RAOM COVID-19 ARCHIVE
July, 2021- December, 2021

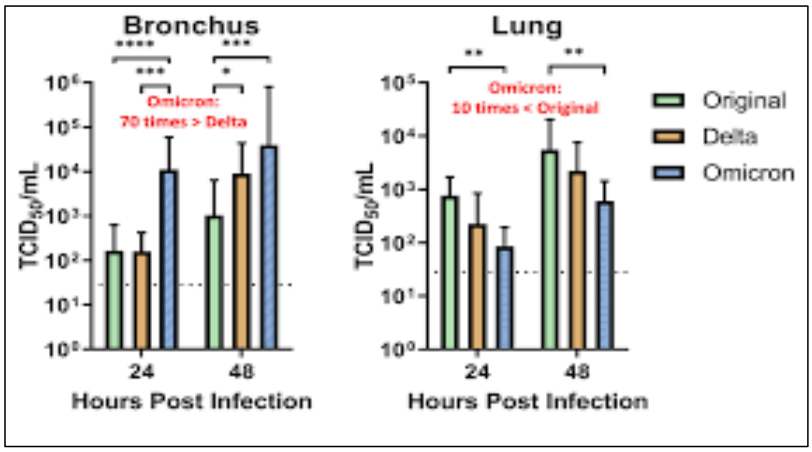
THE VIRUS

Omicron SARS-CoV-2 can infect faster and better than delta in human bronchus but with less severe infection in lung. 15 December 2021. **www.med.hku.hk/en/news/press/20211215-omicron-sars-cov-2-infection.**

BACKGROUND: Ex vivo cultures of the respiratory tract have been used to investigate emerging virus infections since 2007, eg., avian influenza, MERS). Here this technique has been applied to understand why the Omicron variant may differ in transmission and disease severity from other SARS-CoV-2 variants.

METHOD: This experimental model was used to compare infection with the Omicron SARS-CoV-2 variant to the original SARS-CoV-2 from 2020 and the Delta variant.

RESULTS: The Omicron variant replicates much faster than the original SARS-CoV-2 virus and Delta variant in the human bronchus. At 24 hours after infection, the Omicron variant replicated around 70 times higher than the Delta variant and the original SARS-CoV-2 virus. By contrast, the Omicron variant replicated less efficiently (more than 10 times lower) in human lung tissue than the original SARS-CoV-2 virus.



CONCLUSIONS: These findings suggest that the Omicron variant may cause less severe disease. By infecting many more people, a very infectious virus may cause more disease and death even though the virus itself may be less pathogenic. Since other studies show that the Omicron variant can partially escape immunity from vaccines and past infection, the overall threat from Omicron variant may be very significant.

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Jansen L, Tegomoh B, Lange K, et al. **Investigation of a SARS-CoV-2 B.1.1.529 (Omicron) Variant Cluster — Nebraska, November–December 2021.** MMWR Morb Mortal Wkly Rep. ePub: 28 December 2021. **DOI: http://dx.doi.org/10.15585/mmwr.mm705152e3external icon**.

- On November 29, the Nebraska DOH was notified of 6 probable cases of COVID-19 in 1 household, including 1 case in a man aged 48 yrs (the index patient) who had recently returned from Nigeria. Omicron infection was suspected.
- Specimens from all 6 persons in the household tested positive for SARS-CoV-2 by RT-PCR testing on 12/1. Genomic sequencing by the Nebraska Public Health Lab identified an identical Omicron genotype from each specimen.
- Phylogenetic analysis was conducted to determine if this cluster represented an independent introduction of Omicron into the United States, and a detailed epidemiologic investigation was conducted.
- The index pt, who was unvaccinated, had a history of domestically acquired symptomatic SARS-CoV-2 infection confirmed by RT-PCR a year prior in 11/2020. He reported unmasked close contact with a masked, coughing person on 11/20/2021, during an international conference in Nigeria. Before his return trip to the US, he had a negative antigen test on 11/21. On 11/23, while still asymptomatic, he had unmasked close contact with 5 household contacts. One household contact was fully vaccinated (second Pfizer-BioNTech vaccine dose received in 8/2021) and had previous symptomatic COVID-19 (RT-PCR confirmed in November 2020), 3 were unvaccinated and had previous symptomatic COVID-19 (RT-PCR confirmed in November 2020), and one was unvaccinated and had mild upper respiratory symptoms in November 2020 with a negative RT-PCR test result
- On 11/24/21, the index pt experienced symptoms consistent with COVID-19 and initially received a (+) SARS-CoV-2 Ag test result on 11/26. All 6 household members experienced symptom onset during 11/24–26; median interval between earliest exposure to the index pt and symptom onset was 73 hrs (range = 33–75 hrs). The index pt and the 4 household contacts with previous confirmed infections described the symptoms and severity of their recent COVID-19 infection as being similar to or milder than those during their first infection with no loss of taste or smell and no subjective fever. The unvaccinated pt without a previous COVID-19 dx experienced cough, joint pain, congestion, fever & chills.
- OBSERVATIONS: In this family cluster of COVID-19 due to the Omicron variant, incubation period was shorter and clinical syndrome was similar to or milder than that associated with previously described variants in persons who have been vaccinated or previously infected. Findings add to existing evidence suggesting an increased potential for reinfection.

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Diamond M, Halfmann P, Maemura T et al. **The SARS-CoV-2 B.1.1.529 Omicron virus causes attenuated infection and disease in mice and hamsters.** Nature in Review. Published online, pre-review. 12/2/ 2021. **DOI: 10.21203/rs.3.rs-1211792/v1**

- BACKGROUND: Several key animal models of SARS-CoV-2 infection and lung pathogenesis have been developed in mice, hamsters, nonhuman primates (NHP) and other animals for rapid testing and evaluation. A key test for potential countermeasures against B.1.1.529 is their activity in pre-clinical rodent models of respiratory tract disease. Here, using the collaborative network of the SARS-CoV-2 Assessment of Viral Evolution (SAVE) program of the NIH-NIAID, we evaluated the ability of multiple B.1.1.529 Omicron isolates to cause infection & disease in immunocompetent & human ACE2 (hACE2) expressing mice & hamsters, two key rodent models of SARS-CoV-2 infection and pathogenesis used to model human disease & evaluate countermeasures.
- RESULTS: Compared to other SARS-CoV-2 isolates (e.g., B.1.351 or B.1.617.2), the B.1.1.529 Omicron variant infection is attenuated in laboratory mice and hamsters for causing infection and/or disease. The basis for the attenuation in rodents remains unknown: (1) One pre-print study suggests that B.1.1.529 replicates faster in the human bronchus and less in lung cells, which may explain its greater transmissibility and putative lower disease severity; although it remains unclear if these observations extend to rodents, we observed less infection of hamster bronchial cells in vivo with B.1.1.529 Omicron than B.1.617.2 Delta virus. (2) We also measured lower viral burden in nasal washes and turbinates in 129 mice compared to other SARS-CoV-2 strains. The attenuation in mice was unexpected given that B.1.1.529 has multiple mutations in the RBD that are sites (K417, E484, Q493, Q498, and N501) associated with adaptation for mice23-25. (3) The attenuation in hamsters also was surprising, given that all prior SARS-CoV-2 variants have replicated relatively equivalently and to high levels in this animal. However, our results showing attenuation of B.1.1.529 in hamsters are consistent with another preliminary report. (4) Despite modeling and binding data suggesting that B.1.1.529 spike can bind more avidly to murine ACE2, we observed attenuation of infection in 129, C57BL/6, and BALB/c mice as compared with previous SARS-CoV-2 variants, with limited weight loss and lower viral burden in the upper and lower respiratory tracts. K18-hACE2 transgenic mice sustained infection in the lungs, these animals did not lose weight.
- In wild-type and hACE2 transgenic hamsters, lung infection, clinical disease, and pathology with B.1.1.529 also were milder compared to historical isolates or other SARS-CoV-2 variants of concern.
- CONCLUSIONS: Overall, experiments from multiple independent laboratories of the SAVE/NIAID network with several different B.1.1.529 isolates demonstrate attenuated lung disease in rodents, which parallels preliminary human clinical data.

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Downes DJ, Cross AR, Hua P et al. **Identification of LZTFL1 as a candidate effector gene at a COVID-19 risk locus.** Nat Genet 2021; 53: 1606–1615. Published: 04 November 2021. **https://doi.org/10.1038/s41588-021-00955-3**

- BACKGROUND: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease (COVID-19) pandemic has caused millions of deaths worldwide. Genome-wide

association studies identified the 3p21.31 region as conferring a twofold increased risk of respiratory failure.

- STUDY DESIGN: This study uses a combined multiomics and machine learning approach to identify the gain-of-function risk A allele of a SNP, rs17713054G>A, as a probable causative variant.
- RESULTS: We show with chromosome conformation capture and gene-expression analysis that the rs17713054-affected enhancer upregulates the interacting gene, leucine zipper transcription factor like 1 (LZTFL1). Selective spatial transcriptomic analysis of lung biopsies from patients with COVID-19 shows the presence of signals associated with epithelial–mesenchymal transition (EMT), a viral response pathway that is regulated by LZTFL1. The higher risk version of the gene probably prevents the cells lining airways and the lungs from responding to the virus properly. But importantly it doesn't affect the immune system, so the researchers expect people carrying this version of the gene to respond normally to vaccines.
- CONCLUSION: We conclude that pulmonary epithelial cells undergoing EMT, rather than immune cells, are likely responsible for the 3p21.31-associated risk. Since the 3p21.31 effect is conferred by a gain-of-function, LZTFL1 may represent a therapeutic target.

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Soria ME, Corton M, Martinez-Gonalez B et al. **High SARS-CoV-2 viral load is associated with a worse clinical outcome of COVID-19 disease.** Access Microbiology 2021; 3:000259 **DOI 10.1099/acmi.0.000259**

- BACKGROUND: COVID-19 severity and progression are determined by several host and virological factors. This study was designed to determine a possible association between viral load, obtained from nasopharyngeal swabs, and the severity of COVID-19 infection.
- STUDY DESIGN: in a cohort of 448 SARS-CoV-2-infected patients from a hospital in Madrid during the first outbreak of the pandemic in Spain, we clinically classified patients as mild, moderate and severe COVID-19 according to clinical parameters including hospitalization requirement, need of O2 therapy, ICU admission &/or death. Also, viral load (Ct values) were determined using SARS-CoV-2-specific oligonucleotides directed to ORF1ab.
- RESULTS: Mean Ct values for mild, moderate & severe COVID-19 pts were 35.75±0.45, 32.69±0.37 and 29.58±0.70, respectively. Univariate analysis showed statistically significant differences among viral load values by infection severity ($P<0.0001$; ANOVA test). High viral load was associated with worse clinical prognosis, independent of previously identified risk factors including age, sex, hypertension, CVD, diabetes, obesity & lung disease.
- CONCLUSION: The data presented here reinforce viral load as a potential biomarker for predicting disease severity in SARS-CoV-2-infected patients. It is also an important parameter in viral evolution since it relates to the numbers and types of variant genomes present in a viral population, a potential determinant of disease progression.

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THE DISEASE

Maslo C, Friedland R, Toublin M et al. **Characteristics and Outcomes of Hospitalized Patients in South Africa During the COVID-19 Omicron Wave Compared with Previous Waves.** JAMA 2021. Published online December 30, 2021. **doi:10.1001/jama.2021.24868**

- BACKGROUND: South Africa has experienced 3 COVID-19 waves: (1) 6-8/2020 (ancestral variant); (2) 11/2020 – 1/2021 (Beta); (3) 5-9/2021 (Delta). Cases again started to increase beginning November 15, 2021, coinciding with the identification of Omicron; as of December 7, 26% community positivity rates with Omicron were reached.
- We assessed hospitalized patients with a positive SARS-CoV-2 test result during the fourth COVID-19 wave compared with previous waves using pt data from Netcare, a private health care group of 49 acute care hospitals (>10 000 beds) across South Africa during the 4th period when 26% positivity rates were reached in the previous waves and compared them with 11/15 to 12/7, 2021.
- RESULTS: The number of pts treated in the hospitals during the same early period of each wave differed (2351 in wave 4 vs maximum 6342 in wave 3); 68-69% of pts presenting to the ED with a positive COVID-19 result were admitted to the hospital in the first 3 waves vs 41.3% in wave 4. Pts hospitalized during wave 4 were younger (median age, 36 yrs vs maximum 59 yrs in wave 3; P < .001) with a higher proportion of females. Significantly fewer patients with comorbidities were admitted in wave 4, and the proportion presenting with an acute respiratory condition was lower (31.6% in wave 4 vs maximum 91.2% in wave 3, P < .001). Of 971 patients admitted in wave 4, 24.2% were vaccinated, 66.4% were unvaccinated, and vaccination status was unknown for 9.4%.
- The proportion of patients requiring oxygen therapy significantly decreased (17.6% in wave 4 vs 74% in wave 3, P < .001) as did the percentage receiving mechanical ventilation. Admission to ICU was 18.5% in wave 4 vs 29.9% in wave 3 (P < .001).
- The median LOS (7-8 days in previous waves) decreased to 3 days in wave 4. **The death rate was between 19.7% in wave 1 and 29.1% in wave 3 and decreased to 2.7% in wave 4.**
- CONCLUSION: Further research is needed to determine if the differences between waves are affected by preexisting acquired or natural immunity or if Omicron may be less pathogenic than previous variant.

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Denson JL, Gillet AS, Brown M et al. **Metabolic Syndrome and Acute Respiratory Distress Syndrome in Hospitalized Patients With COVID-19.** JAMA Netw Open 2021; 4(12):e2140568. **doi:10.1001/jamanetworkopen.2021.40568**

- To determine whether metabolic syndrome is associated with an increased risk of ARDS and death from COVID-19, data from the Critical Care Medicine Discovery Viral Respiratory Illness Universal Study collected from 181 hospitals across 26 countries from February 15, 2020, to February 18, 2021 were assessed. Outcomes were compared between pts with metabolic syndrome (defined as ≥3 of the following criteria: obesity, prediabetes or diabetes, hypertension, and dyslipidemia) and a control population without metabolic syndrome.
- RESULTS: Among 46 441 pts hospitalized with COVID-19, a total of 5069 pts (17.5%) with metabolic syndrome were compared with 23 971 control patients (82.5%) without metabolic syndrome. In adjusted analyses, metabolic syndrome was associated with increased risk of

ICU admission (adjusted OR 1.32 [95% CI, 1.14-1.53]), invasive mechanical ventilation (OR 1.45 [95% CI, 1.28-1.65]), ARDS (OR 1.36 [95% CI, 1.12-1.66]), mortality (OR, 1.19 [95% CI, 1.08-1.31]) and prolonged hospital LOS (median [IQR], 8.0 [4.2-15.8] days vs 6.8 [3.4-13.0] days; P < .001) & ICU LOS (median [IQR], 7.0 [2.8-15.0] days vs 6.4 [2.7-13.0] days; P < .001).

- Each additional metabolic syndrome criterion was associated with increased risk of ARDS in an additive fashion (1 criterion: 1147 patients with ARDS [10.4%]; P = .83; 2 criteria: 1191 patients with ARDS [15.3%]; P < .001; 3 criteria: 817 patients with ARDS [19.3%]; P < .001; 4 criteria: 203 patients with ARDS [24.3%]; P < .001).
- CONCLUSIONS: These findings suggest that metabolic syndrome was associated with increased risks of ARDS and death in patients hospitalized with COVID-19. The association with ARDS was cumulative for each metabolic syndrome criteria present.

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Lo Vecchio A, Garazzino S, Smarrazzo A et al. **Factors Associated with Severe Gastrointestinal Diagnoses in Children With SARS-CoV-2 Infection or Multisystem Inflammatory Syndrome.** JAMA Netw Open 2021; 4(12):e2139974. **doi:10.1001/jamanetworkopen.2021.39974**

- To describe the clinical, radiological, and histopathologic characteristics of children with COVID-19 presenting with severe GI manifestations to identify factors associated with a severe outcome, a multicenter retrospective cohort study (2/25/2020 – 1/20/2021) enrolled inpatient and outpatient children (aged <18 years) with acute SARS-CoV-2 infection, confirmed by positive RT-PCR or fulfilling the US CDC criteria for MIS-C. The study was conducted by pediatricians working in primary care or hospitals in Italy participating in the COVID-19 Registry of the Italian Society of Pediatric Infectious Diseases
- RESULTS: Overall, 685 children (386 boys [56.4%]; median age, 7.3 [IQR, 1.6-12.4] years) were included. Of these children, 628 (91.7%) were diagnosed with acute SARS-CoV-2 infection and 57 (8.3%) with MIS-C. The presence of GI symptoms was associated with a higher chance of hospitalization (OR, 2.64; 95% CI, 1.89-3.69) & ICU admission (OR, 3.90; 95% CI, 1.98–7.68). Overall, 65 children (9.5%) showed severe GI involvement, including disseminated adeno-mesenteritis (39.6%), appendicitis (33.5%), abdominal fluid collection (21.3%), pancreatitis (6.9%), or intussusception (4.6%); 27/65 (41.5%) underwent surgery. Severe GI manifestations were associated with older age (5-10 years: OR, 8.33; 95% CI, 2.62-26.5; >10 years: OR, 6.37; 95% CI, 2.12-19.1, compared with preschool-age), abdominal pain (adjusted OR [aOR], 34.5; 95% CI, 10.1-118), lymphopenia (aOR, 8.93; 95% CI, 3.03-26.3), or MIS-C (aOR, 6.28; 95% CI, 1.92-20.5). Diarrhea was associated with a higher chance of adenomesenteritis (aOR, 3.13; 95% CI, 1.08-9.12) or abdominal fluid collection (aOR, 3.22; 95% CI, 1.03-10.0).
- CONCLUSIONS: In this multicenter cohort study of Italian children with SARS-CoV-2 infection or MIS-C, 9.5% had severe GI involvement, most frequently associated with MIS-C. Prompt identification may improve the management of these serious complications.

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SARS-CoV-2 variants of concern and variants under investigation in England. Technical briefing: Update on hospitalization and vaccine effectiveness for Omicron VOC-21NOV-01 (B.1.1.529). UK Health Security Agency. 31 December 2021.

- The British Health Security Agency analyzed 528,176 Omicron cases and 573,012 Delta cases between Nov. 22 and Dec. 26 to assess the risk of hospitalization in England. The researchers included all cases diagnosed in the community and then assessed the risk of general admission to the hospital or admission through emergency care.
- RESULTS: The risk of presentation to emergency care or hospital admission with Omicron was approximately half of that for Delta (Hazard Ratio 0.53, 95% CI: 0.50 to 0.57).
- The risk of hospital admission from emergency departments with Omicron was approximately one-third of that for Delta (Hazard Ratio 0.33, 95% CI: 0.30 to 0.37).
- The risk of hospitalization was lower for Omicron cases after 2 and 3 doses of vaccine, with an 81% (77 to 85%) reduction in risk of hospitalization after 3 doses compared to unvaccinated Omicron cases.

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D'Agnillo F, Walters KA, Yong LX et al. **Lung epithelial and endothelial damage, loss of tissue repair, inhibition of fibrinolysis, and cellular senescence in fatal COVID-19.** Science Translational Medicine 14 Oct 2021: 13, Issue 620. **DOI: 10.1126/scitranslmed.abj7790**

- BACKGROUND: The pathological mechanisms underlying COVID-19 respiratory distress and the interplay with aggravating risk factors have not been fully defined. To evaluate this, lung autopsy samples from 18 patients with fatal COVID-19 were examined.
- All autopsied individuals died between March and July 2020, within 3 to 47 days of symptom onset; they were also diagnosed with at least 1 high-risk factor associated with severe COVID-19. Antemortem plasma samples from 6 of these cases were also evaluated using deep sequencing of SARS-CoV-2 RNA, multiplex plasma protein measurements, and pulmonary gene expression and imaging analyses.
- FINDINGS: Prominent histopathological features in this case series included progressive diffuse alveolar damage with excessive thrombosis and late-onset pulmonary tissue and vascular remodeling.
- Acute damage at the alveolar-capillary barrier was characterized by the loss of surfactant protein expression with injury to alveolar epithelial cells, endothelial cells, respiratory epithelial basal cells, and defective tissue repair processes.
- SARS-CoV-2 infected respiratory epithelial cells—which aid in generating and repairing lung tissue—via a different process than influenza. Fatal influenza often results from secondary bacterial co-pathogenesis, while fatal COVID-19, produces pulmonary damage & associated immune responses so severe that coinfection is unnecessary for the disease to become deadly.
- Individuals who died more than 20 days following initial COVID-19 symptoms exhibited high levels of pulmonary fibrosis. Furthermore, several individuals had widespread thrombosis, and all had diffuse alveolar damage.
- Other key findings included impaired clot fibrinolysis with increased concentrations of plasma and lung plasminogen activator inhibitor-1 and modulation of cellular senescence markers, including p21 and sirtuin-1, in both lung epithelial and endothelial cells.
- SUMMARY: Together, these findings further define the molecular pathological features underlying the pulmonary response to SARS-CoV-2 infection and provide insights into signaling pathways that may be amenable to therapeutic intervention.

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Wanga V, Gerdes ME, Shi DS, et al. **Characteristics and Clinical Outcomes of Children and Adolescents Aged <18 Years Hospitalized with COVID-19 — Six Hospitals, United States, July–August 2021**. MMWR Morb Mortal Wkly Rep 2021;70:1766–1772. DOI: **http://dx.doi.org/10.15585/mmwr.mm705152a3**

- BACKGROUND: During 6/2021, the highly transmissible B.1.617.2 (Delta) variant of SARS-CoV-2, became the predominant circulating strain in the US. Pediatric COVID-19–related hospitalizations increased during 7-8/2021 following emergence of the Delta variant and peaked in 9/2021. CDC partnered with 6 children's hospitals to review medical record data for patients aged <18 yrs with COVID-19–related hospitalizations during 7-8/2021.
- RESULTS: Among 915 pts identified, 713 (77.9%) were hospitalized for COVID-19 as the primary or contributing reason for hospitalization, 177 (19.3%) had incidental positive SARS-CoV-2 test results (asymptomatic or mild infection unrelated to the reason for hospitalization), and 25 (2.7%) had multisystem inflammatory syndrome in children (MIS-C).
- Among 713 hospitalized pts, 24.7% were <1 yr, 17.1% were 1–4 yrs, 20.1% were 5–11 yrs, and 38.1% were 12–17 yrs. Approximately two thirds of pts (67.5%) had one or more underlying medical conditions, with obesity being the most common (32.4%); among pts aged 12–17 yrs, 61.4% had obesity. Among hospitalized COVID-19 pts, 15.8% had a viral coinfection (66.4% with RSV infection). Approximately one half (54.0%) of hospitalized pts received O2 support, 29.5% were admitted to the ICU and 1.5% died; of those requiring respiratory support, 14.5% required invasive mechanical ventilation. Approximately 1/3 (33.9%) of hospitalized COVID-19 pts <5 yrs had viral coinfection.
- A higher percentage of pts hospitalized for COVID-19 with any underlying condition were admitted to the ICU (34.7%) compared with those without (18.5%) ($p<0.001$). Duration of hospitalization was longer for pts with obesity (median = 4 days [IQR = 2.0–7.5 days]) than for those without obesity (median = 2 days [IQR = 1.0–5.0 days]) ($p<0.001$). 41.1% of obese pts were admitted to ICU vs 23.9% of non-obese pts ($p<0.001$). A higher proportion of pts with viral coinfection required O2 support (69.0%) compared with those without viral coinfection (51.2%) ($p<0.001$).
- Among 272 vaccine-eligible (aged 12–17 yrs) pts hospitalized for COVID-19, one (0.4%) was fully vaccinated and 12 (4.4%) were partially vaccinated with an mRNA COVID-19 vaccine.
- SUMMARY: In 6 U.S. hospitals during July–August, 2021, ~3/4 of pediatric pts with COVID-19–related hospitalizations were hospitalized for acute COVID-19. The majority were Black or Hispanic & were <5 or 12–17 yrs. One third of pts < 4 yrs had a viral coinfection, ~1/3 of pts aged 5–11 yrs & ~2/3 of pts aged 12–17 yrs had obesity. 54.0% of hospitalized pts received O2 support, 29.5% were admitted to ICU & 1.5% died. **Less than 1% of vaccine-eligible pts were fully vaccinated against COVID-19.**

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

- BACKGROUND: Although myocarditis and pericarditis were not observed as adverse events in coronavirus disease 2019 (COVID-19) vaccine trials, there have been numerous reports of suspected cases following vaccination in the general population.

- STUDY DESIGN: To evaluate this, we undertook a self-controlled case series study of people aged >/=16 yrs vaccinated for COVID-19 in England between 1/12/2020 and 8/24/2021 to investigate hospital admission or death from myocarditis, pericarditis and cardiac arrhythmias in the 1–28 days following adenovirus (ChAdOx1, n = 20,615,911) or messenger RNA-based (BNT162b2, n = 16,993,389; mRNA-1273, n = 1,006,191) vaccines or a SARS-CoV-2 positive test (n = 3,028,867).
- RESULTS: The risk of myocarditis was rare but increased with all 3 types of the vaccines: two extra myocarditis events with adenovirus (ChAdOx1) vaccine, one event with BNT162b2 mRNA vaccine and six events with mRNA-1273 vaccine after the first dose; and an extra 10 myocarditis events after a second dose of mRNA-1273 per 1 million vaccinated. In comparison, SARS-CoV-2 positivity was associated with a markedly higher risk of myocarditis (extra 40 myocarditis events per 1 million patients following SARS-CoV-2 positive test), pericarditis and cardiac arrhythmias. The risk of myocarditis was higher with mRNA-1273 vaccine following the 2nd dose when compared with other vaccines. Risk of myocarditis was higher in persons <40 yrs.
- CONCLUSIONS: There is a small increased risk of myocarditis after vaccines against SARS-CoV2 infection with mRNA based & adenovirus COVID-19 vaccines. The risk associated with vaccination was significantly lower than the risk associated with the COVID-19 infection itself.

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Suh YJ, Hong H, Ohana M et al. **Pulmonary Embolism and Deep Vein Thrombosis in COVID-19: A Systematic Review and Meta-Analysis.** Radiology 2021; 298:E70–E80. **https://doi.org/10.1148/radiol.2020203557.**

- BACKGROUND: The association of pulmonary embolism (PE) with deep vein thrombosis (DVT) in patients with coronavirus disease 2019 (COVID-19) remains unclear, and the diagnostic accuracy of D-dimer tests for PE is unknown.
- PURPOSE: To conduct meta-analysis of the study-level incidence of PE and DVT and to evaluate the diagnostic accuracy of D-dimer tests for PE from multicenter individual patient data, a systematic literature search identified studies evaluating the incidence of PE or DVT in patients with COVID-19 from January 1, 2020, to June 15, 2020. Outcomes were pooled using a random-effects model and were further evaluated using meta-regression analysis. The diagnostic accuracy of D-dimer tests for PE was estimated on the basis of individual patient data using the summary receiver operating characteristic curve.
- RESULTS: Twenty-seven studies with 3342 patients with COVID-19 were included in the analysis. The pooled incidence rates of PE and DVT were 16.5% (95% CI: 11.6, 22.9; I2 = 0.93) and 14.8% (95% CI: 8.5, 24.5; I2= 0.94), respectively. PE was more frequently found in patients admitted to the ICU (24.7% [95% CI: 18.6, 32.1] vs 10.5% [95% CI:5.1, 20.2] in those not admitted to ICU) and in studies with universal screening using CT pulmonary angiography. DVT was present in 42.4% of patients with PE. D-dimer tests had an area under the receiver operating characteristic curve of 0.737 for PE, and D-dimer levels of 500 and 1000 mg/L showed high sensitivity (96% and 91%, respectively) but low specificity (10% and 24%, respectively).
- CONCLUSION: Pulmonary embolism (PE) and deep vein thrombosis (DVT) occurred in 16.5% and 14.8% of patients with COVID-19, respectively, and more than half of patients with PE lacked DVT. The cutoffs of D-dimer levels used to exclude PE in preexisting guidelines seem applicable to patients with COVID-19.

EPIDEMIOLOGY

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.
- 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-related hospitalization 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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Starke KR, Reissig D, Petereit-Haack G et al. **The isolated effect of age on the risk of COVID-19 severe outcomes: a systematic review with meta-analysis.** British Med J 2021; Volume 6, Issue 12. **http://orcid.org/0000-0002-6614-2381**

- The aim of this review was to quantify the isolated effect of age on hospitalization, admission to intensive care unit (ICU), mechanical ventilation and death.
- METHODS: An umbrella review, in which Pubmed, Embase and preprint databases were searched on 10 December 2020, for relevant reviews on COVID-19 disease severity. Two independent reviewers evaluated primary studies using predefined inclusion and exclusion criteria. Results were extracted, and each study assessed for risk of bias. The isolated effect of age was estimated by meta-analysis.
- RESULTS: Seventy studies met our inclusion criteria (case mortality: n=14, in-hospital mortality: n=44, hospitalization: n=16, admission to ICU: n=12, mechanical ventilation: n=7). The risk of in-hospital and case mortality increased per age year by 5.7% and 7.4%, respectively (effect size [ES] in-hospital mortality=1.057, 95% CI 1.038 to 1.054; ES case mortality=1.074, 95% CI 1.061 to 1.087), while the risk of hospitalisation increased by 3.4% per age year (ES=1.034, 95% CI 1.021 to 1.048). No increased risk was observed for ICU admission and intubation by age year. There was no evidence of a specific age threshold at which risk accelerates considerably. The confidence of evidence was high for mortality and hospitalization.
- CONCLUSIONS: Our results show a best-possible quantification of the continuous increase in COVID-19 disease severity due to age.

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Pijls G, Iolani S, Atherley A et al. **Demographic risk factors for COVID-19 infection, severity, ICU admission and death: a meta-analysis of 59 studies.** http://orcid.org/0000-0001-5351-5057

- OBJECTIVE: We aimed to describe the associations of age and sex with the risk of COVID-19 in different severity stages ranging from infection to death via Systematic review and meta-analysis.
- RESULTS: We screened 11.550 titles and included 59 studies comprising 36.470 patients in the analyses. The methodological quality of the included papers was high (8.2 out of 9). Men had a higher risk for infection with COVID-19 than women (relative risk (RR) 1.08, 95% CI 1.03 to 1.12). When infected, they also had a higher risk for severe COVID-19 disease (RR 1.18, 95% CI 1.10 to 1.27), a higher need for intensive care (RR 1.38, 95% CI 1.09 to 1.74) and a higher risk of death (RR 1.50, 95% CI 1.18 to 1.91).
- The analyses also showed that patients aged 70 years and above have a higher infection risk (RR 1.65, 95% CI 1.50 to 1.81), a higher risk for severe COVID-19 disease (RR 2.05, 95% CI 1.27 to 3.32), a higher need for intensive care (RR 2.70, 95% CI 1.59 to 4.60) and a higher risk of death once infected (RR 3.61, 95% CI 2.70 to 4.84) compared with patients younger than 70 years.

- CONCLUSIONS: Meta-analyses on 59 studies comprising 36.470 patients showed that men and pts aged 70 and above have a significantly higher risk for COVID-19 infection, severe disease, ICU admission and death.

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Ma Q, Liu J, Liu Q et al. **Global Percentage of Asymptomatic SARS-CoV-2 Infections Among the Tested Population and Individuals with Confirmed COVID-19 Diagnosis: A Systematic Review and Meta-analysis.** JAMA Netw Open. 2021; 4(12):e2137257. **doi:10.1001/jamanetworkopen.2021.37257**

- Background: Asymptomatic infections are potential sources of transmission for COVID-19. This systematic review evaluated the percentage of asymptomatic infections among individuals undergoing testing (tested population) and those with confirmed COVID-19 (confirmed population).
- METHODS: Cross-sectional studies, cohort studies, case series studies, and case series on transmission reporting the number of asymptomatic infections among the tested and confirmed COVID-19 populations that were published in Chinese or English were included.
- RESULTS: Ninety-five unique eligible studies were included, covering 29 776 306 individuals undergoing testing. The pooled percentage of asymptomatic infections among the tested population was 0.25% (95% CI, 0.23%-0.27%), higher in nursing home residents or staff (4.52% [95% CI, 4.15%-4.89%]), air or cruise travelers (2.02% [95% CI, 1.66%-2.38%]), and pregnant women (2.34% [95% CI, 1.89%-2.78%]). The pooled percentage of asymptomatic infections among the confirmed population was 40.50% (95% CI, 33.50%-47.50%), higher in pregnant women (54.11% [95% CI, 39.16%-69.05%]), air or cruise travelers (52.91% [95% CI, 36.08%-69.73%]), and nursing home residents or staff (47.53% [95% CI, 36.36%-58.70%]).
- CONCLUSIONS & RELEVANCE: In this meta-analysis of the percentage of asymptomatic SARS-CoV-2 infections among populations tested for and with confirmed COVID-19, the pooled percentage of asymptomatic infections was 0.25% among the tested population and 40.50% among the confirmed population. The high percentage of asymptomatic infections highlights the potential transmission risk of asymptomatic infections in communities.

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TREATMENT

Diaz R, Orlandini A, Castellana N et al. **Effect of Colchicine vs Usual Care Alone on Intubation and 28-Day Mortality in Patients Hospitalized With COVID-19: A Randomized Clinical Trial.** JAMA Netw Open Published 12/29/2021; 4(12):e2141328. **doi:10.1001/jamanetworkopen.2021.41328**

- BACKGROUND: To assess the efficacy of colchicine in hospitalized pts with COVID-19 pneumonia, the COLCOVID trial was a multicenter, open-label RCT performed from 4/17/2020 – 3/28/2021 in adults with confirmed or suspected SARS-CoV-2 infection followed for up to 28 days.
- Participants received colchicine vs usual care if they were hospitalized with COVID-19 symptoms and had severe acute respiratory syndrome or oxygen desaturation. Colchicine was administered orally in a loading dose of 1.5 mg immediately after randomization, followed by 0.5 mg orally within 2 hours of the initial dose and 0.5 mg orally twice a day for 14 days or discharge, whichever occurred first.
- RESULTS: 1279 hospitalized pts (mean [SD] age, 61.8 [14.6] years; 449 [35.1%] women/ 830 [64.9%] men) were randomized, including 639 pts in the usual care group & 640 pts in the colchicine group. Corticosteroids were used in 1171 patients (91.5%). The coprimary outcome of mechanical ventilation or 28-day death occurred in 160 pts (25.0%) in the colchicine group & 184 pts (28.8%) in the usual care group (hazard ratio [HR], 0.83; 95% CI, 0.67-1.02; P = .08). The 2nd coprimary outcome, 28-day death, occurred in 131 pts (20.5%) in the colchicine group & 142 pts (22.2%) in the usual care group (HR, 0.88; 95% CI, 0.70-1.12).
- CONCLUSION: Colchicine did not significantly reduce mechanical ventilation or 28-day mortality in patients hospitalized with COVID-19 pneumonia.

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O'brien MP, Forleo-Neto E, Sarkar N et al. **Effect of Subcutaneous Casirivimab and Imdevimab Antibody Combination vs Placebo on Development of Symptomatic COVID-19 in Early Asymptomatic SARS-CoV-2 Infection. A Randomized Clinical Trial.** JAMA. Published online January 14, 2022. **doi:10.1001/jama.2021.24939**

- BACKGROUND: Casirivimab & imdevimab are neutralizing, human sequence monoclonal Abs that bind nonoverlapping epitopes on the SARS-CoV-2 spike protein receptor–binding domain & block virus entry. In vitro, the 2-Ab combination reduces the risk of emergence of treatment-induced SARS-CoV-2 variants and retains neutralization potency against already circulating VOCs/VOIs, including B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma) & B.1.617.2 (Delta). In vivo, casirivimab + imdevimab combination Rx has proven effective in treating COVID-19 outpts and in preventing infection in close-contact settings. This study evaluates the impact of subcutaneous casirivimab and imdevimab, 1200 mg on the development of symptomatic COVID-19 in infected close contacts of symptomatic pts.
- DESIGN: RCT of close household contacts of a SARS-CoV-2–infected index case at 112 sites in the US, Romania, and Moldova enrolled 7/132020–1/28/28, 2021. Asymptomatic individuals ≥12 yrs were eligible if identified within 96 hrs of index case (+) test. Results are from 314 individuals (+) on PCR SARS-CoV-2 testing randomized 1:1 to receive 1 dose of

subcutaneous casirivimab + imdevimab, 1200 mg (600 mg of each; n = 158), or placebo (n = 156).

- OUTCOMES: Primary end point was the proportion of seronegative participants who developed symptomatic COVID-19 during the 28-day efficacy assessment period. The key secondary efficacy end points were the number of weeks of symptomatic SARS-CoV-2 infection and the number of weeks of high viral load (>4 log10 copies/mL).
- RESULTS: Subcutaneous casirivimab + imdevimab, 1200 mg, significantly prevented progression to symptomatic disease (29/100 [29.0%] vs 44/104 [42.3%] with placebo; odds ratio, 0.54 [95% CI, 0.30-0.97]; P = .04; absolute risk difference, −13.3% [95% CI, −26.3% to −0.3%]). Casirivimab + imdevimab reduced the number of symptomatic wks per 1000 participants (895.7 weeks vs 1637.4 weeks with placebo; P = .03), an approximately 5.6-day reduction in symptom duration. Treatment with casirivimab + imdevimab reduced the number of high viral load weeks per 1000 participants (489.8 weeks vs 811.9 weeks with placebo; P = .001). The proportion of participants receiving casirivimab + imdevimab who had >/=1 treatment-emergent AE was 33.5% vs 48.1% for placebo, including events related (25.8% vs 39.7%) or unrelated (11.0% vs 16.0%) to COVID-19.
- CONCLUSIONS: Among asymptomatic SARS-CoV-2 RT-qPCR–positive individuals living with an infected household contact, treatment with subcutaneous casirivimab + imdevimab Ab combination vs placebo significantly reduced the incidence of symptomatic COVID-19.

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Berger JS, Kornblith LZ, Gong MN et al. **Effect of P2Y12 Inhibitors on Survival Free of Organ Support Among Non–Critically Ill Hospitalized Patients With COVID-19: A Randomized Clinical Trial.** JAMA. 2022;327(3):227-236. Published 1/19/2022. **doi:10.1001/jama.2021.23605.**

- BACKGROUND: Platelet inhibition represents a potential therapeutic target for improved clinical outcomes in patients with COVID-19.
- METHOD: To evaluate the benefits & risks of adding a P2Y12 inhibitor to anticoagulant therapy among non–critically ill pts hospitalized for COVID-19, an open-label, bayesian, adaptive RCT of 562 non–critically ill pts hospitalized for COVID-19 was conducted between 2/2021 and 6/2021 at 60 hospitals in Brazil, Italy, Spain & the US. Pts were randomized to a therapeutic dose of heparin plus a P2Y12 inhibitor (n = 293) or a therapeutic dose of heparin only (usual care) (n = 269) in a 1:1 ratio for 14 days or until hospital discharge.
- OUTCOMES: The composite primary outcome was organ support–free days evaluated on an ordinal scale that combined in-hospital death &, for those who survived to hospital discharge, the number of days free of respiratory or cardiovascular organ support up to day 21 of the index hospitalization. The primary safety outcome was major bleeding by 28 days.
- RESULTS: Enrollment of non–critically ill pts was discontinued when the prespecified criterion for futility was met. All 562 patients who were randomized (mean age, 52.7 [SD, 13.5] years; 41.5% women) completed the trial and 87% received a therapeutic dose of heparin by the end of study day 1. In the P2Y12 inhibitor group, ticagrelor was used in 63% of patients and clopidogrel in 37%. The median # of organ support–free days was 21 (IQR, 20-21 days) among pts in the P2Y12 inhibitor group & 21 (IQR, 21-21 days) in the usual care group. Major bleeding occurred in 6 pts (2.0%) in the P2Y12 inhibitor group & two (0.7%) in the usual care group.

- CONCLUSIONS: Among non–critically ill patients hospitalized for COVID-19, the use of a P2Y12 inhibitor in addition to a therapeutic dose of heparin vs a therapeutic dose of heparin only, did not result in an increased odds of improvement in organ support–free days within 21 days during hospitalization.

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Memel ZN, Lee JJ, Foulkes AS et al. **Association of Statins and 28-Day Mortality Rates in Patients Hospitalized with Severe Acute Respiratory Syndrome Coronavirus 2 Infection.** The Journal of Infectious Diseases, Volume 225 (1): 1 January 2022, Pages 19–29. **https://doi.org/10.1093/infdis/jiab539**

- **BACKGROUND:** Statins may be protective in severe acute SARS-CoV-2 infection.
- **STUDY DESIGN:** To evaluate the effect of in-hospital statin use on 28-day mortality rates and intensive care unit (ICU) admission among pts with SARS-CoV-2, pts were stratified into 4 groups: statins used before hospitalization (treatment continued or discontinued in the hospital) and those who did not (treatment newly initiated in the hospital or never initiated). In a cohort study of 1179 patients with SARS-CoV-2, record review was used to assess demographics, laboratory measurements, comorbid conditions, and time from admission to death, ICU admission, or discharge. Using marginal structural Cox models, we estimated hazard ratios (HRs) for death and ICU admission.
- **RESULTS:** Among 1179 patients, 676 (57%) were male, 443 (37%) were >65 years old, and 493 (46%) had a BMI ≥30. In this cohort, 154 patients (13%) died and 841 (71%) were discharged within 28 days. Overall, statin usage during hospitalization decreased the hazard of death (HR, 0.566 [95% CI, .372–.862]; P=.008). In the subgroup of pts not using statin therapy before hospitalization, statin initiation at hospitalization decreased the hazard of death (HR, 0.493 [95% CI, .253–.963]; P=.04). Of the subgroup of pts who were using statin therapy before hospitalization, continued statin usage also decreased the hazard of death (HR, 0.270 [95% CI, .114–.637]; P=.003) In unadjusted analyses, patients on statins during hospitalization had similar rates of death as those not on statins during hospitalization (108 [14%] vs 46 [11%], respectively; P=.27), but higher rates of ongoing hospitalization at 28 days (144 [19%] vs 40 [10%]; P<.001) and ICU admission (276 [36%] vs 85 [21%]; P<.001) Inpatient statin use was associated with improved time to death for pts aged >65 yrs but not for those ≤65 yrs old.

CONCLUSION: Statin use during hospitalization for SARS-CoV-2 infection was associated with reduced 28-day mortality rates. Well-designed randomized control trials are needed to better define this relationship.

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Gandhi RT, Malani PN, delRio C. **COVID-19 Therapeutics for Non-hospitalized Patients.** JAMA. Published online January 14, 2022. **doi:10.1001/jama.2022.0335**

Excellent review article summarizing COVID-19 treatment options in the Omicron era.

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Perkins GD, Ji C, Connolly BA et al. **Effect of Noninvasive Respiratory Strategies on Intubation or Mortality Among Patients with Acute Hypoxemic Respiratory Failure and**

COVID-19: The RECOVERY-RS Randomized Clinical Trial. JAMA. Published online January 24, 2022. **doi:10.1001/jama.2022.0028**

- BACKGROUND: Continuous positive airway pressure (CPAP) & high-flow nasal oxygen (HFNO) have been used for acute hypoxemic respiratory failure in pts with COVID-19. Uncertainty exists regarding the effectiveness and safety of these noninvasive respiratory strategies.
- OBJECTIVE: To determine whether CPAP or HFNO vs conventional O2 therapy, improves clinical outcomes in hospitalized pts with COVID-19–related acute hypoxemic respiratory failure.
- DESIGN: A parallel group, adaptive, RCT of 1273 hospitalized adults with COVID-19–related acute hypoxemic respiratory failure was conducted between 4/66, 2020 & 5/3, 2021, across 48 acute care hospitals in the UK and Jersey. Final follow-up occurred on June 20, 2021. Pts were randomized to receive CPAP (n = 380), HFNO (n = 418), or conventional O2 therapy (n = 475).
- OUTCOME: Composite of tracheal intubation or mortality within 30 days.
- RESULTS: The trial was stopped prematurely due to declining COVID-19 case numbers in the UK and the end of the funded recruitment period. Of the 1273 randomized pts (mean age, 57.4 [95% CI, 56.7 to 58.1] years; 66% male; 65% White race), primary outcome data were available for 1260. Crossover between interventions occurred in 17.1% of participants (15.3% in the CPAP group, 11.5% in the HFNO group & 23.6% in the conventional O2 therapy group). The requirement for tracheal intubation or mortality within 30 days was significantly lower with CPAP (36.3%; 137/377 pts) vs conventional O2 therapy (44.4%; 158/356 pts) (absolute difference, −8% [95% CI, −15% to −1%], P = .03), but was not significantly different with HFNO (44.3%; 184/415 pts) vs conventional O2 therapy (45.1%; 166/368 pts) (absolute difference, −1% [95% CI, −8% to 6%], P = .83). Adverse events occurred in 34.2% of participants in the CPAP group, 20.6% in the HFNO group, and 13.9% in the conventional O2 therapy group.
- CONCLUSION: Among pts with acute hypoxemic respiratory failure due to COVID-19, an initial strategy of CPAP significantly reduced the risk of tracheal intubation or mortality compared with conventional O2 therapy, but there was no significant difference between an initial strategy of HFNO compared with conventional O2 therapy.

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Troxel AB, Petkova E, Goldfeld K et al. **Association of Convalescent Plasma Treatment with Clinical Status in Patients Hospitalized With COVID-19: A Meta-analysis.** JAMA Network Open. 2022;5(1):e2147331. **doi:10.1001/jamanetworkopen.2021.47331**

- BACKGROUND: COVID-19 convalescent plasma (CCP) is a potentially beneficial treatment for COVID-19 but definite evidence of clinical benefit is lacking. This study aims to compile individual patient data from RCTs of CCP and to monitor the data until accumulated evidence enables reliable conclusions regarding the clinical outcomes associated with CCP.
- DATA COURCES: From May to August 2020, a systematic search was performed for trials of CCP in the literature, clinical trial registry sites, and medRxiv. Domain experts at local, national, and international organizations were consulted regularly. Eligible trials enrolled hospitalized pts with confirmed COVID-19, not receiving mechanical ventilation &

randomized them to CCP or control. The administered CCP was required to have measurable antibodies assessed locally.

- OUTCOMES: Prespecified coprimary end points—the World Health Organization (WHO) 11-point ordinal scale analyzed using a proportional odds model & a binary indicator of WHO score of >/=7 capturing the most severe outcomes including mechanical ventilation through death, analyzed using a logistic model—were assessed at 14 days after randomization.
- RESULTS: Eight international trials collectively enrolled 2369 participants (1138 randomized to control and 1231 randomized to CCP). A total of 2341 participants (median [IQR] age, 60 [50-72] years; 845 women [35.7%]) had primary outcome data as of April 2021. The median (IQR) of the ordinal WHO scale was 3 (3-6); the cumulative OR was 0.94 (95% credible interval [CrI], 0.74-1.19; posterior probability of OR <1 of 71%). A total of 352 patients (15%) had WHO score greater than or equal to 7; the OR was 0.94 (95% CrI, 0.69-1.30; posterior probability of OR <1 of 65%). Adjusted for baseline covariates, the ORs for mortality were 0.88 at day 14 (95% CrI, 0.61-1.26; posterior probability of OR <1 of 77%) and 0.85 at day 28 (95% CrI, 0.62-1.18; posterior probability of OR <1 of 84%). Heterogeneity of treatment effect sizes was observed across an array of baseline characteristics.
- CONCLUSION: This M-A found no association of CCP with better clinical outcomes for the typical pt. Findings suggest that real-time individual pt data pooling and M-A during a pandemic are feasible, offering a model for future research, providing a rich data resource.

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O'Brien MP, Forleo-Neto E, Sarkar N et al. **Effect of Subcutaneous Casirivimab and Imdevimab Antibody Combination vs Placebo on Development of Symptomatic COVID-19 in Early Asymptomatic SARS-CoV-2 Infection: A Randomized Clinical Trial.** JAMA. 2022;327(5):432-441. **doi:10.1001/jama.2021.24939.**

- OBJECTIVE: To evaluate the effect of combination subcutaneous casirivimab and imdevimab on progression from early asymptomatic SARS-CoV-2 infection to symptomatic COVID-19.
- STUDY DESIGN: RCT double-blind, placebo-controlled, phase 3 trial of close household contacts of a SARS-CoV-2–infected index case at 112 sites in the US, Romania, and Moldova enrolled 7/13/2020–1/28/2021. Asymptomatic individuals (aged ≥12 yrs) were eligible if identified within 96 hrs of index case (+) test collection. Results from 314 individuals (+) on SARS-CoV-2 RT-qPCR testing are reported. Subjects were randomized 1:1 to receive 1 dose of subcutaneous casirivimab/imdevimab (600 mg each; n = 158) vs placebo (n = 156).
- OUTCOMES: The primary end point was the proportion of seronegative participants who developed symptomatic COVID-19 during the 28-day efficacy assessment period. The key secondary efficacy end points were the number of weeks of symptomatic SARS-CoV-2 infection and the number of weeks of high viral load (>4 log10 copies/mL).
- RESULTS: Among 314 randomized participants (mean age, 41.0 years; 51.6% women), 310 (99.7%) completed the efficacy assessment period; 204 were asymptomatic and seronegative at baseline and included in the primary efficacy analysis. Subcutaneous casirivimab and imdevimab, 1200 mg, significantly prevented progression to symptomatic disease (29/100 [29.0%] vs 44/104 [42.3%] with placebo; odds ratio, 0.54 [95% CI, 0.30-0.97]; P = .04; absolute risk difference, −13.3% [95% CI, −26.3% to −0.3%]). Casirivimab and imdevimab reduced the number of symptomatic weeks per 1000 participants (895.7 weeks

vs 1637.4 weeks with placebo; P = .03), an approximately 5.6-day reduction in symptom duration per symptomatic participant. Treatment with casirivimab and imdevimab also reduced the number of high viral load weeks per 1000 participants (489.8 weeks vs 811.9 weeks with placebo; P = .001).

- CONCLUSIONS: Among asymptomatic SARS-CoV-2 RT-qPCR–(+) individuals living with an infected household contact, subcutaneous casirivimab & imdevimab antibody combination treatment vs placebo significantly reduced the incidence of symptomatic COVID-19.

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MITIGATION/PREVENTION

Bar-ON YM, Goldberg Y, Mandel M et al. **Protection against Covid-19 by BNT162b2 Booster across Age Groups.** New Engl J Med, December 8, 2021. **DOI: 10.1056/NEJMoa2115926**

- Response to a booster dose of the BNT162b2 messenger RNA vaccine (Pfizer–BioNTech) vaccine against SARS-C0V-2 infection was evaluated using the results of a booster campaign in Israel which was gradually expanded to persons in younger age groups,
- METHODS: Data was extracted for the period from July 30 to October 10, 2021, from the Israel Ministry of Health database regarding 4,696,865 persons 16 years of age or older who had received two doses of BNT162b2 at least 5 months earlier and compared the rates of confirmed coronavirus disease 2019 (Covid-19), severe illness, and death among those who had received a booster dose at least 12 days earlier (booster group) with the rates among those who had not received a booster (non-booster group).
- RESULTS: The rate of confirmed infection was significantly lower in the booster group than in the non-booster group by a factor of approximately 10 (range across five age groups, 9.0 to 17.2) The adjusted rate difference ranged from 57.0 to 89.5 infections per 100,000 person-days in the primary analysis. The rates of severe illness were lower in the booster group by a factor of 17.9 (95% confidence interval [CI], 15.1 to 21.2) and 6.5 (95% CI, 5.1 to 8.2), respectively, among those 60 years of age or older and by a factor of 21.7 (95% CI, 10.6 to 44.2) and 3.7 (95% CI, 1.3 to 10.2) among those 40 to 59 years of age. The adjusted rate difference was 5.4 cases of severe illness per 100,000 person-days among those 60 years of age or older and 0.6 among those 40 to 59 years of age. Among those 60 years of age or older, mortality was lower by a factor of 14.7 (95% CI, 10.0 to 21.4) in the secondary analysis. The adjusted rate difference was 2.1 and 0.8 deaths per 100,000 person-days.
- CONCLUSION: Across all age groups studied, rates of confirmed Covid-19 and severe illness were substantially lower among participants who received a booster dose of the BNT162b2 vaccine than among those who did not.

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Mills MC, Ruttenauer T. **The effect of mandatory COVID-19 certificates on vaccine uptake: synthetic-control modelling of six countries.** The Lancet Public Health. Published: December 13, 2021. **DOI: https://doi.org/10.1016/S2468-2667(21)00273-5**

- BACKGROUND: Mandatory COVID-19 certification (showing vaccination, recent negative test, or proof of recovery) has been introduced in some countries. We aimed to investigate the effect of certification on vaccine uptake.
- METHODS: We designed a synthetic control model comparing six countries (Denmark, Israel, Italy, France, Germany, and Switzerland) that introduced certification (April–August, 2021), with 19 control countries. Using daily data on cases, deaths, vaccinations, and country-specific information, we produced a counter-factual trend estimating what might have happened in similar circumstances if certificates were not introduced. The main outcome was daily COVID-19 vaccine doses.
- FINDINGS: COVID-19 certification led to increased vaccinations 20 days before implementation in anticipation, with a lasting effect up to 40 days after. Countries with pre-

intervention uptake that was below average had a more pronounced increase in daily vaccinations compared with those where uptake was already average or higher. In France, doses exceeded 55 672 (95% CI: 49 668–73 707) vaccines per million population or, in absolute terms, 3 761 440 (3 355 761–4 979 952) doses before mandatory certification and 72 151 (37 940–114 140) per million population after certification (4 874 857 [2 563 396–7 711 769] doses). We found no effect in countries that already had average uptake (Germany), or an unclear effect when certificates were introduced during a period of limited vaccine supply (Denmark). Increase in uptake was highest for people younger than 30 yrs after the introduction of certification. Access restrictions linked to certain settings (nightclubs and events with >1000 people) were associated with increased uptake in those younger than 20 yrs. When certification was extended to broader settings, uptake remained high in the youngest group, but increases were also observed in those aged 30–49 yrs.

- INTERPRETATION: Mandatory COVID-19 certification increases vaccine uptake, but interpretation and transferability of findings need to be considered in the context of pre-existing levels of vaccine uptake and hesitancy, eligibility changes, and the pandemic trajectory.

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Andrews N, Stowe J, Kirsebom F et al. **Effectiveness of COVID-19 vaccines against the Omicron (B.1.1.529) variant of concern.** NEJM 2022. March 2, 2022.
DOI: 10.1056/NEJMoa2119451

- BACKGROUND: The rapid increase in coronavirus disease 2019 (Covid-19) cases due to omicron (B.1.1.529) variant of severe acute respiratory syndrome coronavirus 2 in highly vaccinated populations has aroused concerns about the effectiveness of current vaccines.
- METHODS: We used a test-negative case–control design to estimate vaccine effectiveness against symptomatic disease caused by the omicron and delta (B.1.617.2) variants in England. Vaccine effectiveness was calculated after primary immunization with two doses of BNT162b2 (Pfizer–BioNTech), ChAdOx1 nCoV-19 (AstraZeneca), or mRNA-1273 (Moderna) vaccine and after a booster dose of BNT162b2, ChAdOx1 nCoV-19, or mRNA-1273.
- RESULTS: Between 11/27/2021-1/12/2022, 886,774 eligible persons infected with omicron, 204,154 eligible persons infected with delta, and 1,572,621 eligible (-) controls were identified. At all time points and for all combinations of primary course and booster vaccines, vaccine effectiveness against symptomatic disease was higher for the delta variant than for the omicron variant. No effect against the omicron variant was noted from 20 weeks after two ChAdOx1 nCoV-19 doses, whereas vaccine effectiveness after two BNT162b2 doses was 65.5% at 2 to 4 weeks, dropping to 8.8% at 25 or more weeks. Among ChAdOx1 nCoV-19 primary course recipients, vaccine effectiveness increased to 62.4% at 2 to 4 weeks after a BNT162b2 booster before decreasing to 39.6% at 10 or more weeks. Among BNT162b2 primary course recipients, vaccine effectiveness increased to 67.2% at 2 to 4 weeks after a BNT162b2 booster before declining to 45.7% at 10 or more weeks. Vaccine effectiveness after a ChAdOx1 nCoV-19 primary course increased to 70.1% at 2 to 4 weeks after an mRNA-1273 booster and decreased to 60.9% at 5 to 9 weeks. After a BNT162b2 primary course, the mRNA-1273 booster increased vaccine effectiveness to 73.9% at 2 to 4 weeks; vaccine effectiveness fell to 64.4% at 5 to 9 weeks.
- CONCLUSIONS: Primary immunization with 2 doses of ChAdOx1 nCoV-19 or BNT162b2 vaccine provided limited protection against symptomatic disease caused by the omicron

variant. A BNT162b2 or mRNA-1273 booster after either ChAdOx1 nCoV-19 or BNT162b2 primary course substantially increased protection, but that protection waned over time.

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Hause AM, Baggs J, Marquez P, et al. **COVID-19 Vaccine Safety in Children Aged 5–11 Years — United States, November 3–December 19, 2021.** MMWR Morb Mortal Wkly Rep 2021; 70:1755–1760. **DOI: http://dx.doi.org/10.15585/mmwr.mm705152a1**

- To characterize safety of the Pfizer-BioNTech COVID-19 vaccine in children aged 5–11 yrs, CDC reviewed AEs after vaccine receipt reported to the Vaccine AE Reporting System (VAERS), a passive vaccine safety surveillance system co-managed by CDC and FDA, and adverse events and health impact assessments reported to v-safe, a voluntary safety surveillance system for AEs after COVID-19 vaccination, from 11/3–12/19, 2021.
- METHODS: VAERS is a national passive vaccine safety surveillance system, jointly managed by CDC & FDA, that monitors AEs after vaccination. VAERS accepts reports from anyone, including health care providers, vaccine manufacturers, and members of the public. Symptoms, signs, and diagnostic findings in VAERS reports are assigned MedDRA terms by VAERS staff members. Reports are classified as serious if any of the following are reported: hospitalization, prolongation of hospitalization, life-threatening illness, permanent disability, congenital anomaly or birth defect, or death. Reports of serious AEs are followed up by VAERS staff members to obtain additional information, including medical records. For reports of death, death certificates and autopsy reports are obtained. CDC MDs review all available information for each decedent to establish cause of death. Reports of myocarditis and pericarditis after receipt of COVID-19 vaccine were identified by a search for selected MedDRA preferred terms; CDC staff members collect information about clinical course and recovery related to myocarditis and pericarditis from pts and health care providers.
  V-safe is a voluntary smartphone-based active safety surveillance system, specifically to monitor AEs after COVID-19 vaccination with children enrolled after the 1st or 2nd vaccine dose. Health surveys in the first week after vaccination include questions about local injection site and systemic reactions (mild, moderate, or severe) and health impacts. CDC's v-safe call center contacts a parent or guardian when a report indicates that a child received medical care for new or worsening symptoms.
- VAERS and v-safe data collected during November 3–December 19, 2021 among children aged 5–11 years who received Pfizer-BioNTech COVID-19 vaccine were analyzed and described overall and by sex, age group, and race/ethnicity.
- RESULTS: ~8.7 million doses of Pfizer-BioNTech COVID-19 vaccine were administered to children aged 5–11 yrs during this period; VAERS received 4,249 reports of AEs after vaccination with Pfizer-BioNTech COVID-19 vaccine in this age group, 4,149 (97.6%) of which were not serious.
- Overall, in 4,149 (97.6%) VAERS reports, 100 (2.4%) were for serious events. Among these, the median age was 9 yrs, 61.0% males. The most commonly reported conditions were fever (29; 29.0%), vomiting (21; 21.0%), and increased troponin (15; 15.0%). Among 12 serious reports of seizure, five children experienced new-onset seizures. Among 15 preliminary reports of myocarditis, 11 were verified and met the case definition for myocarditis; of these, seven recovered, and four were recovering at time of the report. VAERS received two reports of death during the analytic period in 2 females, aged 5 and 6 yrs, both with complicated

medical histories and fragile health before vaccination. No causal association between death and vaccination was suggested.

- ~42,504 children aged 5–11 years were enrolled in v-safe after vaccination with Pfizer-BioNTech COVID-19 vaccine; after dose 2, a total of 17,180 (57.5%) local and 12,223 systemic (40.9%) reactions (including injection-site pain, fatigue, or headache) were reported.
- SUMMARY: Trial participants who received Pfizer-BioNTech COVID-19 vaccine frequently reported local (86.2%) and systemic (66.6%) reactions via v-safe that were mostly mild (i.e., did not interfere with normal daily activities) or moderate (some interference with normal daily activities).
- Among VAERS reports, the only serious event was myocarditis, verified in 11 reports after administration of approximately eight million vaccine doses. In a previous active vaccine safety surveillance system, no confirmed reports of myocarditis were observed during the 1–21 days or 1–42 days after 333,000 vaccine doses were administered to children of the same age. These 11 cases appear consistent with other reports of myocarditis after mRNA COVID-19 vaccination regarding time to symptom onset and a mild clinical course. Two deaths after Pfizer-BioNTech COVID-19 vaccine were reported for children with multiple chronic medical conditions; on initial review, no causal association was suggested between death and vaccination
- CONCLUSION: Local and systemic reactions after vaccination were commonly reported to VAERS and v-safe for vaccinated children aged 5–11 years. Serious adverse events were rare and self-resolving.

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Dejnirattisa W, Huo J, Zhou D et al. **Omicron-B.1.1.529 leads to widespread escape from neutralizing antibody responses.** bioRxiv preprint; posted December 22, 2021. **doi:https://doi.org/10.1101/2021.12.03.471045**;

- BACKGROUND: The new SARS CoV-2 viral isolate – Omicron B.1.1.529 - contains far more mutations in Spike (S) than previous variants and is spreading rapidly. To evaluate the variant's response in immunized individuals, researchers studied the neutralization of Omicron by a large panel of sera collected from convalescent early pandemic, Alpha, Beta, Gamma and Delta-infected individuals, together with vaccinees receiving three doses of the Oxford/AstraZeneca (AZD1222) or the Pfizer BioNtech (BNT16b2) vaccines.
- METHOD: Sera were collected from ptss infected early in the pandemic (n=32) before the emergence
- of the variants of concern (VOC), along with cases infected with Alpha (n=18), Beta (n=14), Gamma (n=16) and Delta (n=42). Neutralization assays were performed against Omicron and compared with neutralization titres for Victoria (an early pandemic strain), Alpha, Beta, Gamma and Delta.
- RESULTS: In all cases neutralization titres to Omicron were substantially reduced compared to either
  the ancestral strain Victoria or to the homologous strain causing infection and in a number of cases immune serum failed to neutralize Omicron at 1/20 dilution. Sera taken from convalescent cases previously infected with a variety of SARS CoV-2 variants show substantial reduction in neutralization titres to Omicron. Compared to Victoria the neutralization titres of sera for Omicron were reduced for early pandemic 16.9-fold

(p<0.0001), Alpha 33.8-fold (p<0.0001), Beta 11.8-fold (p=0.0001), Gamma 3.1-fold (p=0.001) and Delta 1.7-fold (p=0.0182).

- To examine the effect of booster vaccination, we tested neutralization of Victoria, Delta & Omicron
  using sera from individuals receiving 3 doses of ADZ1222 (n=41) or BNT162b2 (n=20).
- SUMMARY: Neutralization titres of Omicron by sera from vaccinees and convalescent subjects infected with early pandemic as well as Alpha, Beta, Gamma, Delta were substantially
  reduced or failed to neutralize. Titres against Omicron were boosted by third vaccine doses and
  are high in cases both vaccinated and infected by Delta.
- CONCLUSION: Mutations in Omicron knock out or substantially reduce neutralization by most of a large panel of potent monoclonal antibodies and antibodies under commercial development. Neutralization titres against Omicron are boosted following a third vaccine dose, meaning that the campaign to deploy booster vaccines should add considerable protection against Omicron infection.

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Levy M. Recher M, Hubert H et al. **Multisystem Inflammatory Syndrome in Children by COVID-19 Vaccination Status of Adolescents in France.** JAMA 2021. Published online December 20, 2021. **doi:10.1001/jama.2021.23262**

- To assess the effect of vaccination on multisystem inflammatory syndrome in children, MIS-C pts in France during the 4th wave of COVID-19 infection were evaluated. All pediatric pts diagnosed with MIS-C by WHO criteria & admitted to one of 41 French PICUs from 9/1-10/31/2021 were included.
- To account for the increasing # of adolescents vaccinated over time, hazard ratios of unvaccinated vs vaccinated adolescents with at least 1 vaccine dose were estimated. Given the delays between vaccine injection and immune response, and between SARS-CoV-2 infection and MIS-C onset, 3 sensitivity analyses were performed with adolescents considered vaccinated at >/= 14, >/= 28, & >/=42 days after the first vaccine dose.
- RESULTS: On 6/15/2021, the beginning of the adolescent COVID-19 vaccination campaign, 2.2% of 4 989 013 adolescents in France were vaccinated with at least 1 dose & 0.2% were fully vaccinated. By 10/31/2021, 76.7% of adolescents had received at least 1 vaccine dose and 72.8% were fully vaccinated.
- From 9/1-10/31/2021, 107 children with MIS-C were hospitalized in France and 33 (31%) were adolescents eligible for vaccination. Adolescents with MIS-C were a median (IQR) age of 13.7 (12.5-14.9) yrs, 27 (81%) male, & 29 (88%) admitted to PICU. Among them, **0** had been fully vaccinated; **7** had received 1 dose with median (IQR) between vaccine injection and MIS-C onset of 25 (17-37) days; and **26** had not been vaccinated. The HR for MIS-C was 0.09 (95% CI, 0.04-0.21; P < .001) after the 1st vaccine dose vs unvaccinated adolescents.
- CONCLUSION: Most adolescents with MIS-C for whom vaccination was indicated in France had not been vaccinated, suggesting that COVID-19 mRNA vaccination was associated with a significantly lower incidence of MIS-C. In most cases where SARS-CoV-2 infection occurred after a single vaccination, the time interval between injection & infection was short indicating the immune response was incomplete.

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Beatty AL, Peyser ND, Butcher XE et al. **Analysis of COVID-19 Vaccine Type and Adverse Effects Following Vaccination.** JAMA Netw Open 2021; 4(12):e2140364. **doi:10.1001/jamanetworkopen.2021.40364**

- To assess COVID-19 vaccine adverse effects in a real-world population, reports from the Citizen Science Study, an online cohort study of adults aged >/= 18 yrs with smartphone or internet access, were analyzed. Participants complete daily, weekly, and monthly surveys on health and COVID-19–related events. This analysis includes participants who provided consent between 3/26/2020 & 5/19/2021, and received at least 1 COVID-19 vaccine dose.
- RESULTS: The 19 586 participants had a median (IQR) age of 54 (38-66) years &13 420 (68.8%) were women. Allergic reaction or anaphylaxis was reported in 26 of 8680 participants (0.3%) after 1 dose of the BNT162b2 (Pfizer/BioNTech) or mRNA-1273 (Moderna) vaccine, 27 of 11 141 (0.2%) after 2 doses of the BNT162b2 or mRNA-1273 vaccine or 1 dose of the JNJ-78436735 (Johnson & Johnson) vaccine.
- The strongest factors associated with adverse effects were vaccine dose (2 doses of BNT162b2 or mRNA-1273 or 1 dose of JNJ-78436735 vs 1 dose of BNT162b2 or mRNA-1273; odds ratio [OR], 3.10; 95% CI, 2.89-3.34; P < .001), vaccine brand (mRNA-1273 vs BNT162b2, OR, 2.00; 95% CI, 1.86-2.15; P < .001; JNJ-78436735 vs BNT162b2: OR, 0.64; 95% CI, 0.52-0.79; P < .001), age (per 10 years: OR, 0.74; 95% CI, 0.72-0.76; P < .001), female sex (OR, 1.65; 95% CI, 1.53-1.78; P < .001), and having had COVID-19 before vaccination (OR, 2.17; 95% CI, 1.77-2.66; P < .001).
- CONCLUSION: In this real-world cohort, serious COVID-19 vaccine adverse effects were rare with full vaccination dose, vaccine brand, younger age, female sex, and having had COVID-19 before vaccination associated with greater odds of adverse effects.

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Hassan AO, Feldmann F, Zhao H et al. **A single intranasal dose of chimpanzee adenovirus-vectored vaccine protects against SARS-CoV-2 infection in rhesus macaques.** Cell Reports Medicine 2021; **https://doi.org/10.1016/j.xcrm.2021.100230**

- BACKGROUND: These researchers recently described a chimpanzee adenovirus (simian Ad36)-based SARS-CoV-2 vaccine (ChAd-SARS-CoV-2-S) encoding for the S protein. Intranasal administration of a single dose of ChAd-SARS-CoV-2-S induced robust humoral and cell-mediated immune responses against the S protein and prevented upper and lower airway infection in mice expressing the human ACE2 receptor.
- STUDY DESIGN: To assess the immunogenicity and protective efficacy of this vaccine in non-human primates, rhesus macaques were immunized with ChAd-Control or ChAd-SARS-CoV-2-S and challenged one month later by combined intranasal and intrabronchial routes with SARS-CoV-2. and then challenged animals 1 month later with SARS-CoV-2 via the combined intranasal and intrabronchial routes.
- RESULTS: Immunization with ChAd-SARS-CoV-2-S resulted in the development of anti-S, anti-RBD, and neutralizing antibodies as well as T cell responses that prevented or limited infection in nasal swabs, bronchoalveolar lavage fluid, and lung tissues after SARS-CoV-2 challenge.

- CONCLUSION: Administration of a single intranasal dose of ChAd-SARS-CoV-2-S vaccine through a non-injection route has the potential to protect at the portal of entry and in distant tissues. Use of this vaccine could limit both virus-induced disease and transmission.

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