. 2.8%]; 3) pregnant patients hospitalized for a respiratory concern were more likely to have a comorbidity or underlying conditions including asthma, hypertension, type 2 diabetes, autoimmune disease, and Class III obesity; 4) three maternal deaths (1.3%) were attributed to COVID-19 for a maternal mortality rate of 1,250/100,000 pregnancies; 5) the COVID-19 case fatality in pregnancy was a significant 13.6-fold higher in pregnant patients compared to similarly aged individuals in Washington State with an absolute difference in mortality rate of 1.2%; and 6) preterm birth was significantly higher among women with severe/critical COVID-19 at delivery than for women who had recovered from COVID-19 (45.4% severe/critical COVID-19 vs. 5.2% mild COVID-19). COVID-19 hospitalization and case fatality rates in pregnant patients were significantly higher compared to similarly aged adults in Washington State. This data indicates that pregnant patients are at risk for severe or critical disease and mortality compared to non-pregnant adults, as well as preterm birth.


Findings: Eighty-eight serology positive pregnant women were included in this study. Antibody levels are higher in symptomatic pregnant women compared to asymptomatic pregnant women. Serology studies in 34 women with symptom onset data reveal that maternal IgM and IgG levels peak around 15 and 30 days post COVID-19 symptoms onset, respectively. Furthermore, studies of fifty neonates born to a subset of serology positive women show that passive immunity in the form of IgG is conferred upon 78% of all neonates. Presence of passive immunity is dependent on maternal antibody levels, and levels of neonatal IgG correlate with maternal IgG levels. Maternal IgG levels and maternal use of oxygen support were predictive of neonatal IgG levels. We demonstrate that maternal serologies correlate with symptomatic maternal infection, and higher levels of maternal antibodies are associated with passive immunity. Maternal IgG levels and maternal use of oxygen support, a marker of disease
severity, predict neonatal IgG levels. These data will further guide the screening for this unique linked population of mothers and their babies, and can aid in developing maternal vaccination strategies.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7804384/

Findings: A total of 67 articles and 427 pregnant patients diagnosed with COVID-19 were analyzed. The most frequently encountered pulmonary findings on chest CT were ground-glass opacities (77.2%, 250/324), posterior lung involvement (72.5%, 50/69), multilobar involvement (71.8%, 239/333), bilateral lung involvement (69.4%, 231/333), peripheral distribution (68.1%, 98/144), and consolidation (40.9%, 94/230). Pregnant patients were also found to present more frequently with consolidation (40.9% vs. 21.0-31.8%) and pleural effusion (30.0% vs. 5.0%) in comparison to the general population. Associated clinical features included antepartum fever (198 cases), lymphopenia (128 cases), and neutrophilia (97 cases). Of the 251 neonates delivered, 96.8% had negative RT-PCR and/or IgG antibody testing for COVID-19. In the eight cases (3.2%) of reported neonatal infection, tests were either conducted on samples collected up to 72 h after birth or were found negative on all subsequent RT-PCR tests. Pregnant patients appear to present more commonly with more advanced COVID-19 CT findings compared to the general adult population. Furthermore, characteristic laboratory abnormalities found in pregnant patients tended to mirror those found in the general patient population. Lastly, results from neonatal testing suggest a low risk of vertical transmission.

https://jamanetwork.com/journals/jamapediatrics/fullarticle/2775945

Findings: The study cohort consisted of 1714 parturient women, with median age of 32 years, of whom 450 (26.3%) identified as Black/non-Hispanic, 879 (51.3%) as White/non-Hispanic, 203 (11.8%) as Hispanic, 126 (7.3%) as Asian, and 56 (3.3%) as other race/ethnicity. Among 1471 mother/newborn dyads for which matched sera were available, SARS-CoV-2 IgG and/or IgM antibodies were detected in 83 of 1471 women (6%) at the time of delivery, and IgG was detected in cord blood from 72 of 83 newborns (87%). IgM was not detected in any cord blood specimen, and antibodies were not detected in any infant born to a seronegative mother. Eleven infants born to seropositive mothers were seronegative: 5 of 11 (45%) were born to mothers with IgM antibody only, and 6 of 11 (55%) were born to mothers with significantly lower IgG concentrations compared with those found among mothers of seropositive infants. Cord blood IgG concentrations were positively correlated with maternal IgG concentrations. Placental transfer ratios more than 1.0 were observed among women with asymptomatic SARS-CoV-2 infections as well as those with mild, moderate, and severe coronavirus disease 2019. Transfer ratios increased with increasing time between onset of maternal infection and delivery. In this cohort study, maternal IgG antibodies to SARS-CoV-2 were transferred across the placenta after asymptomatic as well as symptomatic infection during pregnancy.
blood antibody concentrations correlated with maternal antibody concentrations and with duration between onset of infection and delivery. Our findings demonstrate the potential for maternally derived SARS-CoV-2 specific antibodies to provide neonatal protection from coronavirus disease 2019.


Findings: Among 181 children with suspected MIS-C, 111 fulfilled the World Health Organization definition (58 females [52%]; median age, 8.6 years). Five children did not receive either treatment. Overall, 3 of 34 children (9%) in the IVIG and methylprednisolone group and 37 of 72 (51%) in the IVIG alone group did not respond to treatment. Treatment with IVIG and methylprednisolone vs IVIG alone was associated with lower risk of treatment failure. IVIG and methylprednisolone therapy vs IVIG alone was also significantly associated with lower risk of use of second-line therapy, hemodynamic support, acute left ventricular dysfunction occurring after initial therapy, and duration of stay in the pediatric intensive care unit. Among children with MIS-C, treatment with IVIG and methylprednisolone vs IVIG alone was associated with a more favorable fever course. Study interpretation is limited by the observational design.

**GUIDELINES & CONSENSUS STATEMENTS**

**ACOG and SMFM Joint Statement on WHO Recommendations Regarding COVID-19 Vaccines and Pregnant Individuals**


**FDA / CDC / NIH / WHO Updates**

**CDC - COVID-19 Vaccinations in the United States**

**FDA reduces N95 mask decontamination cycles to 4,** January 22 2021.

**Commentary & News**

**UK finds more coronavirus cases with 'concerning' mutations.**
**Public Health England Technical Brief**


White House directs HHS to make it easier to enlist doctors and nurses to give coronavirus vaccine shots

Pfizer to Deliver U.S. Vaccine Doses Faster Than Expected

Sanofi to provide support to BioNTech in manufacturing their COVID-19 vaccine to help address public health needs

Novavax COVID-19 Vaccine Demonstrates 89.3% Efficacy in UK Phase 3 Trial


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