RAOM COVID-19 ARCHIVE

April-June, 2021

CONTENTS:

THE VIRUS

Frampton D, Rampling T, Cross A et al. **Genomic characteristics and clinical effect of the emergent SARS-CoV-2 B.1.1.7 lineage in London, UK: a whole-genome sequencing and hospital-based cohort study.** Lancet (Inf Dis) 2021. Published: April 12, 2021. **DOI:https://doi.org/10.1016/S1473-3099(21)00170-5**

- BACKGROUND: Emergence of variants with specific mutations in key epitopes in the spike protein of SARS-CoV-2 raises concerns pertinent to mass vaccination campaigns and use of monoclonal antibodies. We aimed to describe the emergence of the B.1.1.7 variant of concern (VOC), including virological characteristics and clinical severity in contemporaneous patients with and without the variant.
- STUDY DESIGN: In this cohort study, samples positive for SARS-CoV-2 on PCR that were collected from Nov 9, 2020, for patients acutely admitted to one of two hospitals on or before Dec 20, 2020, in London, UK, were sequenced and analysed for the presence of VOC-defining mutations. We fitted Poisson regression models to investigate the association between B.1.1.7 infection and severe disease (defined as point 6 or higher on the WHO ordinal scale within 14 days of symptoms or positive test) and death within 28 days of a positive test and did supplementary genomic analyses in a cohort of chronically shedding patients and in a cohort of remdesivir-treated patients. Viral load was compared by proxy, using PCR cycle threshold values and sequencing read depths.
- RESULTS: Of 496 patients with samples positive for SARS-CoV-2 on PCR and who met inclusion criteria, 341 had samples that could be sequenced. 198 (58%) of 341 had B.1.1.7 infection and 143 (42%) had non-B.1.1.7 infection. We found no evidence of an association between severe disease and death and lineage (B.1.1.7 vs non-B.1.1.7) in unadjusted analyses (prevalence ratio [PR] 0·97 [95% CI 0·72–1·31]), or in analyses adjusted for hospital, sex, age, comorbidities, and ethnicity (adjusted PR 1·02 [0·76–1·38]). We detected no B.1.1.7 VOC-defining mutations in 123 chronically shedding immunocompromised patients or in 32 remdesivir-treated patients. Viral load by proxy was higher in B.1.1.7 samples than in non-B.1.1.7 samples, as measured by cycle threshold value (mean 28·8 [SD 4·7] vs 32·0 [4·8]; p=0·0085) and genomic read depth (1280 [1004] vs 831 [682]; p=0·0011).

CONCLUSION: Emerging evidence exists of increased transmissibility of B.1.1.7 and we found increased virus load by proxy for B.1.1.7 in our data. We did not identify an association of the variant with severe disease in this hospitalized cohort.

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Mack CD, DiFiori J, Tai CG et al. **SARS-CoV-2 Transmission Risk Among National Basketball Association Players, Staff, and Vendors Exposed to Individuals with Positive Test Results After COVID-19 Recovery During the 2020 Regular and Postseason**. JAMA Intern Med. Published online April 22, 2021. **doi:10.1001/jamainternmed.2021.2114**

- To assess whether individuals who have clinically recovered from COVID-19 but continue to test positive still transmit SARS-CoV-2, a retrospective cohort study used data collected from June 11, 2020, to October 19, 2020, as part of the NBA closed campus program in Orlando, Florida, which required daily RT-PCR testing and ad hoc serological testing for SARS-CoV-2 IgG antibodies.
- Persistent positive cases were those who recovered from a documented SARS-CoV-2 infection, satisfied US Centers for Disease Control and Prevention criteria for discontinuation of isolation precautions, and had at least 1 postinfection positive RT-PCR test(s) result. Exposures were person-days of participation in indoor, unmasked activities that involved direct exposure between persistent positive cases and noninfected individuals.
- RESULTS: Among 3648 individuals who participated, 36 (1%) were persistent positive cases, most of whom were younger than 30 years (24 [67%]) and male (34 [94%]). Antibodies were detected in 91.7%; all remained asymptomatic following the index persistent positive RT-PCR result. Cases were monitored for up to 100 days (mean [SD], 51 [23.9] days), during which there were at least 1480 person-days of direct exposure activities, with no transmission events or secondary infections of SARS-CoV-2 detected (0 new cases).
- CONCLUSIONS: In this retrospective cohort study of the 2020 NBA closed campus occupational health program, recovered individuals who continued to test positive for SARS-CoV-2 following discontinuation of isolation were not infectious to others. These findings support time-based US Centers of Disease Control and Prevention recommendations for ending isolation.

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ZHU X, Mannar D, Srivastava SS et al. **Cryo-EM Structure of the N501Y SARS-CoV-2 Spike Protein in Complex with a Potent Neutralizing Antibody.** BioRxiv 2021. **doi: https://doi.org/10.1101/2021.01.11.426269**

- BACKGROUND: The most important SARS-CoV-2 variants occur in the spike protein with variants in pre- and postfusion conformations reported, including complexes with ACE2 and a variety of antibodies. Mutations like those from the UK and South Africa that emerge in the receptor binding domain (RBD) of the spike protein are especially of interest given their potential to alter the kinetics and strength of interaction of the virus with target cells. These mutations could also affect the binding of antibodies capable of binding and blocking engagement of the virus with ACE2. A common feature of both the UK and South African variants is the mutation of residue 501 in the RBD from Asn to Tyr (N501Y). X-ray crystallography and cryo-EM structural studies have identified N501 as a key residue in the interaction interface between RBD and ACE2. N501 is involved in critical contacts with

several ACE2 residues. Studies carried out in a mouse model before the identification of the new UK variant have suggested that mutations of residue 501 could be linked to increased receptor binding and infectivity. Understanding the impact of N501Y on antibody neutralization, ACE2 binding, and viral entry is therefore of fundamental interest in efforts to prevent the spread of COVID-19.

- STUDY: Using cryo-EM, these researchers studied structures of SARS-CoV-2 spike protein ectodomains with and without the N501Y mutation, in complex with the VH fragment of the potent neutralizing antibody, VH -Fc ab8. The mutation results in localized structural perturbations near Y501 with enhanced ACE-2 attachment and viral cell entry. However, VH -Fc ab8 retains the ability to bind and neutralize pseudotyped viruses expressing the N501Y mutant with efficiencies comparable to that of unmutated viruses.
- CONCLUSION: Results show that despite the higher affinity of ACE2 for the N501Y mutant, it can still be neutralized efficiently by an antibody that binds epitopes in the receptor binding domain of the SARSCoV-2 spike protein.

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Wacharapluesadee, S., Tan, C.W., Maneeorn, P. et al. **Evidence for SARS-CoV-2 related coronaviruses circulating in bats and pangolins in Southeast Asia**. Nat Commun 12, 972 (2021). **https://doi.org/10.1038/s41467-021-21240-1**

- BACKGROUND: Among the many questions unanswered for the COVID-19 pandemic are the origin of SARS-CoV-2 and the potential role of intermediate animal host(s) in the early animal-to-human transmission. The discovery of RaTG13 bat coronavirus in China suggested a high probability of a bat origin.
- STUDY DESIGN: Here we report molecular and serological evidence of SARS-CoV-2 related coronaviruses (SC2r-CoVs) actively circulating in bats in Southeast Asia.
- RESULTS: Whole genome sequences were obtained from five independent bats (Rhinolophus acuminatus) in a Thai cave yielding a single isolate (named RacCS203) which is most related to the RmYN02 isolate found in Rhinolophus malayanus in Yunnan, China.
- SARS-CoV-2 neutralizing antibodies were also detected in bats of the same colony and in a pangolin at a wildlife checkpoint in Southern Thailand.
- Antisera raised against the receptor binding domain (RBD) of RmYN02 was able to cross-neutralize SARS-CoV-2 despite the fact that the RBD of RacCS203 or RmYN02 failed to bind ACE2.
- CONCLUSION: Although the origin of the virus remains unresolved, our study extended the geographic distribution of genetically diverse SC2r-CoVs from Japan and China to Thailand over a 4800-km range. Cross-border surveillance is urgently needed to find the immediate progenitor virus of SARS-CoV-2.

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Muller NF, Wagner C, Frazar CD et al. **Viral genomes reveal patterns of the SARS-CoV-2 outbreak in Washington State.** Science Translational Medicine 26 May 2021: 13(595): eabf0202. **DOI: 10.1126/scitranslmed.abf0202.**

- BACKGROUND: The primary strain of SARS-CoV-2 leaving China was 614D but in late 2020, population genetic analysis in the United Kingdom indicated that a new strain -- 614G -- increased in frequency relative to 614D in a manner consistent with a selective advantage.

- In the UK, 614G was associated with higher viral load and younger age of pts but there was no evidence that spike 614G variant pts had higher COVID-19 mortality or clinical severity.
- After initial introduction in 2/2020, SARS-CoV-2 has been introduced repeatedly into Washington State from different parts of the globe with viruses introduced later differing genetically from those introduced earlier.
- STUDY DESIGN: This study focused on differences between the spread of lineages of 614D and 614G in the context of regional differences within Washington State, using viral genetic sequence data isolated between February and July 2020. Researchers tested the impact of temporal differences in county level workplace mobility trends, the role of introductions from outside the state in driving caseloads, and potential transmissibility and disease severity differences between the two spike variants.
- RESULTS: The Washington State outbreak was caused by repeated introductions and shaped by temporal differences in mobility reductions: in early February, an introduction of a 614D variant fueled the early outbreak in March and April, but this lineage was supplanted through multiple introductions of 614G, and past April, the majority of viruses were 614G → a substantially higher fraction of 614G cases were caused by new introductions than for 614D cases.
- D614G leads to higher viral load, implying greater transmissibility, without apparent effects on virulence.
- CONCLUSION: The surge in 614G in Washington State was explainable by its repeated introduction into the state as well as local differences in lockdown measures—both human-catalyzed factors.

Ong SWX, Chiew CJ, Ang LW et al. **Clinical and virological features of SARS-CoV-2 variants of concern: a retrospective cohort study comparing B.1.1.7 (Alpha), B.1.315 (Beta), and B.1.617.2 (Delta)** Clinical Infectious Diseases: ciab721, https://doi.org/10.1093/cid/ciab721. Published: 23 August 2021.

- This retrospective study, we compared outcomes of patients infected with 3 SARS-CoV-2 variants of concern, B.1.1.7, B.1.351, and B.1.617.2. with those with wild-type strains from early 2020.
- National surveillance data from 1-January-2021 to 22-May-2021 were obtained and outcomes in relation to VOC were explored. Clinical outcomes were compared with a cohort of 846 patients admitted from January-April 2020.
- RESULTS: 829 patients in Singapore in the study period were infected with these 3 VOCs. The majority of infections by the three VOCs were non-severe: 30 (4%) required supplemental
  oxygen and 10 (1%) were admitted to ICU or died After adjusting for age and sex, B.1.617.2 (Delta variant) was associated with higher odds of oxygen requirement, ICU admission, or death (adjusted odds ratio (aOR) 4.90, [95% CI 1.43-30.78]).
- 157 of these patients were admitted to our center. After adjusting for age, sex, comorbidities, and vaccination, aOR for pneumonia with B.1.617.2 was 1.88 [95% CI 0.95-3.76]) compared with wild-type. These differences were not seen with B.1.1.7 and B.1.351.

- Vaccination status was associated with decreased severity. B.1.617.2 was associated with significantly lower PCR Ct values and longer duration of Ct value ≤30 (median duration 18 days for B.1.617.2, 13 days for wild-type).
- CONCLUSIONS: There was a signal toward increased severity associated with the Delta variant, B.1.617.2. The association of B.1.617.2 with lower Ct value and longer viral shedding provides a potential mechanism for increased transmissibility. These findings provide an impetus for the rapid implementation of vaccination programs.

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Li B, Deng A, Li K et al. **Viral infection and transmission in a large well-traced outbreak caused by the Delta SARS-CoV-2 variant.** medRxiv 2021. Published on line, 7/12/2021. **https://doi.org/10.1101/2021.07.07.21260122**

- To evaluate SARS-CoV-2 delta variant transmission, 62 people and their close contacts who were infected in the initial Delta outbreak in Guangzhou from May 21 to June 18 were studied via daily PCR. Data were compared with similar sampling from 63 people infected with an earlier version of the virus from the first wave in 2020.
- RESULTS: Viral load for the first positive PCR test was 1,260 times higher for Delta compared with the variant in the initial wave of infections.
- Time from exposure to the first positive PCR test was also shorter with Delta, 4 days vs. 6 days.
- High-quality sequencing data and reliable epidemiological data indicated some minor intra-host single nucleotide variants (iSNVs) could be transmitted between hosts and finally fixed in the virus population during the outbreak. The minor iSNVs transmission between donor-recipient contribute at least 4 of 31 substitutions identified in the outbreak suggesting some iSNVs could quickly arise and reach fixation when the virus spread rapidly.
- CONCLUSIONS: A faster replication rate, a reduced incubation period and greater viral shedding are all factors that contribute to the Delta variant's increased infectiousness and transmissibility.

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Bergwerk M, Gonen T, Lustig Y et al. **Covid-19 Breakthrough Infections in Vaccinated Health Care Workers.** NEJM – published online July 28, 2021. **DOI: 10.1056/NEJMoa2109072**

- To characterize breakthrough infections in vaccinated individuals, extensive evaluations of health care workers who were symptomatic (including mild symptoms) or had known infection exposure were performed
- Evaluations included epidemiologic investigations, repeat RT-PCR assays, antigen-detecting rapid diagnostic testing (Ag-RDT), serologic assays, and genomic sequencing.
- Correlates of breakthrough infection were assessed in a case–control analysis using matched pts with breakthrough infection who had antibody titers obtained within a week before SARS-CoV-2 detection (peri-infection period) with four to five uninfected controls.
- RESULTS: Among 1497 fully vaccinated health care workers for whom RT-PCR data were available, 39 SARS-CoV-2 breakthrough infections were documented. Neutralizing antibody titers in case patients during the peri-infection period were lower than those in matched uninfected controls (case-to-control ratio, 0.361; 95% confidence interval, 0.165 to 0.787).

Higher peri-infection neutralizing antibody titers were associated with lower infectivity (higher Ct values).

- Most breakthrough cases were mild or asymptomatic, although 19% had persistent symptoms (>6 weeks). The B.1.1.7 (alpha) variant was found in 85% of samples tested. A total of 74% of case pts had a high viral load (Ct value, <30) at some point during their infection; however, of these, only 17 (59%) had a positive result on concurrent Ag-RDT. No secondary infections were documented.
- CONCLUSIONS: Among fully vaccinated health care workers, the occurrence of breakthrough infections with SARS-CoV-2 was correlated with neutralizing antibody titers during the peri-infection period. Most breakthrough infections were mild or asymptomatic, although persistent symptoms did occur.

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Vitale J, Mumoli N, Clerici P et al. Assessment of SARS-CoV-2 Reinfection 1 Year After Primary Infection in a Population in Lombardy, Italy. JAMA Intern Med. Published online May 28, 2021. **doi:10.1001/jamainternmed.2021.2959**

- To investigate the incidence of SARS-CoV-2 primary infection and reinfection among individuals who, during the first wave of the pandemic in Italy (February to July 2020) were PCR positive for COVID-19, repeat RT-PCR testing was performed in symptomatic and asymptomatic patients of any age recruited from screening and contact-tracing programs.
- Cases were defined as those with infection who were PCR-positive and controls as those without infection who were PCR-negative, per WHO guidelines.
- Cohorts were considered to be at risk from the time of the first definition (date of (+) test result for cases; date of second (-) test result for controls) until the end of the observation (February 28, 2021) or a new positive PCR test result. Reinfections were defined by a second RT-PCR positivity beyond 90 days after complete resolution of the first infection and with at least 2 consecutive negative test results between episodes.
- RESULTS: During F/U, 5 reinfections (0.31%; 95% CI, 0.03%-0.58%) were confirmed in the cohort of 1579 positive patients. Only 1 was hospitalized, and 4 pts had a close relationship with health facilities.
- Of 13 496 persons who initially were not infected with SARS-CoV-2, 528 (3.9%; 95% CI, 3.5%-4.2%) subsequently developed a primary infection.
- The incidence density per 100 000 person days was 1.0 (95% CI, 0.5-1.5) for reinfections compared with 15.1 (95% CI, 14.5-15.7) for new infections, a significant difference between cohorts. (HR, 0.06; 95% CI, 0.05-0.08; log-rank test P < .001)
- CONCLUSIONS: After recovery from COVID-19, reinfections are rare events and patients who have recovered from COVID-19 have a lower risk of reinfection. Natural immunity to SARS-CoV-2 appears to confer a protective effect for at least a year. However, the observation ended before SARS-CoV-2 variants began to spread, and it is unknown how well natural immunity to the wild-type virus will protect against variants.

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Butler-Laporte G, Lawandi A, Scholler I et al. **Comparison of Saliva and Nasopharyngeal Swab Nucleic Acid Amplification Testing for Detection of SARS-CoV-2: A Systematic Review and Meta-analysis.** JAMA Intern Med. 2021;181(3):353-360**.** **doi:10.1001/jamainternmed.2020.8876**

- To assess the diagnostic accuracy of saliva NAAT for COVID-19, a SR & MA was conducted on 8/29/2020.
- Studies needed to provide enough data to measure salivary NAAT sensitivity and specificity compared with imperfect nasopharyngeal swab NAAT as a reference test.
- Main Outcomes and Measures: The primary outcome was pooled sensitivity and specificity. Two secondary analyses were performed: one restricted to peer-reviewed studies, and a post hoc analysis limited to ambulatory settings.
- RESULTS: The search strategy yielded 16 unique studies identified for quantitative synthesis. There was significant variability in patient selection, study design, and stage of illness at which patients were enrolled. 15 studies included ambulatory patients, and 9 exclusively enrolled from an outpatient population with mild or no symptoms.
- In the primary analysis, the saliva NAAT pooled sensitivity was 83.2% (95% credible interval [CrI], 74.7%-91.4%) and the pooled specificity was 99.2% (95% CrI, 98.2%-99.8%). The nasopharyngeal swab NAAT had a sensitivity of 84.8% (95% CrI, 76.8%-92.4%) and a specificity of 98.9% (95% CrI, 97.4%-99.8%). Results were similar in secondary analyses.
- CONCLUSIONS: Saliva NAAT diagnostic accuracy is similar to that of NP swab NAAT, especially in the ambulatory setting. These findings support larger-scale research on the use of saliva NAAT as an alternative to nasopharyngeal swabs.

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THE DISEASE

Taquet M, Geddes JR, Husain M et al. **6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records.** Lancet (Psych) 2021; Published: April 06, 2021. **DOI:https://doi.org/10.1016/S2215-0366(21)00084-5**

- To evaluate neurological and psychiatric sequelae of COVID-19, a retrospective analysis of EMRs was performed in 236,379 survivors of COVID-19. Results were compared to findings in one matched control cohort of pts diagnosed with influenza, and a second matched cohort diagnosed with any respiratory tract infection including influenza in the same time period.
- We estimated the incidence of 14 neurological and psychiatric outcomes in the 6 months after a
  confirmed diagnosis of COVID-19 & compared incidences with those in propensity score-matched cohorts of patients with influenza or other respiratory tract infections. To evaluate the impact of COVID-19 severity, results were re-analyzed based on hospitalization, ICU admission & acute COVID-19 encephalopathy.
- RESULTS: For the whole group, the estimated incidence of a neurological or psychiatric diagnosis in the following 6 months was 33·62% (95% CI 33·17–34·07), with 12·84% (12·36–13·33) receiving their
  first such diagnosis. For pts who had been admitted to an ICU, the estimated incidence of a diagnosis
  was 46·42% (44·78–48·09) and for a first diagnosis was 25·79% (23·50–28·25).
- Regarding individual diagnoses, the whole COVID-19 cohort had estimated incidences of 17·39% (17·04–17·74) for anxiety disorder, and 1·40% (1·30–1·51) for psychotic disorder. In the group with ITU admission, estimated incidences were 19·15% (17·90–20·48) for anxiety disorder, & 2·77% (2·31–3·33) for psychotic disorder.
- Most diagnostic categories were more common in pts who had COVID-19 than in those who had influenza (hazard ratio [HR] 1·44, 95% CI1·40–1·47, for any diagnosis; 1·78, 1·68–1·89, for any first diagnosis) and those who had other respiratory tract infections, & were higher in control pts who had more severe illness.
- CONCLUSION: This study provides evidence for substantial neurological and psychiatric morbidity in the 6 months after COVID-19 infection, with greatest risks in pts who had severe COVID-19.

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Belay ED, Abrams J, Oster ME et al. **Trends in Geographic and Temporal Distribution of US Children With Multisystem Inflammatory Syndrome During the COVID-19 Pandemic.** JAMA Pediatr. Published online April 6, 2021. **doi:10.1001/jamapediatrics.2021.0630**

- To describe the clinical characteristics and geographic and temporal distribution of the largest cohort of patients with MIS-C in the United States to date, cross-sectional analysis was conducted on clinical & laboratory data collected from pts with MIS-C with illness onset from March 2020 to January 2021.
- Geographic and temporal distribution of MIS-C was compared with that of COVID-19 nationally, by region & level of urbanicity by county. Clinical/laboratory findings & changes over time were described by age group & by presence or absence of preceding COVID-19.

- RESULTS: A total of 1733 patients with MIS-C were identified; 994 (57.6%) were male and 1117 (71.3%) were Hispanic or non-Hispanic Black. Gastrointestinal symptoms, rash, and conjunctival hyperemia were reported by 53% (n = 931) to 67% (n = 1153) of patients.
- A total of 937 patients (54%) had hypotension or shock, and 1009 (58.2%) were admitted for intensive care. Cardiac dysfunction was reported in 484 patients (31.0%), pericardial effusion in 365 (23.4%), myocarditis in 300 (17.3%), and coronary artery dilatation or aneurysms in 258 (16.5%).
- Pts aged 0 to 4 years had the lowest proportion of severe manifestations, although 171 pts (38.4%) had hypotension or shock and 197 (44.3%) were admitted for intensive care.
- Patients aged 18 to 20 years had the highest proportions with myocarditis (17 [30.9%]), pneumonia (20 [36.4%]), acute respiratory distress syndrome (10 [18.2%]), and polymerase chain reaction positivity (39 [70.9%]). These older adolescents also had the highest proportion reporting preceding COVID-19–like illness (63%).
- Younger children presented more frequently with conjunctival findings, rash, and abdominal pain, while adolescents present more frequently with chest pain, shortness of breath, and cough. In this study, cardiac dysfunction and a diagnosis of myocarditis was significantly more likely in adolescents but there was no significant difference in the age of children with coronary artery dilation, found in 18.3% of children aged 0 to 4 years and 14.6% of children aged 18 to 20 years.
- Nationally, the first 2 MIS-C peaks followed the COVID-19 peaks by 2 to 5 weeks. The cumulative MIS-C incidence per 100 000 persons younger than 21 years was 2.1 and varied from 0.2 to 6.3 by state. Twenty-four patients (1.4%) died.
- CONCLUSIONS AND RELEVANCE: In this cross-sectional study of a large cohort of patients with MIS-C, 2 peaks that followed COVID-19 peaks by 2 to 5 weeks were identified. The geographic and temporal association of MIS-C with the COVID-19 pandemic suggested that MIS-C resulted from delayed immunologic responses to SARS-CoV-2 infection. Clinical manifestations varied by age and by presence or absence of preceding COVID-19.

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Kustin T, Harel N, Finkel U et al. **Evidence for increased breakthrough rates of SARS-CoV-2 variants of concern in BNT162b2 mRNA vaccinated individuals.** medRxiv, April, 2021. **https://doi.org/10.1101/2021.04.06.21254882**

- The BNT162b2 mRNA vaccine has demonstrated high protection levels against COVID-19, yet apprehension exists that several variants of concerns (VOCs) can surmount the immune defenses generated by the vaccines.
- To evaluate this. Israeli researchers performed a case-control study that examined the distribution of SARS-CoV-2 variants observed in infections of vaccinated individuals (“breakthrough cases”) and matched infections of unvaccinated individuals. If there is lower vaccine effectiveness against one of the VOCs, its proportion among the breakthrough cases should be higher than among unvaccinated cases.
- RESULTS: Vaccinees that tested positive at least a week after the second dose were disproportionally infected with B.1.351, as compared with unvaccinated individuals (odds ratio of 8:1). Those who tested positive between two weeks after the first dose and one week after the second dose, were disproportionally infected by B.1.1.7 (odds ratio of 26:10),
- Findings suggest reduced vaccine effectiveness against both VOCs at particular time windows following vaccination.

- Nevertheless, the B.1.351 incidence in Israel to-date remains low and vaccine effectiveness remains high among those fully vaccinated.
- These results overall suggest that vaccine breakthrough infection may be more frequent with both VOCs, yet a combination of mass-vaccination with two doses coupled with non-pharmaceutical interventions control and contain their spread.

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Villar J, Ariff S, Gunier RB et al. **Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection: The INTERCOVID Multinational Cohort Study**. JAMA Pediatr. Published online, April 22, 2021. **doi:10.1001/jamapediatrics.2021.1050**

- To evaluate maternal and neonatal risks of COVID-19 in pregnancy, a cohort study took place from March to October 2020, involving 43 institutions in 18 countries with consecutive unmatched, not-infected women concomitantly enrolled immediately after each infected woman was identified, at any stage of pregnancy or delivery & at the same level of care with follow-up until hospital discharge.
- Primary outcome measures were indices of maternal & severe neonatal/perinatal morbidity & mortality; the individual components of these indices were secondary outcomes.
- 706 pregnant women with COVID-19 diagnosis and 1424 without COVID-19 diagnosis were enrolled, with mean [SD] age, 30.2 [6.1] years.
- RESULTS: Women with COVID-19 were at higher risk for preeclampsia/eclampsia (relative risk [RR], 1.76; 95% CI, 1.27-2.43), severe infections (RR, 3.38; 95% CI, 1.63-7.01), ICU admission (RR, 5.04; 95% CI, 3.13-8.10), **mortality (RR, 22.3; 95% CI, 2.88-172),** preterm birth (RR, 1.59; 95% CI, 1.30-1.94), medically indicated preterm birth (RR, 1.97; 95% CI, 1.56-2.51), severe neonatal morbidity index (RR, 2.66; 95% CI, 1.69-4.18) & severe perinatal morbidity/mortality index (RR, 2.14; 95% CI, 1.66-2.75).
- Fever and shortness of breath for any duration was associated with increased risk of severe maternal complications (RR, 2.56; 95% CI, 1.92-3.40) & neonatal complications (RR, 4.97; 95% CI, 2.11-11.69).
- Asymptomatic women with COVID-19 diagnosis remained at higher risk only for maternal morbidity (RR, 1.24; 95% CI, 1.00-1.54) and preeclampsia (RR, 1.63; 95% CI, 1.01-2.63).
- CONCLUSIONS: COVID-19 in pregnancy was associated with consistent, substantial increases in severe maternal morbidity and mortality and neonatal complications when pregnant women with and without COVID-19 diagnosis were compared when mothers were symptomatic.

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The Writing Committee for the COMEBAC Study Group. **Four-Month Clinical Status of a Cohort of Patients After Hospitalization for COVID-19.** JAMA. 2021;325(15):1525-1534. Published online 3/17/2021. **doi:10.1001/jama.2021.3331**

- To evaluate longer-term sequelae of COVID-19, a prospective uncontrolled cohort study was performed. Survivors of COVID-19 hospitalized in a French university hospital between 3/11 & 5/ 29, 2020, underwent telephone assessment 4 mos after discharge, between 7/15 & 9/18, 2020. Pts with relevant symptoms & all pts hospitalized in an ICU underwent ambulatory assessment.

- RESULTS: Among 834 eligible pts, 478 were evaluated by telephone (mean age, 61 years [SD, 16 years]; 201 men, 277 women). 244 pts (51%) declared at least 1 symptom that did not exist before COVID-19: fatigue in 31%, cognitive symptoms in 21%, and new-onset dyspnea in 16%.
- There was further evaluation in 177 pts (37%), including 97 of 142 former ICU patients. The median 20-item Multidimensional Fatigue Inventory score (n = 130) was 4.5 (I/Q range, 3.0-5.0) for reduced motivation and 3.7 (I/Q range, 3.0-4.5) for mental fatigue (possible range, 1 [best] to 5 [worst]). On the Short-Form Health Survey score (n = 145), mean score was 25 (I/Q range, 25.0-75.0) for the subscale "role limited owing to physical problems" (range, 0 [best] to 100 [worst]).
- Lung CT scan abnormalities were found in 108/171 patients (63%), mainly subtle ground-glass opacities. Fibrotic lesions were observed in 33/171 patients (19%), involving <25% of parenchyma in all but one. Fibrotic lesions were observed in 19/49 survivors (39%) with acute RDS.
- Among 94 former ICU pts, anxiety, depression & posttraumatic symptoms were observed in 23%, 18%, and 7%, respectively. The LV ejection fraction was <50% in 8/ 83 ICU pts (10%). New-onset chronic kidney disease was observed in 2 ICU pts.
- CONCLUSIONS: Four months after hospitalization for COVID-19, a cohort of pts frequently reported symptoms not previously present & lung-scan abnormalities were common. Findings are limited by the absence of a control group & of pre-COVID assessments in this cohort.

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Lampert J, Miller M, Halperin JL et al. **Prognostic Value of Electrocardiographic QRS Diminution in Patients With COVID-19.** J Am Coll Cardiol. 2021 Published online 4/21/2021; 17: 2258–2259.

- To evaluate QRS volume on ECG as a predictor of COVID-19 outcome, results in consecutive patients (n = 140) both observed on telemetry and having a final disposition—death or discharge—were analyzed.
- Low QRS amplitude (LoQRS) was defined by a composite of: 1) QRS amplitude <5 mm in the limb leads AND <10 mm in the precordial leads; 2) QRS amplitude <5 mm in the limb leads OR <10 mm in the precordial leads; or 3) QRS amplitude diminution by ≥50% compared with the baseline or admission ECG in the limb leads or precordial leads (a composite of leads V1 to V3 and V4 to V6).
- RESULTS: LoQRS occurred in 24.3% of COVID-19 patients and was more frequent in patients who died compared with those who survived to discharge (48.1% vs. 10.2%; p < 0.001). A 50% or greater decrease in QRS amplitude occurred in 17.1% of patients (36.5% vs. 5.7% in the mortality and discharged groups, respectively; p < 0.001). QRS amplitude met the threshold <5 mm in the limb leads or <10 mm in the precordial leads in 15.7% of patients, and was more prevalent in those who died (28.9% vs. 8.0%; p = 0.001).
- Overall mortality occurred in 37.1% of the COVID-19 cohort, but was 73.5% in patients with LoQRS compared with 25.5% in patients without LoQRS (p < 0.001)
- Patients with LoQRS had higher median levels of D-dimer (2.1 vs. 1.2 μg/ml; p = 0.01), C-reactive protein (130 vs. 102 mg/l; p = 0.05), and pro-calcitonin (0.3 vs. 0.1 ng/ml; p = 0.04). There were no significant differences in median admission (60.45 vs. 36.0; p = 0.31) or peak

(131.9 vs. 63.0; p = 0.18) B-type natriuretic peptide (BNP) levels between LoQRS and stable-QRS groups, respectively.

- When adjusted for baseline clinical variables including age, body mass index, chronic kidney disease, smoking, liver disease, and hypertension, LoQRS was independently associated with mortality (hazard ratio [HR]: 4.18; 95% confidence interval [CI]: 2.33 to 7.51; p < 0.001). This strong association persisted after adjustment for presenting troponin, peak troponin, peak D-dimer, C-reactive protein, and last available albumin in addition to baseline clinical covariates (HR: 2.83; 95% CI: 1.28 to 6.23; p = 0.01), and when intubation and inotrope or vasopressor requirement were added to the model (HR: 2.31; 95% CI: 1.03 to 5.20; p = 0.042).
- A significant interaction between myocardial injury (troponin level >0.03 ng/ml) and LoQRS was demonstrated by Cox proportional hazards models (p-interaction = 0.037). Patients with LoQRS and
  concomitant myocardial injury had higher mortality than expected for exhibiting both findings.

• CONCLUSION: LoQRS is an independent predictor of mortality in hospitalized patients with COVID-19, captures a dynamic process during the course of illness, and underscores the prognostic utility of both an absolute and relative reduction in QRS amplitude.

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Pineles B et al. **In-hospital mortality in a cohort of hospitalized pregnant and nonpregnant patients with COVID-19**. Ann Intern Med 2021; **DOI: 10.7326/M21-0974.**

- BACKGROUND: Studies examining pregnant pts with COVID-19 have shown an increased risk for death in pregnant versus nonpregnant patients of reproductive age. However, these data are based on registries that are limited by a significant proportion of missing data, including pregnancy status, and likely have biased case ascertainment.
- To evaluate the risk for in-hospital death among pregnant and nonpregnant patients of reproductive age hospitalized with COVID-19, we did a retrospective cohort study of pts in the Premier Healthcare Database, an all-payer data repository that captures 20% of U.S. hospitalizations. All female inpts aged 15 to 45 years hospitalized from April to November 2020 with COVID-19 were included.
- Only pts with a (+) RCR test for SARS-C0V-2 and a viral pneumonia diagnosis were included.
- There were 1062 pregnant and 9815 nonpregnant pts hospitalized with COVID-19 and viral pneumonia. Pregnant patients were younger and more likely to have public insurance than nonpregnant patients. Pregnant patients were also less likely to have most comorbid conditions, including hypertension, chronic pulmonary disease, diabetes, and obesity.
- RESULTS: In-hospital death occurred in 0.8% (n = 9) of pregnant patients and 3.5% (n = 340) of nonpregnant patients hospitalized with COVID-19 and viral pneumonia. Among the subgroup of pts admitted to an intensive care unit, in-hospital mortality was 3.5% (9 of 255) in pregnant patients and 14.9% (283 of 1898) in nonpregnant patients. Among those who received mechanical ventilation, in-hospital death occurred in 8.6% (9 of 105) of pregnant patients and 31.4% (294 of 937) of nonpregnant patients.
- Pregnant pts who died ranged in age from 23 to 44 years. Eight of 9 were non-Hispanic Black or Hispanic. Six were obese, and 7 had at least 1 comorbid condition. Gestational ages ranged from 23 to 39 weeks, and 7 of 9 deliveries were live births.

- CONCLUSION: Overall and within multiple subgroups, this study found a substantially lower rate of in-hospital mortality in pregnant patients than nonpregnant patients hospitalized with COVID-19 and viral pneumonia. In this large, geographically diverse cohort of reproductive-aged patients hospitalized with COVID-19, in-hospital mortality was low in pregnant patients.

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Lowe KE, Zein J, Hatipoglu U et al. **Association of Smoking and Cumulative Pack-Year Exposure With COVID-19 Outcomes in the Cleveland Clinic COVID-19 Registry.** JAMA Intern Med 2021;181(5):709-711. **doi:10.1001/jamainternmed.2020.8360**

- To assess the cumulative effect of smoking over time on COVID-19 outcomes, pts in the Cleveland Clinic COVID-19 Registry were classified by their cumulative recorded smoking exposure. Those who reported that they were never smokers were compared with patients reporting 0 to 10 pack-years, 10 to 30 pack-years, and more than 30 pack-years.
- Multivariable logistic regression models were used to determine the odds ratio for hospitalization, admission to the ICU given hospitalization, and death given a positive COVID-19 test for each pack-year cohort compared with never smokers. Regression models were run unadjusted & adjusted for identified confounders.
- RESULTS: Of the 7102 pts in the cohort, 6020 (84.8%) were never smokers, 172 (2.4%) were current smokers, and 910 (12.8%) were former smokers. Findings showed a dose-response association between pack-years and adverse COVID-19 outcomes→ Patients who smoked > 30 pack-years had a 2.25 times higher odds of hospitalization (95% CI, 1.76-2.88), and were 1.89 times more likely to die following a COVID-19 diagnosis (95% CI, 1.29-2.76) when compared with never smokers.
- CONCLUSION: These results suggest that cumulative exposure to cigarette smoke is an independent risk factor for hospital admission and death from COVID-19. Smoking is imperfectly classified in patient records, and former smokers are potentially classified as never smokers, while pack-years may be under-recorded. Nonetheless, in this single central registry of pts who tested positive for COVID-19 that increased cumulative smoking was associated with a higher risk of hospitalization and mortality from COVID-19 in a dose-dependent manner.

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Chou S H-Y, Beghi E, Helbok R et al. **Global Incidence of Neurological Manifestations Among Patients Hospitalized With COVID-19**—A Report for the GCS-NeuroCOVID Consortium and the ENERGY Consortium. JAMA Netw Open. May 11, 2021;4(5):e2112131. **doi:10.1001/jamanetworkopen.2021.12131**

- To determine the neurological phenotypes, incidence, and outcomes among adults hospitalized with COVID-19, this cohort study included patients with confirmed COVID-19 at 28 centers, representing 13 countries and 4 continents from March 1 to October 2020. Three cohorts were included: (1) the GCS-NeuroCOVID all COVID-19 cohort (n = 3055), which included consecutive hospitalized patients with COVID-19 with and without neurological manifestations; (2) the GCS-NeuroCOVID COVID-19 neurological cohort (n = 475), which comprised consecutive patients hospitalized with COVID-19 who had confirmed neurological manifestations; and (3) the ENERGY cohort (n = 214), which included patients with COVID-19 who received formal neurological consultation.

- Neurological phenotypes were classified as self-reported symptoms or neurological signs and/or syndromes assessed by clinical evaluation. Composite incidence was reported for groups with at least 1 neurological manifestation. The main outcome measure was in-hospital mortality.
- RESULTS: A total of 3083 of 3743 patients (82%) across cohorts had any neurological manifestation (self-reported neurological symptoms and/or clinically captured neurological sign and/or syndrome). The most common self-reported symptoms included headache (37%) and anosmia or ageusia (26%). The most prevalent neurological signs and/or syndromes were acute encephalopathy (49%), coma (17%), and stroke (6%), while meningitis and/or encephalitis were rare (0.5%).
- Presence of clinically captured neurologic signs and/or syndromes was associated with increased risk of in-hospital death (adjusted odds ratio [aOR], 5.99; 95% CI, 4.33-8.28). Presence of preexisting neurological disorders (aOR, 2.23; 95% CI, 1.80-2.75) was associated with increased risk of developing neurological signs and/or syndromes with COVID-19.
- CONCLUSIONS AND RELEVANCE: In this multicohort study, neurological manifestations were prevalent among patients hospitalized with COVID-19 and were associated with higher in-hospital mortality.

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Kompaniyets L, Agathis NT, Nelson JM et al. **Underlying Medical Conditions Associated With Severe COVID-19 Illness Among Children.** JAMA Netw Open. June 7, 2021;4(6):e2111182. **doi:10.1001/jamanetworkopen.2021.11182**

- To examine the risk of severe COVID-19 illness among children associated with underlying medical conditions and medical complexity, this cross-sectional study included all pts aged </=18 yrs with COVID-19 from a database of > 800 hospitals seen in an ED or inpatient encounter from 3/2020 through 1/2021.
- Two measures of severe illness were utilized: (1) hospitalization &(2) severe illness when hospitalized, a single severity indicator for experiencing an intensive care unit (ICU) or stepdown unit admission, invasive mechanical ventilation (IMV), or death.
- RESULTS: Among 43 465 patients with COVID-19 </=18 yrs, the strongest risk factors for hospitalization were type 1 diabetes ([aRR], 4.60; 95% CI, 3.91-5.42) and obesity (aRR, 3.07; 95% CI, 2.66-3.54), and the strongest risk factors for severe COVID-19 illness were type 1 diabetes (aRR, 2.38; 95% CI, 2.06-2.76) and cardiac and circulatory congenital anomalies (aRR, 1.72; 95% CI, 1.48-1.99).
- Prematurity was a risk factor for severe COVID-19 illness among children younger than 2 years (aRR, 1.83; 95% CI, 1.47-2.29). Chronic and complex chronic disease were risk factors for hospitalization, with aRRs of 2.91 (95% CI, 2.63-3.23) and 7.86 (95% CI, 6.91-8.95), respectively, as well as for severe COVID-19 illness, with aRRs of 1.95 (95% CI, 1.69-2.26) and 2.86 (95% CI, 2.47-3.32), respectively.
- CONCLUSIONS: This cross-sectional study found a higher risk of severe COVID-19 illness among children with medical complexity and certain underlying conditions, specifically T1DM, cardiac and circulatory congenital anomalies, and obesity.

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Daniels CD, Rajpal S, Greenshields JT et al. **Prevalence of Clinical and Subclinical Myocarditis in Competitive Athletes with Recent SARS-CoV-2 Infection: Results From the Big Ten COVID-19 Cardiac Registry.** JAMA Cardiol. Published online May 27, 2021. **doi:10.1001/jamacardio.2021.2065**

- The Big Ten Conference requires comprehensive cardiac testing including cardiac magnetic resonance (CMR) imaging for all athletes with COVID-19. Results of this testing were surveyed to determine the prevalence of myocarditis in competitive athletes after COVID-19 infection.
- Myocarditis was categorized as clinical or subclinical based on the presence of cardiac symptoms and CMR findings.
- RESULTS: Representing 13 universities, cardiovascular testing was performed in 1597 athletes (964 men [60.4%]) from 13 universities were evaluated. 37 (27 men) were diagnosed with COVID-19 myocarditis (overall 2.3%; range per program, 0%-7.6%); 9 had clinical myocarditis and 28 had subclinical myocarditis. If cardiac testing was based on cardiac symptoms alone, only 5 athletes would have been detected (detected prevalence, 0.31%).
- CMR imaging for all athletes yielded a 7.4-fold increase in detection of myocarditis (clinical and subclinical).
- Follow-up CMR imaging performed in 27 (73.0%) demonstrated resolution of T2 elevation in all (100%) and late gadolinium enhancement in 11 (40.7%).
- CONCLUSIONS: CMR imaging provides a more complete understanding of the prevalence of clinical and subclinical myocarditis in college athletes after COVID-19 infection. Further imaging and F/U are needed.

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Kadri SS, Sun J, Lawandi A et al. **Association Between Caseload Surge and COVID-19 Survival in 558 U.S. Hospitals, March to August 2020.** Ann Inter Med. Published on line, 7/6/2021. https://doi.org/10.7326/M21-1213

- To determine the association between hospitals' severity-weighted COVID-19 caseload and COVID-19 mortality risk and identify effect modifiers of this relationship, a retrospective cohort study of 558 U.S. hospitals in the Premier Healthcare Database reviewing adult COVID-19–coded inpatients admitted from March to August 2020 with discharge dispositions by October 2020.
- Each hospital-month was stratified by percentile rank on a surge index (a severity-weighted measure of COVID-19 caseload relative to pre–COVID-19 bed capacity). The effect of surge index on risk-adjusted odds ratio (aOR) of in-hospital mortality or discharge to hospice was calculated using hierarchical modeling; interaction by surge attributes was assessed.
- RESULTS: Of 144 116 inpts with COVID-19, 78 144 (54.2%) were admitted to hospitals in the top surge index decile. Overall, 25 344 (17.6%) died; crude COVID-19 mortality decreased over time across all surge index strata. However, compared with nonsurging (<50th surge index percentile) hospital-months, aORs in the 50th to 75th, 75th to 90th, 90th to 95th, 95th to 99th, and greater than 99th percentiles were 1.11 (95% CI, 1.01 to 1.23), 1.24 (CI, 1.12 to 1.38), 1.42 (CI, 1.27 to 1.60), 1.59 (CI, 1.41 to 1.80), and 2.00 (CI, 1.69 to 2.38), respectively.

- The surge index was associated with mortality across ward, intensive care unit, and intubated patients. The surge–mortality relationship was stronger in June to August than in March to May (slope difference, 0.10 [CI, 0.033 to 0.16]) despite greater corticosteroid use and more judicious intubation during later and higher-surging months.
- CONCLUSION: Nearly 1 in 4 COVID-19 deaths (5868 [CI, 3584 to 8171]; 23.2%) was potentially attributable to hospitals strained by surging caseload. Despite improvements in COVID-19 survival between March and August 2020, surges in hospital COVID-19 caseload remained detrimental to survival and potentially eroded benefits gained from emerging treatments.

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Jiang DH, Roy DJ, Gu BJ et al. **Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection: A State-of-the-Art Review**. J Am Coll Cardiol Basic Trans Science. Sep 15, 2021. Epublished DOI: 10.1016/j.jacbts.2021.07.002

- In the literature, Self-reported symptoms after COVID-19 persisted for 1 to 2 months after initial diagnosis in up to 13% of patients; 4.5% experienced symptoms beyond 2 months, and 2.6% for 3 months or longer, according to mobile app data from U.K., U.S., and Swedish populations.
- To further assess postacute sequelae of severe Acute Respiratory Syndrome Coronavirus 2 Infection (PASC), we conducted a comprehensive database search for studies published between December 1, 2019, through May 31, 2021. The search focused exclusively on PASC, defined as any symptoms that began or persisted after 28 days of laboratory-confirmed SARS-CoV-2 infection.
- After comprehensive review, 143 papers were deemed relevant. PASC complications were summarized by body system. Data on at-risk populations (defined by age, sex, race/ethnicity, income, or geography) was abstracted when available.
- RESULTS: This review of published reports through May 31, 2021, found that manifestations of postacute sequelae of severe acute respiratory syndrome coronavirus 2 infection (PASC) affect between 33% and 98% of coronavirus disease 2019 survivors and comprise a wide range of symptoms and complications in the pulmonary, cardiovascular, neurologic, psychiatric, gastrointestinal, renal, endocrine, and musculoskeletal systems in both adult and children.
- Persistent dyspnea is among the most common symptoms reported by patients recovering from COVID-19, is experienced by up to 88% of survivors, and can take 3 months or longer to resolve.
- Chest pain was reported by up to 43%) and tachycardia/palpitations by up to 11%.
- Persistent olfactory and gustatory deficits were reported by 4% to 53% of patients beyond 4 weeks of acute infection.
- Although data on PASC risk factors and vulnerable populations are scarce, evidence points to a disproportionate impact on racial/ethnic minorities, older patients, patients with preexisting conditions, and rural residents.

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Bozkurt B, Kamat I, Hotez P. **Myocarditis with COVID-19 mRNA Vaccines.** Circulation. Originally published 20 Jul 2021. **https://doi.org/10.1161/CIRCULATIONAHA.121.056135**

- Per CDC, myocarditis/pericarditis rates are approximately 12.6 cases per million doses of second dose mRNA vaccine among 12-39-year-olds. This is a review of all reported cases.
- Pts with myocarditis invariably presented with chest pain, usually 2-3 days after a second dose of mRNA vaccination. 79% were in males, with the majority in individuals younger than 30
  years with a median age of 24.
- In 484 probable myocarditis/pericarditis cases, 86% had reports of chest pain on presentation, 61% ST or T wave changes on electrocardiogram (ECG), 64% elevated cardiac enzymes and 17% abnormal cardiac imaging. Cardiac MRI was abnormal in all tested patients, with findings suggestive of myocarditis such as late gadolinium enhancement and myocardial edema.
- Mechanisms for development of myocarditis are not clear but molecular mimicry between the spike protein of SARS-CoV-2 and self-antigens, trigger of preexisting dysregulated immune pathways in certain individuals, immune response to mRNA and activation of immunological pathways & dysregulated cytokine expression have been proposed.
- In addition to supportive care, nonsteroidal anti-inflammatory drugs, steroids, and colchicine were used for management of some patients & a few patients were treated with intravenous immunoglobulin + aspirin; some with LV dysfunction were initiated on beta-blocker and angiotensin converting enzyme inhibitor therapy due to left ventricular systolic dysfunction.
- All reported cases recovered rapidly without residua but limitation of extreme exertion has been advised post recovery.
- CONCLUSION: This analysis of reported myocarditis cases post mRNA vaccination against SARS-CoV-2 suggests this is a mild, self-limited process.

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Hippisley-Cox j, Patone M, Mei XW et al. **Risk of thrombocytopenia and thromboembolism after covid-19 vaccination and SARS-CoV-2 positive testing: self-controlled case series study**. BMJ 2021; 374 doi: **https://doi.org/10.1136/bmj.n1931** (Published 27 August 2021)

- To assess the association between covid-19 vaccines and risk of thrombocytopenia and thromboembolic events in England among adults, a self-controlled case series study was performed using national data on covid-19 vaccination and hospital admissions.
- Patient level data were obtained for approximately 30 million people vaccinated in England between 1 December 2020 and 24 April 2021. Electronic health records were linked with death data from the Office for National Statistics, SARS-CoV-2 positive test data, and hospital admission data from the United Kingdom's health service (NHS).
- STUDY POPULATION: Participants: 29 121 633 people were vaccinated with first doses (19 608 008 with Oxford-AstraZeneca (ChAdOx1 nCoV-19) and 9 513 625 with Pfizer-BioNTech (BNT162b2 mRNA)) and 1 758 095 people had a positive SARS-CoV-2 test.
- OUTCOMES: Primary outcomes were hospital admission or death associated with thrombocytopenia, venous thromboembolism, and arterial thromboembolism within 28 days of three exposures: first dose of the ChAdOx1 nCoV-19 vaccine; first dose of the BNT162b2 mRNA vaccine; and a SARS-CoV-2 positive test. Secondary outcomes were subsets of the

primary outcomes: cerebral venous sinus thrombosis (CVST), ischaemic stroke, myocardial infarction & other rare arterial thrombotic events.

- RESULTS: The study found increased risk of thrombocytopenia after ChAdOx1 nCoV-19 vaccination (incidence rate ratio 1.33, 95% confidence interval 1.19 to 1.47 at 8-14 days) and after a positive SARS-CoV-2 test (5.27, 4.34 to 6.40 at 8-14 days); increased risk of venous thromboembolism after ChAdOx1 nCoV-19 vaccination (1.10, 1.02 to 1.18 at 8-14 days) and after SARS-CoV-2 infection (13.86, 12.76 to 15.05 at 8-14 days); and increased risk of arterial thromboembolism after BNT162b2 mRNA vaccination (1.06, 1.01 to 1.10 at 15-21 days) and after SARS-CoV-2 infection (2.02, 1.82 to 2.24 at 15-21 days). Secondary analyses found increased risk of CVST after ChAdOx1 nCoV-19 vaccination (4.01, 2.08 to 7.71 at 8-14 days), after BNT162b2 mRNA vaccination (3.58, 1.39 to 9.27 at 15-21 days), and after a positive SARS-CoV-2 test; increased risk of ischemic stroke after BNT162b2 mRNA vaccination (1.12, 1.04 to 1.20 at 15-21 days) and after a positive SARS-CoV-2 test; and increased risk of other rare arterial thrombotic events after ChAdOx1 nCoV-19 vaccination (1.21, 1.02 to 1.43 at 8-14 days) and after a positive SARS-CoV-2 test.
- CONCLUSION: Increased risks of hematological and vascular events that led to hospital admission or death were observed for short time intervals after first doses of the ChAdOx1 nCoV-19 and BNT162b2 mRNA vaccines. However, the risks of these events were substantially higher and more prolonged after SARS-CoV-2 infection than after vaccination in the same population.

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Barda N, et al. **Safety of the BNT162b2 mRNA Covid-19 vaccine in a nationwide setting.** N Engl J Med 2021; DOI: 10.1056/NEJMoa2110475.

- BACKGROUND: Data from the largest health care organization in Israel was used to evaluate the safety of the BNT162b2 mRNA vaccine.
- For each potential adverse event, in a population of persons with no previous diagnosis of that event, we individually matched vaccinated persons to unvaccinated persons according to SD and clinical variables. To place these results in context, we performed a similar analysis of the same adverse events involving SARS-CoV-2–infected persons matched to uninfected persons.
- RESULTS: Vaccination analysis: Vaccinated and control groups each included a mean of 884,828 persons. Vaccination was most strongly associated with an elevated risk of myocarditis (risk ratio, 3.24; 95% confidence interval [CI], 1.55 to 12.44; risk difference, 2.7 events per 100,000 persons; 95% CI, 1.0 to 4.6), lymphadenopathy (risk ratio, 2.43; 95% CI, 2.05 to 2.78; risk difference, 78.4 events per 100,000 persons; 95% CI, 64.1 to 89.3), appendicitis (risk ratio, 1.40; 95% CI, 1.02 to 2.01; risk difference, 5.0 events per 100,000 persons; 95% CI, 0.3 to 9.9), and herpes zoster infection (risk ratio, 1.43; 95% CI, 1.20 to 1.73; risk difference, 15.8 events per 100,000 persons; 95% CI, 8.2 to 24.2).
- SARS-CoV-2 infection analysis: SARS-CoV-2 infection was associated with a substantially increased risk of myocarditis (risk ratio, 18.28; 95% CI, 3.95 to 25.12; risk difference, 11.0 events per 100,000 persons; 95% CI, 5.6 to 15.8) and of additional serious adverse events, including pericarditis, arrhythmia, deep-vein thrombosis, pulmonary embolism, myocardial infarction, intracranial hemorrhage, and thrombocytopenia.

- CONCLUSIONS: In this real world study in a nationwide mass vaccination setting, the BNT162b2 vaccine was not associated with an elevated risk of most of the adverse events examined. The vaccine was associated with an excess risk of myocarditis (1 to 5 events per 100,000 persons). However, the excess risk of myocarditis (3.95 to 25.12 events per 100,000 individuals) & of other serious adverse effects was far greater with SARS-CoV-2 infection.

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Patone M, Handunnetthi L, Saatci D et al. **Neurological complications after first dose of COVID-19 vaccines and SARS-CoV-2 infection.** Nature Medicine. Published: 25 October 2021. **DOI: 10.1038/s41591-021-01556-7.**

- To evaluate rare neurological complications associated with COVID-19 infection and vaccinations, a self-controlled case series study was used to investigate hospital admissions from neurological complications in the 28 days after a first dose of ChAdOx1nCoV-19 (n = 20,417,752) or BNT162b2 (n = 12,134,782), and after a SARS-CoV-2-positive test (n = 2,005,280).
- METHODS: The English National Immunisation (NIMS) Database of COVID-19 vaccination includes data on vaccine type, date and doses for all people vaccinated in England. We linked NIMS, at the individual patient level, to national data for mortality, hospital admissions and SARS-CoV-2 infection data to examine the associations between the first dose of ChAdOx1nCoV-19 or BNT162b2 vaccines and neurological complications: acute CNS demyelinating events, encephalitis meningitis and myelitis, Guillain–Barré syndrome, Bell's palsy, myasthenic disorders, hemorrhagic stroke and subarachnoid hemorrhage. We used the same population to investigate the associations between a positive SARS-CoV-2 test as a secondary exposure and the same neurological conditions.
- RESULTS: Within 28 days of a positive SARS-CoV-2 test, there was a substantially higher risk of the 7 neurologic outcomes studied, including encephalitis, meningitis, or myelitis, myasthenic disorders, and Guillain-Barré syndrome (GBS), totaling 123, 163, and 145 excess cases per 10 million people, respectively. After vaccination, there was an increased risk of Guillain–Barré syndrome (incidence rate ratio (IRR), 2.90; 95% confidence interval (CI): 2.15–3.92 at 15–21 days after vaccination) and Bell's palsy (IRR, 1.29; 95% CI: 1.08–1.56 at 15–21 days) with ChAdOx1nCoV-19. There was an increased risk of hemorrhagic stroke (IRR, 1.38; 95% CI: 1.12–1.71 at 15–21 days) with BNT162b2.
- There was a substantially higher risk of all neurological outcomes in the 28 days after a positive SARS-CoV-2 test including Guillain–Barré syndrome (IRR, 5.25; 95% CI: 3.00–9.18).
- Overall, we estimated 38 excess cases of Guillain–Barré syndrome per 10 million people receiving ChAdOx1nCoV-19 and 145 excess cases per 10 million people after a positive SARS-CoV-2 test.
- CONCLUSION: In summary, the risk of neurologic complications is significantly greater with SARS-C0V-2 infection than after COVID-19 vaccines.

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Villar J, Ariff S, Gunier RB et al. **Maternal and Neonatal Morbidity and Mortality Among Pregnant Women With and Without COVID-19 Infection: The INTERCOVID Multinational Cohort Study.** JAMA Pediatr. 2021;175(8):817-826. **doi:10.1001/jamapediatrics.2021.1050**

Objective To evaluate the risks associated with COVID-19 in pregnancy on maternal and neonatal outcomes compared with not-infected, concomitant pregnant individuals.

Design, Setting, and Participants In this cohort study that took place from March to October 2020, involving 43 institutions in 18 countries, 2 unmatched, consecutive, not-infected women were concomitantly enrolled immediately after each infected woman was identified, at any stage of pregnancy or delivery, and at the same level of care to minimize bias. Women and neonates were followed up until hospital discharge.

Exposures COVID-19 in pregnancy determined by laboratory confirmation of COVID-19 and/or radiological pulmonary findings or 2 or more predefined COVID-19 symptoms.

Main Outcomes and Measures The primary outcome measures were indices of (maternal and severe neonatal/perinatal) morbidity and mortality; the individual components of these indices were secondary outcomes. Models for these outcomes were adjusted for country, month entering study, maternal age, and history of morbidity.

Results A total of 706 pregnant women with COVID-19 diagnosis and 1424 pregnant women without COVID-19 diagnosis were enrolled, all with broadly similar demographic characteristics (mean [SD] age, 30.2 [6.1] years). Overweight early in pregnancy occurred in 323 women (48.6%) with COVID-19 diagnosis and 554 women (40.2%) without. Women with COVID-19 diagnosis were at higher risk for preeclampsia/eclampsia (relative risk [RR], 1.76; 95% CI, 1.27-2.43), severe infections (RR, 3.38; 95% CI, 1.63-7.01), intensive care unit admission (RR, 5.04; 95% CI, 3.13-8.10), maternal mortality (RR, 22.3; 95% CI, 2.88-172), preterm birth (RR, 1.59; 95% CI, 1.30-1.94), medically indicated preterm birth (RR, 1.97; 95% CI, 1.56-2.51), severe neonatal morbidity index (RR, 2.66; 95% CI, 1.69-4.18), and severe perinatal morbidity and mortality index (RR, 2.14; 95% CI, 1.66-2.75). Fever and shortness of breath for any duration was associated with increased risk of severe maternal complications (RR, 2.56; 95% CI, 1.92-3.40) and neonatal complications (RR, 4.97; 95% CI, 2.11-11.69). Asymptomatic women with COVID-19 diagnosis remained at higher risk only for maternal morbidity (RR, 1.24; 95% CI, 1.00-1.54) and preeclampsia (RR, 1.63; 95% CI, 1.01-2.63). Among women who tested positive (98.1% by real-time polymerase chain reaction), 54 (13%) of their neonates tested positive. Cesarean delivery (RR, 2.15; 95% CI, 1.18-3.91) but not breastfeeding (RR, 1.10; 95% CI, 0.66-1.85) was associated with increased risk for neonatal test positivity.

Conclusions and Relevance In this multinational cohort study, COVID-19 in pregnancy was associated with consistent and substantial increases in severe maternal morbidity and mortality and neonatal complications when pregnant women with and without COVID-19 diagnosis were compared. The findings should alert pregnant individuals and clinicians to implement strictly all the recommended COVID-19 preventive measures.

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Matta J, Wiernik E, Robineau O et al. **Association of Self-reported COVID-19 Infection and SARS-CoV-2 Serology Test Results with Persistent Physical Symptoms Among French Adults During the COVID-19 Pandemic**. JAMA Intern Med. Published online November 8, 2021. **doi:10.1001/jamainternmed.2021.6454**

- BACKGROUND: After an infection by SARS-CoV-2, many patients present with persistent physical symptoms that may impair their quality of life. Beliefs regarding the causes of these symptoms may influence their perception and promote maladaptive health behaviors.
- OBJECTIVE: To examine the associations of self-reported COVID-19 infection and SARS-CoV-2 serology test results with persistent physical symptoms (eg, fatigue, breathlessness, or impaired attention) in the general population during the COVID-19 pandemic.
- STUDY DESIGN: Participants in this cross-sectional analysis were 26 823 individuals from the French population-based CONSTANCES cohort, included between 2012 and 2019. Between May and November 2020, an enzyme-linked immunosorbent assay was used to detect anti–SARS-CoV-2 antibodies. Between December 2020 and January 2021, the participants reported whether they believed they had experienced COVID-19 infection and had physical symptoms during the previous 4 weeks that had persisted for at least 8 weeks. Participants who reported having an initial COVID-19 infection only after completing the serology test were excluded.
- OUTCOMES: Logistic regressions for each persistent symptom as the outcome were computed in models including both self-reported COVID-19 infection and serology test results and adjusting for age, sex, income, and educational level.
- RESULTS: Of 35 852 volunteers invited to participate in the study, 26 823 (74.8%) with complete data were included in the present study (mean [SD] age, 49.4 [12.9] years; 13 731 women [51.2%]). Self-reported infection was positively associated with persistent physical symptoms, with odds ratios ranging from 1.39 (95% CI, 1.03-1.86) to 16.37 (95% CI, 10.21-26.24) except for hearing impairment (odds ratio, 1.45; 95% CI, 0.82-2.55) and sleep problems (odds ratio, 1.14; 95% CI, 0.89-1.46). A serology test result positive for SARS-COV-2 was positively associated only with persistent anosmia (odds ratio, 2.72; 95% CI, 1.66-4.46), even when restricting the analyses to participants who attributed their symptoms to COVID-19 infection. Further adjusting for self-rated health or depressive symptoms yielded similar results. There was no significant interaction between belief and serology test results.
- CONCLUSIONS AND RELEVANCE: The findings of this cross-sectional analysis of a large, population-based French cohort suggest that persistent physical symptoms after COVID-19 infection may be associated more with the belief in having been infected with SARS-CoV-2 than with having laboratory-confirmed COVID-19 infection. Further research in this area should consider underlying mechanisms that may not be specific to the SARS-CoV-2 virus. A medical evaluation of these patients may be needed to prevent symptoms due to another disease being erroneously attributed to “long COVID.”

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EPIDEMIOLOGY

Sami S, et al. **Community Transmission of SARS-CoV-2 Associated with a Local Bar Opening Event -- Illinois, February 2021.** MMWR Morb Mortal Wkly Rep 2021; ePub: 5 April **DOI: 10.15585/mmwr.mm7014e3.**

- During February 2021, an opening event held indoors at a rural Illinois bar that accommodates approximately 100 persons led to a COVID-19 outbreak. Although masks and social distancing were recommended by signage, this was not enforced.
- There were 6 bar tenders in the unventilated space which accomodates 100 people.
- Through routine testing and contact tracing, local health department staff members identified a cluster of cases linked to the bar event, including a case in an asymptomatic attendee who received a confirmed COVID-19 diagnosis the day before the event.
- By 2 weeks after the event, 29 confirmed bar attendee cases were identified, including 26 (89.7%) in bar patrons and three (10.3%) in employees.
- At least 71 close contacts of persons with bar attendee COVID-19 were reported, among whom 37 received testing & 17 received a positive test result within 14 days of the contact. Two persons with secondary COVID-19 were school-related contacts of persons with bar attendee COVID-19, three were long-term care facility(LTCF) contacts, and 12 were household contacts.
- As a result of the school-related contacts, the school district closed for 2 weeks because 13 staff members were in isolation, in quarantine, or absent because their own child was quarantined.
- One bar attendee who worked at a LTCF was asymptomatic but received a positive test result during routine COVID-19 testing 4 days after the event. All LTCF residents and staff members were then tested: three secondary cases in persons who were close contacts of the bar attendee with COVID-19 were identified. None had received a COVID-19 vaccination.
- 12 household contacts in 8 different households had positive SARS-CoV-2 test results, including 5 school-aged children. Secondary household cases were linked to 9 of 29 bar attendee cases.
- Before the event, the Illinois DPH reported a 7-day average daily COVID-19 incidence of 41–42 cases/ 100,000 persons in the county; 14 days after the event, the 7-day average daily incidence had more than doubled, to 86–87 cases/ 100,000 persons.
- CONCLUSION: As community businesses begin to reopen, adherence to public health prevention and mitigation guidelines to reduce additional community transmission remains very important.

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Brown CM, Vostok J, Johnson H, et al. **Outbreak of SARS-CoV-2 Infections, Including COVID-19 Vaccine Breakthrough Infections, Associated with Large Public Gatherings — Barnstable County, Massachusetts, July 2021.** MMWR Morb Mortal Wkly Rep. ePub: 30 July 2021. **DOI: http://dx.doi.org/10.15585/mmwr.mm7031e2external icon.**

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Paul LA, Daneman N, Schwartz KL et al. **Association of Age and Pediatric Household Transmission of SARS-CoV-2 Infection.** JAMA Pediatr. Published online August 16, 2021. doi:10.1001/jamapediatrics.2021.2770

- To assess differences in the odds of household transmission of SARS-CoV-2 by younger children compared with older children, a population-based cohort study took place between 6/1 and 12/31, 2020, in Ontario, Canada. Private households in which the index case individual of laboratory-confirmed SARS-CoV-2 infection was younger than 18 years were included. Pediatric index cases were categorized as 0 to 3, 4 to 8, 9 to 13, and 14 to 17 years.
- The main outcome was household transmission, defined as households where at least 1 secondary case occurred 1 to 14 days after the pediatric index case.
- RESULTS: A total of 6280 households had pediatric index cases, and 1717 households (27.3%) experienced secondary transmission. Children aged 0 to 3 years had the highest odds of transmitting SARS-CoV-2 to household contacts compared with children aged 14 to 17 years (OR, 1.43; 95% CI, 1.17-1.75). Children aged 4 to 8 years and 9 to 13 years also had increased odds of transmission (aged 4-8 years: OR, 1.40; 95% CI, 1.18-1.67; aged 9-13 years: OR, 1.13; 95% CI, 0.97-1.32).
- CONCLUSION: Younger children may be more likely to transmit SARS-CoV-2 infection compared with older children, and the highest odds of transmission was observed for children aged 0 to 3 years.

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Yates T, Zaccardi F, Islam N et al. **Obesity, ethnicity and risk of critical care, mechanical ventilation and mortality in patients admitted to hospital with COVID-19: Analysis of the ISARIC CCP-UK cohort.** OBESITY 2021; First published: 23 March 2021 https://doi.org/10.1002/oby.23178

- To investigate the association of obesity with in-hospital COVID-19 outcomes in different ethnic groups, records of pts admitted to hospital with COVID-19 in the UK through the Clinical Characterisation Protocol UK (CCP-UK) from 6th February to 12th October 2020 were evaluated. Ethnicity was classified as: white, South Asian, black and other minority ethnic groups. Outcomes were admission to critical care, mechanical ventilation and in-hospital mortality, adjusted for age, sex and chronic diseases.
- RESULTS: [54,254 pts; mean age = 76 years; 45.0% women; white]; [3,728 pts; mean age =57 years; 41.1%; South Asian]; 2,523 pts; mean age = 58 years; 44.9%; black]; 5,427 pts; mean age=61 years; 40.8%; other ethnicities.
- Obesity was associated with all outcomes in all ethnic groups, with associations strongest for black ethnicities. When stratified by ethnicity and obesity status, the OR for admission to critical care, mechanical ventilation and mortality in black ethnicities with obesity were 3.91 (3.13, 4.88), 5.03 (3.94, 6.63), 1.93 (1.49, 2.51) respectively, compared to white ethnicities without obesity.
- CONCLUSIONS: Obesity was associated with an elevated risk of in-hospital COVID-19 outcomes in all ethnic groups, with associations strongest in black ethnicities.

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Gao M, Piernas C, Hippisley-cox J et al. **Associations between body-mass index and COVID-19 severity in 6·9 million people in England: a prospective, community-based, cohort study.** Lancet 2021; Published: April 28, 2021. **DOI:https://doi.org/10.1016/S2213-8587(21)00089-9**

- To examine this association between obesity and COVID-19 severity, including interactions with demographic and behavioural characteristics, type 2 diabetes, and other health conditions, a prospective, community-based, cohort study used de-identified patient-level data from the QResearch database of general practices in England, UK for registered pts >/=20 years between 1/24/2020 and 4/30/202 with available BMI data.
- Data extracted included demographic, clinical, clinical values linked with England's database of positive SARS-CoV-2 test results, and death certificates from the Office of National Statistics. Outcomes, as a proxy measure of severe COVID-19, were admission to hospital, admission to an ICU and death due to COVID-19.
- RESULTS: Among 6 910 695 eligible individuals (mean BMI 26·78 kg/m2 [SD 5·59]), 13 503 (0·20%) were admitted to hospital, 1601 (0·02%) to an ICU, and 5479 (0·08%) died after a positive test for SARS-CoV-2. There was a J-shaped association between BMI & hospital admission due to COVID-19 (adjusted hazard ratio [HR] per kg/m2 from the nadir at BMI of 23 kg/m2 of 1·05 [95% CI 1·05–1·05]) & death (1·04 [1·04–1·05]), & a linear association across the whole BMI range with ICU admission (1·10 [1·09–1·10]).
- We found a significant interaction between BMI and age and ethnicity, with higher hazard ratio per kg/m2 above BMI 23 kg/m2 for younger people (adjusted HR per kg/m2 above BMI 23 kg/m2 for hospital admission 1·09 [95% CI 1·08–1·10] in 20–39 years age group vs 80–100 years group 1·01 [1·00–1·02]) and Black people than White people (1·07 [1·06–1·08] vs 1·04 [1·04–1·05]).
- Risk of admission to hospital & ICU due to COVID-19 associated with unit increase in BMI was slightly lower in people with T2DM, HTN and cardiovascular disease vs those without these morbidities.
- INTERPRETATION: At a BMI of more than 23 kg/m2, we found a linear increase in risk of severe COVID-19 leading to admission to hospital and death, and a linear increase in admission to an ICU across the whole BMI range, not attributable to excess risks of related diseases. The relative risk due to increasing BMI is particularly notable people younger than 40 years and of Black ethnicity.

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Jones JM, Stone M, Sulaeman H, et al. **Estimated US Infection- and Vaccine-Induced SARS-CoV-2 Seroprevalence Based on Blood Donations, July 2020-May 2021.** JAMA. Published online September 02, 2021. **doi:10.1001/jama.2021.15161**

- Objective: To estimate trends in SARS-CoV-2 seroprevalence related to infection and vaccination in the US population.
- Design, Setting, and Participants: In a repeated cross-sectional study conducted each month during July 2020 through May 2021, 17 blood collection organizations with blood donations from all 50 US states; Washington, DC; and Puerto Rico were organized into 66 study-specific regions, representing a catchment of 74% of the US population. For each study region, specimens from a median of approximately 2000 blood donors were selected and

tested each month until May 31,2021; a total of 1 594 363 specimens were initially selected and tested.

- Main Outcomes and Measures: Proportion of persons with detectable SARS-CoV-2 spike and nucleocapsid antibodies. Seroprevalence was weighted for demographic differences between the blood donor sample and general population. Infection-induced seroprevalence was defined as the prevalence of the population with both spike and nucleocapsid antibodies. Combined infection- and vaccination-induced seroprevalence was defined as the prevalence of the population with spike antibodies. The seroprevalence estimates were compared with cumulative COVID-19 case report incidence rates.
- RESULTS: Among 1 443 519 specimens included, 50.8%) were from women, 12.1% were from persons aged 16-29 yrs, 20.2% were from persons aged > 65 yrs and older; 2.5% were from non-Hispanic Black persons, & 6.1%) were from Hispanic persons. The overall infection-induced SARS-CoV-2 seroprevalence estimate increased from 3.5% (95% CI, 3.2%-3.8%) in July 2020 to 20.2% (95% CI, 19.9%-20.6%) in May 2021; the combined infection- and vaccination-induced seroprevalence estimate in May 2021 was 83.3% (95% CI, 82.9%-83.7%). By May 2021, 2.1 SARS-CoV-2 infections (95% CI, 2.0-2.1) per reported COVID-19 case were estimated to have occurred.
- CONCLUSIONS: Based on a sample of blood donations in the US from July 2020 through May 2021, vaccine- and infection-induced SARS-CoV-2 seroprevalence increased over time and varied by age, race/ethnicity & geographic region. The combined infection- and vaccination-induced seroprevalence estimate in May 2021 was 83.3% (95% CI, 82.9%-83.7%). By May 2021, 2.1 SARS-CoV-2 infections (95% CI, 2.0-2.1) per reported COVID-19 case were estimated to have occurred.

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Hagan LM, et al. **Outbreak of SARS-CoV-2 B.1.617.2 (Delta) variant infections among incarcerated persons in a federal prison -- Texas, July-August 2021.** MMWR 2021; Published September 21, 2021.

- Hagan and colleagues examined data from an outbreak at a federal prison involving 233 inmates in two housing units in July 2021. On July 8, 3 inmates reported symptoms such as nasal inflammation, cough, headache, myalgia, and rhinorrhea, but were not tested for SARS-CoV-2. On July 12, 18 inmates, including the prior three who reported symptoms, were symptomatic and tested with rapid antigen tests. Eleven of 18 were fully vaccinated. From July 12 to August 14, all 233 inmates with reported or known exposures were given rapid antigen testing, and some were tested via rapid testing and RT-PCR. A subset of 70 people provided symptom data through questionnaires, and daily nasal swabs for up to 20 days.
- RESULTS: Overall, 79% of the 233 inmates were fully vaccinated, and almost three-quarters of all inmates tested positive for SARS-CoV-2. Among 58 specimens undergoing genomic sequencing, all were from the Delta variant.
- Thirty-nine of 42 unvaccinated inmates tested positive (93%) versus 129 of 185 vaccinated inmates (70%; P=0.002). Among fully vaccinated seronegative people, attack rates were significantly higher among those who received Pfizer versus the Moderna vaccine (85% vs 54%, P<0.001). But 76% of fully vaccinated inmates who received the Pfizer/BioNTech vaccine were vaccinated at least 4 months prior to the outbreak, while all the fully vaccinated Moderna recipients were vaccinated within 4 months of the outbreak.

- Three of four of those hospitalized were unvaccinated, and one unvaccinated person required ICU care, including mechanical ventilation, and ultimately died, they noted.
- CONCLUSIONS: The high number of infections in vaccinated persons and presence of infectious virus in specimens from both unvaccinated and vaccinated infected persons underscore the importance of implementing and maintaining multiple COVID-19 prevention strategies in settings where physical distancing is challenging, even when vaccination coverage is high.

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Semenzato L, Botton J, Drouin J et al. **Chronic diseases, health conditions and risk of COVID-19-relatedhospitalization and in-hospital mortality during the first wave of the epidemic in France: a cohort study of 66 million people.** The Lancet Regional Health - Europe 8 (2021) 100158. **https://doi.org/10.1016/j.lanepe.2021.100158.**

Field Code Changed

- To assess conditions associated with increased risk with COVID-19 infection, a French cohort was constituted comprising all people alive on February 15, 2020. Data were censored at 15 June 2020 for COVID-19-related hospitalization and at 15 July 2020 for death for patients still hospitalized for COVID-19 on 15 June 2020.
- Cox proportional hazards models were used to estimate hazard ratios (HR) for the associations between 47 potential comorbidities and the risk of COVID-19-related hospitalization or death.
- RESULTS: In a population of 66,050,090 people, 87,809 people (134 per 100,000) were hospitalized for COVID-19 between February 15, 2020 and June 15, 2020 and a subgroup of 15,661 people (24 per 100,000) died in hospital.
- A much higher risk was observed with increasing age, reaching a risk of hospitalization for COVID-19 > 5 fold higher and a risk of COVID-19-related in-hospital mortality >100-fold higher in people aged ≥85 years (absolute risks of 750 and 268 per 100,000, respectively) vs. people aged 40-44 yrs.
- Men were at higher risk of COVID-19-related hospitalization aHR 1·38 [1·36-1·40]) and COVID-19-related in-hospital mortality (aHR 2·08 [2·01-2·16]) compared to women.
- All chronic health conditions except dyslipidemia were positively associated with an increased risk of COVID-19-related hospitalization and in-hospital mortality.
- The strongest associations for COVID-19-related hospitalization and in-hospital mortality were observed in people with Down syndrome (7·0 [6·1-8·1] and 22·9 [17·1-30·7]), mental retardation (3·8 [3·5-4·2] and 7·3 [6·1-8·8]), kidney transplantation (4·6 [4·2-5·0] and 7·1 [6·0-8·4]), lung transplantation (3·5 [2·4-5·3] and 6·2 [2·8-14·0]) ESRD on dialysis (4·2 [3·9-4·4] and 4·7 [4·2-5·2]) and active lung cancer (2·6 [2·4-2·8] and 4·0 [3·5-4·6]).

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Pulliam JR, van Schalkwyk C, Govender N et al. **Increased risk of SARS-CoV-2 reinfection associated with emergence of the Omicron variant in South Africa.** medRxiv Dec 3, 2021. **doi: https://doi.org/10.1101/2021.11.11.21266068**

- OBJECTIVE: To examine whether SARS-CoV-2 reinfection risk has changed through time in South Africa, in the context of the emergence of the Beta, Delta, and Omicron variants

- DESIGN: Retrospective analysis of routine epidemiological surveillance data on SARS-CoV-2 with specimen receipt dates between 04 March 2020 and 27 November 2021, collected through South Africa's National Notifiable Medical Conditions Surveillance System.
- PARTICIPANTS: 2,796,982 individuals with laboratory-confirmed SARS-CoV-2 who had a positive test result at least 90 days prior to 27 November 2021. Individuals having sequential positive tests at least 90 days apart were considered to have suspected reinfections.
- OUTCOME MEASURES: Incidence of suspected reinfections through time.
- RESULTS: 35,670 suspected reinfections were identified among 2,796,982 individuals with laboratory-confirmed SARS-CoV-2. Although increases in the hazard of primary infection were observed following the introduction of both the Beta and Delta variants, no corresponding increase was observed in the reinfection hazard: the estimated HR for reinfection versus primary infection was lower during waves driven by the Beta & Delta variants than for the first wave (relative HR for wave 2 versus wave 1: 0.75 (CI95: 0.59-0.97); for wave 3 versus wave 1:0.71 (CI95: 0.56-0.92).
- In contrast, the recent spread of the Omicron variant has been associated with a decrease in the hazard of primary infection and an increase in reinfection hazard. The estimated HR for reinfection vs primary infection for the period from 1/11/ 2021 to 27/11/2021 vs wave 1 was 2.39 (CI95: 1.88-3.11).
- CONCLUSION: Population-level evidence suggests that the Omicron variant is associated with substantial ability to evade immunity from prior infection. In contrast, there is no population-wide epidemiological evidence of immune escape associated with the Beta or Delta variants. Urgent questions remain regarding whether Omicron is also able to evade vaccine-induced immunity & the implications of reduced immunity to infection on protection against severe disease and death.

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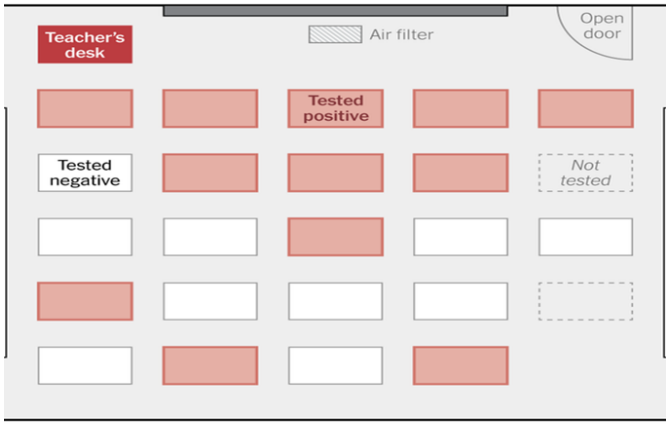
Arias E, Tejada-Vera B, Ahmad F et al. **Provisional Life Expectancy Estimates for 2020.** Vital Statistics Rapid Release. Report No. 015 □ July 2021

- BACKGROUND: This report presents life expectancy estimates calculated using abridged period life tables based on provisional death counts for 2020, by sex, for the total, Hispanic, non-Hispanic white and non-Hispanic black populations.
- Provisional mortality rates are typically computed using death data after a 3-month lag following date of death, as completeness and timeliness of provisional death data can vary by many factors, including cause of death, month of the year, and age of the decedent.
- Mortality data used in this report include over 99% of the deaths that occurred in 2020.
- REsULTS: In 2020, life expectancy at birth for the total U.S. population was 77.3 years, declining by 1.5 years from 78.8 in 2019. Life expectancy at birth for males was 74.5 years in 2020, representing a decline of 1.8 years from 76.3 years in 2019. For females, life expectancy declined to 80.2 years, decreasing 1.2 years from 81.4 years in 2019.
- For females and males, the decline in life expectancy was mostly due to increases in mortality due to COVID-19.
- Between 2019 and 2020, life expectancy decreased by 3.0 years for the Hispanic population (81.8 to 78.8) and by 2.9 years for the non-Hispanic black population (74.7 to 71.8) and by 1.2 years for the non-Hispanic white population (78.8 to 77.6).

- CONCLUSIONS: U.S. life expectancy at birth for 2020, based on nearly final data, was 77.3 years, the lowest it has been since 2003. Male life expectancy (74.5) declined to a level not seen since 2003, while female life expectancy (80.2) returned to the lowest level since 2005.
- Mortality due to COVID-19 had, by far, the single greatest effect on the decline in life expectancy at birth, overall, among men and women, and for the three race and Hispanic-origin groups.
- **********
- Lam-Hine T, McCurdy SA, Santora L, et al. **Outbreak Associated with SARS-CoV-2 B.1.617.2 (Delta) Variant in an Elementary School — Marin County, California, May–June 2021.** MMWR Morb Mortal Wkly Rep 2021;70:1214–1219.
  DOI: http://dx.doi.org/10.15585/mmwr.mm7035e2
- BACKGROUND: On May 25, 2021, the Marin County Department of Public Health (MCPH) was notified by an elementary school that on May 23, an unvaccinated teacher had reported receiving a positive test result for SARS-CoV-2, the virus that causes COVID-19. The teacher reported becoming symptomatic on May 19, but continued to work for 2 days before receiving a test on May 21. On occasion during this time, the teacher read aloud unmasked to the class despite school requirements to mask while indoors. Beginning May 23, additional cases of COVID-19 were reported among other staff members, students, parents, and siblings connected to the school.
- DESIGN: Case investigation and contact tracing that included whole genome sequencing (WGS) of available specimens was performed. A total of 27 COVID-19 cases were identified in the school, including that of the teacher. During May 23–26, among the teacher's 24 students, 22 students, all ineligible for vaccination because of age, received testing for SARS-CoV-2; 12(50%) received positive test results. The attack rate in the two rows seated closest to the teacher's desk was 80% (eight of 10) and was 28% (four of 14) in the three back rows (Fisher's exact test; p = 0.036).(See below)
- CONCLUSION: This outbreak of COVID-19 that originated with an unvaccinated teacher highlights the importance of vaccinating school staff members who are in close indoor contact with children ineligible for vaccination as schools reopen and the importance of masking. The outbreak's attack rate highlights the Delta variant's increased transmissibility and potential for rapid spread, especially in unvaccinated populations such as schoolchildren too young for vaccination.


Teacher's desk
Air filter
Open door
Tested positive
Tested negative
Not tested

TREATMENT

Ramakrishnan S, Nicolau DV, Langford B et al. **Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomized controlled trial**. Lancet Inf Dis. Published: April 09, 2021. DOI:https://doi.org/10.1016/S2213-2600(21)00160-0

• BACKGROUND. Multiple reports of pts admitted to hospital with COVID-19 showed that those with chronic respiratory disease were significantly under-represented. We hypothesized that widespread use of inhaled glucocorticoids among these patients was responsible for this finding.

• To test the hypothesis that inhaled glucocorticoids would be effective treatment for early COVID-19, we performed an open-label, parallel-group, phase 2 RCT of inhaled budesonide, compared with usual care, in adults within 7 days of the onset of mild COVID-19 symptoms. Pts were stratified for age (≤40 years or >40 years), sex, and number of comorbidities (≤1 and ≥2).

• The primary endpoint was COVID-19-related urgent care visit, including ED assessment or hospitalization, analyzed for both the per-protocol and intention-to-treat (ITT) populations. The secondary outcomes were self-reported clinical recovery (symptom resolution), viral symptoms, body temperature, blood O2 saturation, and SARS-CoV-2 viral load.

• The trial was stopped early after independent statistical review concluded that study outcome would not change with further participant enrolment.

• RESULTS: From 7/16 to 12/9, 2020, 146 participants were randomly assigned—73 to usual care and 73 to budesonide. For the per-protocol population (n=139), the primary outcome occurred in ten (14%) participants in the usual care group and one (1%) of 69 participants in the budesonide group (difference in proportions 0·131, 95% CI 0·043 to 0·218; p=0·004). For the ITT population, the primary outcome occurred in 11 (15%) participants in the usual care group and two (3%) participants in the budesonide group (difference in proportions 0·123, 95% CI 0·033 to 0·213; p=0·009).

• Clinical recovery was shorter in the budesonide group compared with the usual care group (median 7 days [95% CI 6 to 9] vs 8 days [7 to 11]; log-rank test p=0·007). Mean proportion of days with fever and the proportion of participants with > 1 day of fever was lower in the budesonide group (2%, SD 6) than the usual care group (8%, SD 18; Wilcoxon test p=0·051). Fewer budesonide participants had persistent symptoms at days 14 and 28 compared with usual care participants (difference in proportions 0·204, 95% CI 0·075 to 0·334; p=0·003). Blood O2 saturations & SARS-CoV-2 load were not different between groups. 5 (7%) budesonide participants reported self-limiting adverse events.

• INTERPRETATION: Early administration of inhaled budesonide reduced the likelihood of needing urgent medical care and reduced time to recovery after early COVID-19.

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Grieco DL, Menga LS, Cesarano M et al. **Effect of Helmet Noninvasive Ventilation vs High-Flow Nasal Oxygen on Days Free of Respiratory Support in Patients With COVID-19 and Moderate to Severe Hypoxemic Respiratory Failure:** The HENIVOT Randomized Clinical Trial. JAMA. 2021;325(17):1731-1743. **doi:10.1001/jama.2021.4682**

- To assess whether helmet noninvasive ventilation can increase the days free of respiratory support in patients with COVID-19 compared with high-flow nasal oxygen alone, a multicenter RCT was performed in 4 ICUs between October and December 2020, end of follow-up February 11, 2021, including 109 patients with COVID-19 and moderate to severe hypoxemic respiratory failure (ratio of partial pressure of arterial oxygen to fraction of inspired oxygen ≤200).
- Pts were randomly assigned to receive continuous treatment with helmet noninvasive ventilation (positive end-expiratory pressure, 10-12 cm H2O; pressure support, 10-12 cm H2O) for at least 48 hrs eventually followed by high-flow nasal oxygen (n = 54) or high-flow oxygen alone (60 L/min) (n = 55).
- RESULTS: 109 pts (99%) completed the trial (median age, 65 years [interquartile range {IQR}, 55-70]; 21 women [19%]). The median days free of respiratory support within 28 days after randomization were 20 (IQR, 0-25) in the helmet group and 18 (IQR, 0-22) in the high-flow nasal oxygen group (mean difference, 2 days [95% CI, −2 to 6]; P = .26). The rate of endotracheal intubation was significantly lower in the helmet group than in the high-flow nasal oxygen group (30% vs 51%; difference, −21% [95% CI, −38% to −3%]; P = .03). The median number of days free of invasive mechanical ventilation within 28 days was significantly higher in the helmet group than in the high-flow nasal oxygen group (28 [IQR, 13-28] vs 25 [IQR 4-28]; mean difference, 3 days [95% CI, 0-7]; P = .04). The rate of in-hospital mortality was 24% in the helmet group and 25% in the high-flow nasal oxygen group (absolute difference, −1% [95% CI, −17% to 15%]; P > .99).
- CONCLUSION: Among patients with COVID-19 and moderate to severe hypoxemia, treatment with helmet noninvasive ventilation, compared with high-flow nasal oxygen, resulted in no significant difference in the number of days free of respiratory support within 28 days. However, intubation rate was significantly lower in the helmet group & days free of mechanical ventilation were significantly higher. There was no difference in mortality rate.

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Banerjee J, Canamar CP, Voyageur C et al. **Mortality and Readmission Rates Among Patients With COVID-19 After Discharge From Acute Care Setting With Supplemental Oxygen.** JAMA Network Open; 2021;4(4):e213990. Published online, 4/4/2021. **doi:10.1001/jamanetworkopen.2021.3990**

- To assess outcomes of patients with COVID-19 pneumonia discharged to home or quarantine housing with ≤ 3L of supplemental home O2, outcomes of 621 adult pts discharged from 2 large urban public hospitals from 3/20 to 8/19/2020 were evaluated.
- Pts were discharged with home O2 equipment, educational resources and nursing telephone F/U within 12 to 18 hours of discharge.
- RESULTS: Of 621 pts (65% male, median age 51 yrs[IQR 45-61 yrs]), all-cause mortality rate was 1.3% (95% CI, 0.6%-2.5%) and 30-day return hospital admission rate was 8.5% (95% CI, 6.2%-10.7%) with a median follow-up time of 26 days (interquartile range, 15-55 days). No deaths occurred in the ambulatory setting.
- CONCLUSIONS: In this cohort study, pts with COVID-19 pneumonia discharged on home O2 had low rates of mortality and return admission. within 30 days of discharge. Ambulatory management of COVID-19 with home O2 has an acceptable safety profile if acute care access is preserved.

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HYill A, Garratt A, Levi J et al. **Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection.** Open Forum Infectious Diseases. Published: 07 July 2021. https://doi.org/10.1093/ofid/ofab358

- Ivermectin, an anti-parasitic drug, has shown in-vitro activity against SARS-COV-2 at high concentrations and has been evaluated in multiple small trials as treatment for COVID-19.
- This meta-analysis investigated ivermectin in 24 randomized clinical trials (3328 patients) identified through systematic searches of PUBMED, EMBASE, MedRxiv and trial registries. Sample sizes ranged from 24 to 400 participants. Eight of the studies had been published, nine were preprints.
- RESULTS: Studies varied widely in terms of dosage, treatment duration, and inclusion criteria. Studies also included a range of comparators, including hydroxychloroquine, lopinavir/ritonavir, standard of care, and placebo.
- In 11 trials (totaling 2,127 pts) that focused on moderate/severe infection, there was a 56% reduction in mortality ([RR] 0.44, 95% CI 0.25-0.77, P=0.004), with 3% of pts on ivermectin dying compared with 9% of controls. However, the total number of deaths was small (128) and there was no difference between ivermectin and controls in the subgroup with severe disease.
- Use of ivermectin was associated with a reduction in time to recovery of 1.58 days compared with controls (95% CI -2.8 to -0.35, P=0.01) and with a shorter duration of hospitalization (-4.27 days, 95% CI -8.6 to -0.06, P=0.05).
- CONCLUSION: Although there are suggested benefits of ivermectin in COVID pts with moderate/severe disease, results need to be validated in larger confirmatory randomized trials.

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Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. JAMA. 2021;326(6):499-518. doi:10.1001/jama.2021.11330. Published 7/11/2021.

- BACKGROUND: Excessive systemic inflammation and raised IL-6 levels resulting from dysregulated host immune responses are associated with adverse clinical outcomes in pts hospitalized with COVID-19. This led to use of IL-6 antagonists – monoclonal antibodies – as treatment but RCTs have shown variable results.
- To estimate the association between administration of IL-6 antagonists compared with usual care or placebo and 28-day all-cause mortality and other outcomes, a SR and M/A were performed of RCTs identified between October 2020 and January 2021.
- Eligible trials randomly assigned patients hospitalized for COVID-19 to a group in whom IL-6 antagonists were administered and to a group in whom neither IL-6 antagonists nor any other immunomodulators except corticosteroids were administered. Among 72 potentially eligible trials, 27 (37.5%) met study selection criteria.
- The primary outcome measure was all-cause mortality at 28 days after randomization. There were 9 secondary outcomes including progression to invasive mechanical ventilation or death and risk of secondary infection by 28 days.

- RESULTS: A total of 10 930 patients (median age, 61 years [range of medians, 52-68 years]; 3560 [33%] were women) participating in 27 trials were included. By 28 days, there were 1407 deaths among 6449 patients randomized to IL-6 antagonists and 1158 deaths among 4481 patients randomized to usual care or placebo (summary OR, 0.86 [95% CI, 0.79-0.95]; P = .003) This corresponds to an absolute mortality risk of 22% for IL-6 antagonists compared with an assumed mortality risk of 25% for usual care or placebo.
- The ORs for the association with progression to invasive mechanical ventilation or death, compared with usual care or placebo, were 0.77 (95% CI, 0.70-0.85) for all IL-6 antagonists, 0.74 (95% CI, 0.66-0.82) for tocilizumab, and 1.00 (95% CI, 0.74-1.34) for sarilumab. Secondary infections by 28 days occurred in 21.9% of patients treated with IL-6 antagonists vs 17.6% of patients treated with usual care or placebo (OR accounting for trial sample sizes, 0.99; 95% CI, 0.85-1.16).
- CONCLUSIONS: In this prospective meta-analysis of clinical trials of pts hospitalized for COVID-19, administration of IL-6 antagonists, compared with usual care or placebo, was associated with lower 28-day all-cause mortality.

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Temple C, Hoang R, Hendrikson RG. **Toxic Effects from Ivermectin Use Associated with Prevention and Treatment of Covid-19**. NEJM, October 20, 2021. **DOI: 10.1056/NEJMc2114907.**

- Ivermectin, an oral treatment for intestinal parasites in animals. may decrease severe acute SARS-CoV-2 replication in vitro, but RCTs have shown no clinical benefit in the prevention or Covid-19. However, “veterinary” use of ivermectin has increased, and the number of prescriptions for use by humans in the United States is 24 times as high as the number before the pandemic. Moreover, the number of such prescriptions in August 2021 was 4 times as high as the number in July 2021.
- To investigate potential toxic effects of Ivermectin use, calls related to this drug for the month of August, 2021 to a statewide poison control center were evaluated.
- RESULTS: The rate of calls regarding ivermectin had been 0.25 calls per month in 2020 and had increased to 0.86 calls per month from January through July 2021; in August 2021, the center received 21 calls. Monthly total call volumes for all poison exposures were stable in 2020-21.
- Of the 21 persons who called in August, 11 were men with median age, 64; range, 20 to 81. Half were reported to have used ivermectin to prevent Covid-19, and the remainder had been using the drug to treat Covid-19 symptoms. Three persons had received prescriptions from physicians or veterinarians, and 17 had purchased veterinary formulations.
- Symptoms developed in most pts within 2 hrs after a large, single, first-time dose. In six, symptoms developed gradually after days to weeks of repeated doses taken every other day or twice weekly.
- 6/ 21 persons were hospitalized for toxic effects from ivermectin use; all 6 reported preventive use, including the 3 who had obtained the drug by prescription. Four received care in an intensive care unit, and none died. Symptoms were gastrointestinal distress in 4 persons, confusion in 3, ataxia and weakness in 2, hypotension in 2, and seizures in 1. Of the persons who were not admitted to a hospital, most had gastrointestinal distress, dizziness, confusion, vision symptoms, or rash.

- CONCLUSION: These cases illustrate the potential toxic effects of ivermectin has potential toxic, side effects including severe episodes of confusion, ataxia, seizures, and hypotension, and the increasing frequency of inappropriate use. There is insufficient evidence to support use of ivermectin to treat or prevent Covid-19 and improper use may result in serious side effects requiring hospitalization.

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The COVID STEROID 2 Trial Group. **Effect of 12 mg vs 6 mg of Dexamethasone on the Number of Days Alive Without Life Support in Adults With COVID-19 and Severe Hypoxemia: The COVID STEROID 2 Randomized Trial.** JAMA. Published online October 21, 2021. **doi:10.1001/jama.2021.18295**

- **Background:** A daily dose with 6 mg of dexamethasone is recommended for up to 10 days in pts with severe and critical COVID-19, but a higher dose may benefit those with more severe disease.
- **Design:** To assess the effects of 12 mg/d vs 6 mg/d of dexamethasone in patients with COVID-19 and severe hypoxemia,a multicenter RCT was conducted between August 2020 and May 2021 at 26 hospitals in Europe and India. 1000 adults with confirmed COVID-19 requiring at least 10 L/min of oxygen or mechanical ventilation were included. End of 90-day follow-up was August 19, 2021.
- **Intervention:** Patients were randomized 1:1 to 12 mg/d of intravenous dexamethasone (n = 503) or 6 mg/d of intravenous dexamethasone (n = 497) for up to 10 days.
- **Outcome:** The primary outcome was # of days alive without life support (invasive mechanical ventilation, circulatory support, or kidney replacement therapy) at 28 days, adjusted for stratification variables. 5 prespecified secondary outcomes are included: # of days alive without life support at 90 days, # of days alive out of the hospital at 90 days, mortality at 28 days and at 90 days, and ≥1 serious adverse reactions at 28 days.
- **Results:** 982/1000 randomized patients were included (median age, 65 [IQR, 55-73] years; 305 [31%] women) and primary outcome data were available for 971 (491 in the 12 mg of dexamethasone group and 480 in the 6 mg of dexamethasone group). Median # of days alive without life support was 22.0 days (IQR, 6.0-28.0 days) in the 12 mg of dexamethasone group and 20.5 days (IQR, 4.0-28.0 days) in the 6 mg of dexamethasone group (adjusted mean difference, 1.3 days [95% CI, 0-2.6 days]; P = .07). Mortality at 28 days was 27.1% in the 12 mg of dexamethasone group vs 32.3% in the 6 mg of dexamethasone group (adjusted relative risk, 0.86 [99% CI, 0.68-1.08]). Mortality at 90 days was 32.0% in the 12 mg of dexamethasone group vs 37.7% in the 6 mg of dexamethasone group (adjusted relative risk, 0.87 [99% CI, 0.70-1.07]). Serious adverse reactions, including septic shock and invasive fungal infections, occurred in 11.3% in the 12 mg of dexamethasone group vs 13.4% in the 6 mg of dexamethasone group (adjusted relative risk, 0.83 [99% CI, 0.54-1.29]).
- **Conclusions:** Among pts with COVID-19 and severe hypoxemia, 12 mg/d of dexamethasone compared with 6 mg/d of dexamethasone did not result in statistically significantly more days alive without life support at 28 days.

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Fischer W, Eron JJ, Holman W et al. **Molnupiravir, an Oral Antiviral Treatment for COVID-19.** medRxiv. Preprint. 2021 Jun 17. **doi: 10.1101/2021.06.17.21258639**

- We report the results of a Phase 2a trial evaluating the safety, tolerability, and antiviral efficacy of molnupiravir in the treatment of COVID-19 (ClinicalTrials.gov NCT04405570).
- METHODS: Eligible participants included outpatients with confirmed SARS-CoV-2 infection & symptom onset within 7 days. Participants were randomized 1:1 to 200 mg molnupiravir or placebo, or 3:1 to molnupiravir (400 or 800 mg) or placebo, twice-daily for 5 days. Antiviral activity was assessed as time to undetectable levels of viral RNA by reverse transcriptase polymerase chain reaction and time to elimination of infectious virus isolation from nasopharyngeal swabs.
- RESULTS: Among 202 treated participants, virus isolation was significantly lower in participants receiving 800 mg molnupiravir (1.9%) versus placebo (16.7%) at Day 3 (p = 0.02). At Day 5, virus was not isolated from any participants receiving 400 or 800 mg molnupiravir, vs 11.1% of those receiving placebo (p = 0.03). Time to viral RNA clearance was decreased & a greater proportion overall achieved clearance in participants administered 800 mg molnupiravir versus placebo (p = 0.01). Molnupiravir was generally well tolerated, with similar numbers of adverse events across all groups.
- CONCLUSIONS: Molnupiravir is the first oral, direct-acting antiviral shown to be highly effective at reducing nasopharyngeal SARS-CoV-2 infectious virus and viral RNA and has a favorable safety and tolerability profile.

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Ospina-Tascón G, et al. **Effect of high-flow oxygen therapy vs conventional oxygen therapy on invasive mechanical ventilation and clinical recovery in patients with severe COVID-19: a randomized clinical trial.** JAMA 2021; DOI: 10.1001/jama.2021.20714.

OBJECTIVE: To determine the effect of high-flow oxygen therapy through a nasal cannula compared with conventional O2 therapy on need for endotracheal intubation & clinical recovery in severe COVID-19.

DESIGN: Randomized, open-label clinical trial conducted in ED and ICUs in 3 hospitals in Colombia. A total of 220 adults with respiratory distress and a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen of less than 200 due to COVID-19 were randomized from August 2020 to January 2021, with last follow-up on February 10, 2021.

INTERVENTIONS: Patients were randomly assigned to receive high-flow oxygen through a nasal cannula (n = 109) or conventional oxygen therapy (n = 111).

OUTCOMES: The co–primary outcomes were need for intubation and time to clinical recovery until day 28 assessed by a 7-category ordinal scale (range, 1-7, with higher scores indicating a worse condition). Effects of treatments were calculated with a Cox proportional hazards model adjusted for hypoxemia severity, age, and comorbidities.

RESULTS: Among 220 randomized pts, 199 were included in the analysis (median age, 60 years; n = 65 women [32.7%]). Intubation occurred in 34 (34.3%) randomized to high-flow oxygen therapy and in 51 (51.0%) randomized to conventional oxygen therapy (hazard ratio, 0.62; 95% CI, 0.39-0.96; P = .03). The median time to clinical recovery within 28 days was 11 (IQR, 9-14) days in pts randomized to high-flow oxygen therapy vs 14 (IQR, 11-19) days in those randomized to conventional oxygen therapy (hazard ratio, 1.39; 95% CI, 1.00-1.92; P = .047). Suspected bacterial pneumonia occurred in 13 pts (13.1%) randomized to high-flow

O2 and in 17 (17.0%) of those randomized to conventional O2 therapy, while bacteremia was detected in 7 (7.1%) vs 11 (11.0%), respectively.

CONCLUSIONS: Among pts with severe COVID-19, use of high-flow oxygen through a nasal cannula significantly decreased need for mechanical ventilation support and time to clinical recovery compared with conventional low-flow oxygen therapy.

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PREVENTION/ MITIGATION

Hacisuleyman E, Hale C, Saito Y et al. **Vaccine Breakthrough Infections with SARS-CoV-2 Variants.** N Engl J Med, 2021. Published online April 21, 2021.
DOI: 10.1056/NEJMoa2105000

- In a cohort of 417 persons who had received the second dose of the Pfizer or Moderna vaccine at least 2 wks previously, we identified 2 women with vaccine breakthrough infection.
- Despite evidence of vaccine efficacy in both women, mild symptoms of COVID-2019 developed & they tested (+) for SARS-CoV-2 by PCR testing. Viral sequencing revealed variants of likely clinical importance, E484K in 1 woman & 3 mutations (T95I, del142–144, D614G) in both. Neither was seriously ill.
- These observations indicate a potential risk of illness after successful vaccination & subsequent infection with variant virus.

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Blumenthal KG, Robinson LB, Camargo CA et al. Acute Allergic Reactions to mRNA COVID-19 Vaccines. JAMA. 2021;325(15):1562-1565. doi:10.1001/jama.2021.3976.

- To evaluate the rate of acute allergic reactions to mRNA COVID-19 vaccines, Mass General Brigham (MGB) employees who received their first dose of an mRNA COVID-19 vaccine (12/16/2020-2/12/2021, with follow-up through 2/18/2021) were prospectively studied.
- Of 64 900 employees who received their first dose of a COVID-19 vaccine, 25 929 (40%) received the Pfizer-BioNTech vaccine and 38 971 (60%) received the Moderna vaccine. At least 1 symptom survey was completed by 52 805 (81%).
- RESULTS: Acute allergic reactions were reported by 1365 employees overall (2.10% [95% CI, 1.99%-2.22%]), more frequently with the Moderna vaccine compared with Pfizer-BioNTech (2.20% [95% CI, 2.06%-2.35%] vs 1.95% [95% CI, 1.79%-2.13%]; P = .03).
- Anaphylaxis was confirmed in 16 employees (0.025% [95% CI, 0.014%-0.040%]): 7 cases from the Pfizer-BioNTech vaccine (0.027% [95% CI, 0.011%-0.056%]) and 9 cases from the Moderna vaccine (0.023% [95% CI, 0.011%-0.044%]) (P = .76)
- Individuals with anaphylaxis were a mean age of 41 (SD, 13) years & 15 (94%) were female; 10 (63%) had an allergy history and 5 (31%) had an anaphylaxis history. Mean time to anaphylaxis onset was 17 (SD, 28; range, 1-120) minutes. One patient was admitted to intensive care, 9 (56%) received IM epinephrine, and all recovered. Three employees, with prior anaphylaxis history, did not seek care.
- CONCLUSION: Severe reactions consistent with anaphylaxis occurred are rare, occurring at a rate of 2.47 per 10 000 vaccinations after mRNA COVID-19 vaccines.

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Angel Y. Spitzer A, Henig O et al. **Association Between Vaccination with BNT162b2 and Incidence of Symptomatic and Asymptomatic SARS-CoV-2 Infections Among Health Care Workers.** JAMA. Published online May 6, 2021. **doi:10.1001/jama.2021.7152**

- To estimate the association of vaccination with the Pfizer-BioNTech BNT162b2 vaccine with symptomatic and asymptomatic SARS-CoV-2 infections, SARS-CoV-2 PCR tests cultures

were performed in vaccinated and unvaccinated health care workers via regular screening with nasopharyngeal swabs between December 20, 2020, and February 25, 2021.

- RESULTS: A total of 6710 health care workers (mean [SD] age, 44.3 [12.5] years; 4465 [66.5%] women) were followed up for a median period of 63 days; 5953 health care workers (88.7%) received at least 1 dose of the BNT162b2 vaccine, 5517 (82.2%) received 2 doses, and 757 (11.3%) were not vaccinated.
- Symptomatic SARS-CoV-2 infection occurred in 8 fully vaccinated health care workers and 38 unvaccinated health care workers (incidence rate, 4.7 vs 149.8 per 100 000 person-days, respectively, adjusted IRR, 0.03 [95% CI, 0.01-0.06]). Asymptomatic SARS-CoV-2 infection occurred in 19 fully vaccinated health care workers and 17 unvaccinated health care workers (incidence rate, 11.3 vs 67.0 per 100 000 person-days, respectively, adjusted IRR, 0.14 [95% CI, 0.07-0.31]).
- CONCLUSIONS: Among health care workers at a single center in Tel Aviv, Israel, receipt of the BNT162b2 vaccine compared with no vaccine was associated with a significantly lower incidence of symptomatic and asymptomatic SARS-CoV-2 infection more than 7 days after the second dose.

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Edara V-V, Lai L, Sahoo MK et al. **Infection and vaccine-induced neutralizing antibody responses to the SARS-CoV-2 B.1.617.1 variant.** bioRxiv preprint posted May 10, 2021. **https://doi.org/10.1101/2021.05.09.443299**

- A second wave of SARS-CoV-2 infections in India is leading to the expansion of SARS-CoV-2 variants. The B.1.617.1 variant has rapidly spread throughout India and to several countries throughout the world.
- In this study, using a live virus assay, we describe the neutralizing antibody response to the B.1.617.1 variant in serum from infected and vaccinated individuals.
- RESULTS: We found that the B.1.617.1 variant is 6.8-fold more resistant to neutralization by sera from COVID-19 convalescent and Moderna and Pfizer vaccinated individuals.
- Despite this, a majority of the sera from convalescent individuals and all sera from vaccinated individuals were still able to neutralize the B.1.617.1 variant.
- CONCLUSIONS: These findings suggest that protective immunity by the mRNA vaccines tested here are likely retained against the B.1.617.1 variant. As the B.1.617.1 variant continues to evolve, it will be important to monitor how additional mutations within the spike impact antibody resistance, viral transmission and vaccine efficacy.

White EM, Yang X, Blackman C et al. **Incident SARS-CoV-2 Infection among mRNA-Vaccinated and Unvaccinated Nursing Home Residents**. New Engl J Med 2021; Published online May 21, 2021. **DOI: 10.1056/NEJMc2104849**

- Using electronic health record data from a large long-term care provider in the United States, we report the incidence of SARS-CoV-2 infection among vaccinated residents and unvaccinated residents of 280 nursing homes across 21 states.
- From immunization records, we identified residents who had received at least one dose of mRNA vaccine as of February 15, 2021; those who had received both doses by February 15, 2021; and those who were present at their facility on the day of the first vaccination clinic but who were not vaccinated as of March 31, 2021.

- We identified incident SARS-CoV-2 infections through March 31, 2021, on the basis of PCR-assay and antigen-test records. Residents were tested every 3 to 7 days when there were confirmed cases in their facility and if they had any new symptoms or potential exposure.
- The sample included 18,242 residents who received at least one dose of mRNA vaccine; 14,669 residents (80.4%) received the Pfizer–BioNTech vaccine, and 3573 (19.6%) received the Moderna vaccine. Of these 18,242 residents, 13,048 also received the second dose of vaccine. A total of 3990 residents were unvaccinated.
- RESULTS: Incidence of infection decreased over time among both vaccinated residents & unvaccinated residents. After receipt of the first vaccine dose, there were 822 incident cases (4.5%) within 0 to 14 days and 250 cases (1.4%) at 15 to 28 days. Among the 13,048 residents who received both doses of vaccine, there were 130 incident cases (1.0%) within 0 to 14 days after receipt of the second dose and 38 cases (0.3%) after 14 days. Among unvaccinated residents, incident cases decreased from 173 cases (4.3%) within 0 to 14 days after the first vaccination clinic to 12 cases (0.3%) at more than 42 days after the clinic.
- Across all the study groups, most infections were asymptomatic, and the incidence of both asymptomatic and symptomatic infections decreased.
- CONCLUSION: These findings show the real-world effectiveness of the mRNA vaccines in reducing the incidence of asymptomatic and symptomatic SARS-CoV-2 infections in a vulnerable nursing home population.

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Turner JS, O'Halloran JA, Kalaidina E et al. **SARS-CoV-2 mRNA vaccines induce persistent human germinal center responses.** Nature (2021). https://doi.org/10.1038/s41586-021-03738-2. Published 6/18/2021.

- SARS-CoV-2 messenger RNA (mRNA)-based vaccines are ~95% effective in preventing coronavirus disease 20191–5 but the dynamics of antibody secreting plasmablasts (PBs) and germinal centre (GC) B cells induced by these vaccines in humans remain unclear. We examined antigen-specific B cell responses in peripheral blood (n=41) and draining lymph nodes (LNs) in 14 individuals who received two doses of BNT162b2, an mRNA-based vaccine encoding full-length SARS-CoV-2 spike (S) gene1.
- RESULTS: Circulating IgG- and IgA-secreting PBs targeting the S protein peaked one week after the second immunization then declined, becoming undetectable three weeks later.
- These PB responses preceded maximal levels of serum anti-S binding and neutralizing antibodies to an early circulating SARS-CoV-2 strain as well as emerging variants, especially in individuals previously infected with SARS-CoV-2, who produced the most robust serologic responses.
- By examining fine needle aspirates of draining axillary LNs, we identified GC B cells that bound S protein in all participants after primary immunization. Remarkably, high frequencies of S-binding GC B cells and PBs were sustained in these draining LNs for $\geq$ 12 wks after the booster immunization.
- CONCLUSION: SARS-CoV-2 mRNA-based vaccination of humans induces a persistent GC B cell response, enabling the generation of robust, sustained humoral immunity.

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Tada T, Zhou H, Samanovic MI et al. **Comparison of Neutralizing Antibody Titers Elicited by mRNA and Adenoviral Vector Vaccine against SARS-CoV-2 Variants**. BioRxiv 2021-preprint. Published on 7/21/2021. **doi: https://doi.org/10.1101/2021.07.19.452771**

- As increasing prevalence of SARS-CoV-2 variants has raised concerns regarding possible decreases in vaccine efficacy, neutralizing antibody titers elicited by mRNA-based and an adenoviral vector-based vaccine against variant pseudotyped viruses were compared.
- RESULTS: Moderna & Pfizer mRNA vaccines, BNT162b2 and mRNA-1273-elicited antibodies showed modest neutralization resistance against Beta, Delta, Delta plus and Lambda variants whereas J&J /Ad26.COV2.S (J & J vaccine)-elicited antibodies from a significant fraction of vaccinated individuals were of low neutralizing titer (IC50 <50).
- CONCLUSIONS: The data underscore the importance of surveillance for breakthrough infections that result in severe COVID-19 and suggest the benefit of a second immunization following J & J/Ad26.COV2.S to increase protection against the variants.

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Harmon A, Chang C, Salcedo N et al. **Validation of an At-Home Direct Antigen Rapid Test for COVID-19JAMA Netw Open. 2021;4(8):e2126931.** August 27, 2021. **doi:10.1001/jamanetworkopen.2021.26931**

- Researchers describe implementation of high-frequency testing using inexpensive, at-home, semiquantitative, direct antigen rapid tests (DARTs) and compare their performance with that of qRT-PCR on self-collected nasal specimens.
- The study included 257 affiliates of 3 coworking laboratories in Cambridge & Boston, Mass. The prevalence of COVID-19 in this area during the study was between <1% and 8%. Individuals self-collected nasal swab specimens twice weekly at home during a 6-month period. Findings were compared with laboratory qRT-PCR tests. Symptom information was collected contemporaneously as was self-reported race and ethnicity.
- A total of 257 participants were enrolled (median age, 35 years; range, 21-72 years), 46.7% women, 62.6% White, 19.1% Asian, 11.3% Hispanic & 3.1% Black. 2951 pairs of nasal swabs were self-collected by participants and tested by qRT-PCR and DART. The sensitivity of DART within days 0 to 12 of symptom onset was 78.9% (60 of 76 swabs; 95% CI, 69.1%-88.8%), and the specificity of DART was 97.1% (2791 of 2875 swabs; 95% CI, 96.3%-97.8%)
- The duration of SARS-CoV-2 nucleocapsid and RNA detection for individual infections ranged from 1 to 12 days, with peak levels observed between 2 and 6 days of symptoms (median, 3 days). The sensitivity of DART was calculated for each day. DART sensitivity was 96.3% (26 of 27 swabs; 95% CI, 89.5%-100.0%) within days 0 to 3 of symptoms.
- Of the 257 individuals, 15 contracted COVID-19. Twice-weekly DART detected 15 of 15 of infections (100%).
- → Twice-weekly surveillance with DART detected infections in 15 individuals, with 96.3% sensitivity on days 0 through 3 of symptoms.

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Abaluck J, Kwong LH, Styczynski A et al. **The Impact of Community Masking on COVID-19: A Cluster-Randomized Trial in Bangladesh. Science 2022 Jan 14;375(6577):eabi9069.** Epub 2022 Jan 14. **doi: 10.1126/science.abi9069.**

- Objectives were to assess the impact of increasing mask-wearing on symptomatic SARS-CoV-2 infections.
- METHODS: We conducted a cluster-randomized trial of community-level mask promotion in rural Bangladesh from November 2020 to April 2021 (N=600 villages, N=342,126 adults). We cross-randomized mask promotion strategies at the village and household level, including cloth vs. surgical masks. All intervention arms received free masks, information on the importance of masking, role modeling by community leaders, and in-person reminders for 8 weeks. The control group did not receive any interventions.
- Outcomes included symptomatic SARS-CoV-2 seroprevalence (primary) and prevalence of proper mask-wearing, physical distancing, and symptoms consistent with COVID-19 (secondary). Mask-wearing and physical distancing were assessed through direct observation at least weekly at mosques, markets, the main entrance roads to villages, and tea stalls. At 5 and 9 weeks follow-up, we surveyed all reachable participants about COVID-related symptoms. Blood samples collected at 10-12 weeks of follow-up for symptomatic individuals were analyzed for SARS-CoV-2 IgG antibodies.
- RESULTS: There were 178,288 individuals in the intervention group and 163,838 individuals in the control group. The intervention increased proper mask-wearing from 13.3% in control villages (N=806,547 observations) to 42.3% in treatment villages (N=797,715 observations) (adjusted percentage point difference = 0.29 [0.27, 0.31]). This tripling of mask usage was sustained during the intervention period and two weeks after. Physical distancing increased from 24.1% in control villages to 29.2% in treatment villages (adjusted percentage point difference = 0.05 [0.04, 0.06]). After 5 months, the impact of the intervention faded, but mask-wearing remained 10 percentage points higher in the intervention group.
- The proportion of individuals with COVID-like symptoms was 7.62% (N=13,273) in the intervention arm and 8.62% (N=13,893) in the control arm. Blood samples were collected from N=10,952 consenting, symptomatic individuals. Adjusting for baseline covariates, the intervention reduced symptomatic seroprevalence by 9.3% (adjusted prevalence ratio (aPR) = 0.91 [0.82, 1.00]; control prevalence 0.76%; treatment prevalence 0.68%). In villages randomized to surgical masks (n = 200), the relative reduction was 11.2% overall (aPR = 0.89 [0.78, 1.00]) and 34.7% among individuals 60+ (aPR = 0.65 [0.46, 0.85]). No adverse events were reported.
- Conclusions: Our intervention demonstrates a scalable and effective method to promote mask adoption and reduce symptomatic SARS-CoV-2 infections. Use of surgical masks was associated with a significantly decreased relative risk of SARS-CoV-2 infection vs cloth masks.

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Rebmann T, Loux TM, Arnold LD et al. **SARS-CoV-2 Transmission to Masked and Unmasked Close Contacts of University Students with COVID-19 — St. Louis, Missouri, January–May 2021.** MMWR Morb Mortal Wkly Rep 2021; 70:1245–1248. DOI: http://dx.doi.org/10.15585/mmwr.mm7036a3.

- In January 2021, Saint Louis University (SLU) implemented a modified quarantine protocol that considered mask use when determining which close contacts required quarantine.* To assess the impact of the protocol, SLU assessed positive SARS-CoV-2 test result rates by masking status of the persons with COVID-19 and their close contacts.

- RESULTS: During January–May 2021, 265 students received a positive SARS-CoV-2 test result; these students named 378 close contacts. Compared with close contacts whose exposure only occurred when both persons were masked (7.7%), close contacts with any unmasked exposure (32.4%) had higher adjusted odds ratios (aORs) of receiving a positive SARS-CoV-2 test result (aOR = 4.9; 95% confidence interval [CI] = 1.4–31.1). Any additional exposures were associated with a 40.0% increase in odds of a positive test result (aOR = 1.4; 95% CI = 1.2–1.6).
- CONCLUSIONS: These findings reinforce that universal masking and fewer encounters in close contact with persons with COVID-19 prevents the spread of SARS-CoV-2 in a university setting. Universities opening for in-person instruction could taking mask use into account when determining which unvaccinated close contacts require quarantine if enforced testing protocols are in place.

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Self WH, Tenforde MW, Rhoads JP, et al. **Comparative Effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) Vaccines in Preventing COVID-19 Hospitalizations Among Adults Without Immunocompromising Conditions — United States, March–August 2021**. MMWR Morb Mortal Wkly Rep. ePub: 17 September 2021. DOI: http://dx.doi.org/10.15585/mmwr.mm7038e1

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Kharbanda EO, Haapala J, DeSilva M et al. **Spontaneous Abortion Following COVID-19 Vaccination During Pregnancy.** JAMA. 2021;326(16):1629-1631. **doi:10.1001/jama.2021.15494**

- To assess a potential role COVID-19 vaccination in spontaneous abortion, data from 8 health systems, representing approximately 3% of the US population were reviewed.
- METHODS: A validated pregnancy algorithm was used to identify and assign gestational ages for spontaneous abortions and ongoing pregnancies occurring over seven 4-wk surveillance periods from 12/15/2020 – 6/28/2021 with spontaneous abortions assigned to a 4-week surveillance period. Ongoing pregnancies between 6 and 19 wks' gestation were identified on the last day of each 4-wk surveillance period and contributed data to 1 or more surveillance periods. Vaccination data came from EHRs, medical and pharmacy claims, and regional or state immunization information systems.
- ANALYSIS: Odds of receiving a COVID-19 vaccine in the 28 days prior to spontaneous abortion were compared with the odds of receiving a COVID-19 vaccine in the 28 days prior to index dates for ongoing pregnancies. Both spontaneous abortions and ongoing pregnancies were assigned to gestational age groups (6-8, 9-13, and 14-19 weeks), surveillance periods, site, maternal age groups (16-24, 25-34, and 35-49 years), number of antenatal visits (≤1 or ≥2), and race and ethnicity.
- RESULTS: Of 105 446 unique pregnancies, 13 160 spontaneous abortions and 92 286 ongoing pregnancies were identified. Overall, 7.8% of women received 1 or more Pfizer-BioNTech vaccines; 6.0% received 1 or more Moderna vaccines; and 0.5% received a Janssen vaccine during pregnancy and before 20 weeks' gestation.
- The proportion of women aged 35 through 49 years with spontaneous abortions was higher (38.7%) than with ongoing pregnancies (22.3%).

- A COVID-19 vaccine was received within 28 days prior to an index date among 8.0% of ongoing pregnancy periods vs 8.6% of spontaneous abortions. Spontaneous abortions did not have an increased odds of exposure to a COVID-19 vaccination in the prior 28 days compared with ongoing pregnancies (adjusted odds ratio, 1.02; 95% CI, 0.96-1.08). Results were consistent for all vaccines and by gestational age group.
- CONCLUSION: Among women with spontaneous abortions, the odds of COVID-19 vaccine exposure were not increased in the prior 28 days compared with women with ongoing pregnancies. Results were consistent for all vaccines and by gestational age group.

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Goldberg Y, et al. **Waning immunity after the BNT162b2 vaccine in Israel.** N Engl J Med 2021; **DOI: 10.1056/NEJMoa2114228.**

- STUDY DESIGN: To evaluate change in immunity after vaccination for COVID-19, investigators used data on confirmed infection and severe disease collected from an Israeli national database for the period of July 11 to 31, 2021, for all Israeli residents who had been fully vaccinated before June 2021. A Poisson regression model was used to compare rates of confirmed SARS-CoV-2 infection and severe Covid-19 among persons vaccinated during different time periods, with stratification according to age group and with adjustment for possible confounding factors.
- RESULTS: Among persons 60 years of age or older, the rate of infection in the July 11–31 period was higher among persons who became fully vaccinated in January 2021 (when they were first eligible) than among those fully vaccinated 2 months later, in March (rate ratio, 1.6; 95% confidence interval [CI], 1.3 to 2.0). Among persons 40 to 59 years of age, the rate ratio for infection among those fully vaccinated in February (when they were first eligible), as compared with 2 months later, in April, was 1.7 (95% CI, 1.4 to 2.1). Among persons 16 to 39 years of age, the rate ratio for infection among those fully vaccinated in March (when they were first eligible), as compared with 2 months later, in May, was 1.6 (95% CI, 1.3 to 2.0). The rate ratio for severe disease among persons fully vaccinated in the month when they were first eligible, as compared with those fully vaccinated in March, was 1.8 (95% CI, 1.1 to 2.9) among persons 60 years of age or older and 2.2 (95% CI, 0.6 to 7.7) among those 40 to 59 years of age; owing to small numbers, the rate ratio could not be calculated among persons 16 to 39 years of age.
- CONCLUSIONS: These findings indicate that immunity against the delta variant of SARS-CoV-2 decreased in all age groups a few months after receipt of the second dose of vaccine.

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Jehm M, McCullough JM, Dale AP, et al. **Association Between K–12 School Mask Policies and School-Associated COVID-19 Outbreaks — Maricopa and Pima Counties, Arizona, July–August 2021.** MMWR Morb Mortal Wkly Rep 2021; 70:1372–1373. **DOI: http://dx.doi.org/10.15585/mmwr.mm7039e1external icon**

- The association between school mask policies and school-associated COVID-19 outbreaks in K–12 public non-charter schools open for in-person learning in Arizona, Maricopa and Pima Counties during July 15–August 31, 2021, was evaluated.
- A school was considered to have a mask requirement if all persons, regardless of vaccination status, were required to wear a mask indoors in school; for inclusion in the

analysis, the mask requirement had to be in place when the school year began. A school-associated outbreak was defined as the occurrence of two or more laboratory-confirmed COVID-19 cases among students or staff members at the school within a 14-day period, at least 7 days after school started.

- RESULTS: Data were available for 1,020 of 1,041 (98.0%) K–12 public noncharter schools in Maricopa and Pima counties. Among the 999 (96.0%) schools included in the analysis, 210 (21.0%) had an early mask requirement, 309 (30.9%) had a late mask requirement enacted a median of 15 days after school started (interquartile range = 9–17 days), and 480 (48.0%) had no mask requirement. During July 15–August 31, 2021, 191 school-associated outbreaks occurred, 16 (8.4%) in schools with early mask requirements, 62 (32.5%) in schools with late mask requirements, and 113 (59.2%) in schools without a mask requirement.
- After adjusting for potential described confounders, the odds of a school-associated COVID-19 outbreak in schools without a mask requirement were 3.5 times higher than those in schools with an early mask requirement (OR = 3.5; 95% CI = 1.8–6.9).
- CONCLUSION: A universal masking policy significantly reduces the risk of school-associated outbreaks of COVID-19

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Cavanaugh AM, Spicer KB, Thoroughman D, Glick C, Winter K. **Reduced Risk of Reinfection with SARS-CoV-2 After COVID-19 Vaccination — Kentucky, May–June 2021.** MMWR Morb Mortal Wkly Rep 2021;70:1081-1083. **DOI: http://dx.doi.org/10.15585/mmwr.mm7032**

- To evaluate infection risk after SARS-CoV-2 infection vs vaccination, a case-control evaluation of the association was conducted during May–June 2021 in Kentucky among persons previously infected with SARS-CoV-2 in 2020.
- STUDY DESIGN: Kentucky residents aged ≥18 years with SARS-CoV-2 infection confirmed by positive nucleic acid amplification test (NAAT) or antigen test results reported in during March–December 2020 were eligible for inclusion. A case-patient was defined as a Kentucky resident with laboratory-confirmed SARS-CoV-2 infection in 2020 and a subsequent positive NAAT or antigen test result during May 1–June 30, 2021 using the state's National Electronic Disease Surveillance System (NEDSS) and a REDCap database that contains laboratory test results and case investigation data, including dates of death for deceased patients. Vaccination status was determined from the Kentucky Immunization Registry (KYIR). Case-patients were considered fully vaccinated if a single dose of Janssen (Johnson & Johnson) or a second dose of an mRNA vaccine (Pfizer-BioNTech or Moderna) was received ≥14 days before the reinfection date. For controls, the same definition was applied, using the reinfection date of the matched case-patient. Partial vaccination was defined as receipt of ≥1 dose of vaccine, but either the vaccination series was not completed or the final dose was received <14 days before the case-patient's reinfection date.
- RESULTS: Overall, 246 case-patients met eligibility requirements and were successfully matched by age, sex, and date of initial infection with 492 controls. Among the population included in the analysis, 60.6% were female, and 204 (82.9%) case-patients were initially infected during October–December 2020 (Table 1). Among case-patients, 20.3% were fully vaccinated, compared with 34.3% of controls (Table 2). Kentucky residents with previous infections who were unvaccinated had 2.34 times the odds of reinfection (OR = 2.34; 95% CI

= 1.58–3.47) compared with those who were fully vaccinated; partial vaccination was not significantly associated with reinfection (OR = 1.56; 95% CI = 0.81–3.01).
- CONCLUSION: Among Kentucky residents who were previously infected with SARS-CoV-2 in 2020, those who were unvaccinated against COVID-19 had significantly higher likelihood of reinfection during May and June 2021.

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Patalon T, Gazit S, Pitzer VF et al. **Odds of Testing Positive for SARS-CoV-2 Following Receipt of 3 vs 2 Doses of the BNT162b2 mRNA Vaccine.** JAMA Int Med; Published Online: November 30, 2021. **doi:10.1001/jamainternmed.2021.7382**

- OBJECTIVE: To evaluate the initial short-term additional benefit of a 3-dose vs a 2-dose regimen against infection of SARS-CoV-2.
- DESIGN, SETTING & PARTICIPANTS: Preliminary retrospective case-control study using 2 approaches: a test-negative design and a matched case-control design. Participants were included from the national centralized database of an Israeli HMO covering 2.5 million members. Data were collected from 3/1 /2020 – 10/4/2021. Analyses focused on the period from 8/1/2021 -10/4/2021 because the booster dose was widely administered from August 1 onward.
- EXPOSURES: Either 2 doses or 3 doses of the BNT162b2 (Pfizer) vaccine.
- MAIN OUTCOMES: Odds of a (+) SARS-CoV-2 PCR test at different time intervals following receipt of the booster dose (0-6, 7-13, 14-20, 21-27, and 28-65 days) compared with receiving only 2 doses.
- RESULTS: The study population included 306 710 HMO members >/=40 years, 55% female who received either 2 or 3 doses of the BNT162b2 vaccine and did not have a positive PCR test For SARS-CoV-2 prior to the start of the F/U period. During this period, there were 500 232 PCR tests performed, 227 380 among those who received 2 doses and 272 852 among those who received 3 doses, with 14 989 (6.6%) and 4941 (1.8%) positive test results in each group, respectively. Comparing those who received a booster and those who received only 2 doses, there was an estimated odds ratio of 0.14 (95% CI, 0.13-0.15) 28 to 65 days following receipt of the booster, an 86% reduction in the odds of testing (+) for SARS-CoV-2).
- CONCLUSION AND RELEVANCE: In this case-control analysis, we showed an association between receipt of the booster dose and a reduction in the odds of testing positive for SARS-CoV-2, potentially counteracting waning immunity in the short term.

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Bozkurt B, Kamat I, Hotez P. **Myocarditis with COVID-19 mRNA Vaccines.** Circulation. Originally published 20 Jul 2021. **https://doi.org/10.1161/CIRCULATIONAHA.121.056135**

- Per CDC, myocarditis/pericarditis rates are approximately 12.6 cases per million doses of second dose mRNA vaccine among 12-39-year-olds. This is a review of all reported cases.
- Pts with myocarditis invariably presented with chest pain, usually 2-3 days after a second dose of mRNA vaccination. 79% were in males, with the majority in individuals younger than 30years with a median age of 24.
- In 484 probable myocarditis/pericarditis cases, 86% had reports of chest pain on presentation, 61% ST or T wave changes on electrocardiogram (ECG), 64% elevated

cardiac enzymes and 17% abnormal cardiac imaging. Cardiac MRI was abnormal in all tested patients, with findings suggestive of myocarditis such as late gadolinium enhancement and myocardial edema.

- Mechanisms for development of myocarditis are not clear but molecular mimicry between the spike protein of SARS-CoV-2 and self-antigens, trigger of preexisting dysregulated immune pathways in certain individuals, immune response to mRNA and activation of immunological pathways & dysregulated cytokine expression have been proposed.
- In addition to supportive care, nonsteroidal anti-inflammatory drugs, steroids, and colchicine were used for management of some patients & a few patients were treated with intravenous immunoglobulin + aspirin; some with LV dysfunction were initiated on beta-blocker and angiotensin converting enzyme inhibitor therapy due to left ventricular systolic dysfunction.
- All reported cases recovered rapidly without residua but limitation of extreme exertion has been advised post recovery.
- CONCLUSION: This analysis of reported myocarditis cases post mRNA vaccination against SARS-CoV-2 suggests this is a mild, self-limited process.