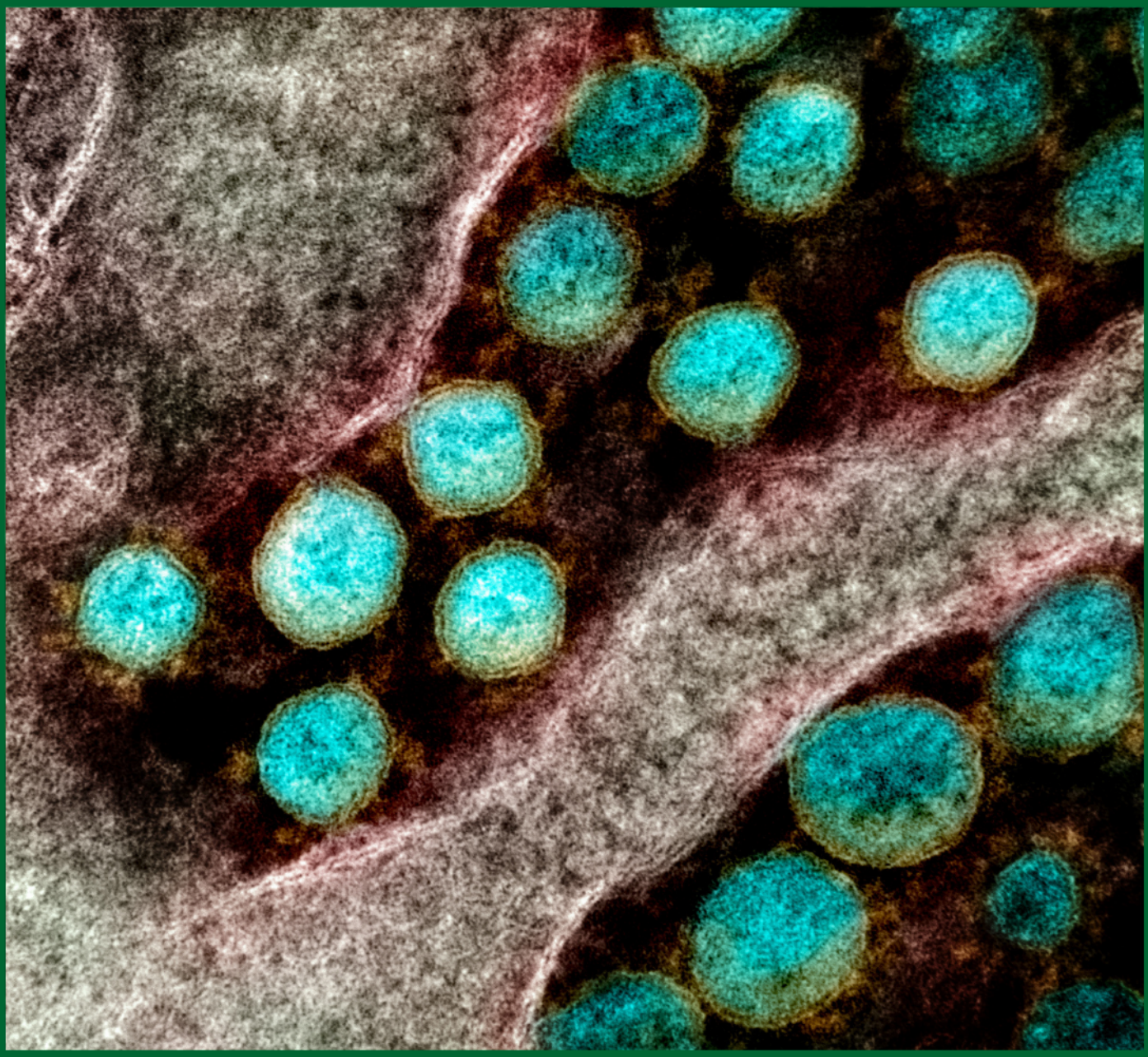
# COVID-19 Rush Journal Club: Diagnosis, Critical Care, and Vaccines



*NOVEL CORONAVIRUS SARS-COV-2. Transmission electron micrograph of SARS-CoV-2 virus particles, isolated from a patient. Image captured and color-enhanced at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. Credit: NIAID Available at: https://www.flickr.com/photos/niaid/49597768397/in/album-72157712914621487/. Accessed April 19, 2020.*

This document is a collection of efforts from students of Rush University. It provides brief reviews of research articles regarding COVID-19. We hope that this will be helpful to clinicians, students, community leaders, and the general public. This document, however, does not act as a replacement of the original source documents. Please use the DOI on each page to read more.


## Student Editors

Alice Burgess, MS3
Joseph Dodson, MS2
Audrey Sung, MS2
John Levinson, MS3
Ayesan Rewane, MSCR

## Student Editors in Chief

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Lindsay Friedman, MS4
Leah Greenfield, MS3
Danesha Lewis, PhD candidate
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Kaitlyn Wehrheim, MS3
Bijan Zarrabi, MS3

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Mete Altintas, PhD - ***Director, Translational and Preclinical Studies***
Rachel Miller, PhD - ***Assistant Professor of Internal Medicine***
Michael Bradaric, PhD - ***Director of Pharmacology, Rush Medical College***
Brinda Bradaric, PhD - ***Assistant Professor, Dept of Health Sciences***
Jitesh Pratap, PhD - ***Assistant Professor, Dept of Cell and Molecular Medicine***
Steve Mangos, PhD - ***Director, Internal Medicine Drug Discovery and Imaging Core***

## Graphic design

Sam Auger, MD
Beth Hall, MD
Joseph deBettencourt, MS4


***Is there a study you'd like us to review? Do you have questions or feedback?***
***Please email: Joseph_b_deBettencourt@rush.edu***

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| Critical Care | Wu CN, et al. High-flow nasal-oxygenation-assisted fiberoptic tracheal intubation in critically ill patients with COVID-19 pneumonia: a prospective randomized controlled trial. Br J Anaesth 2020 [Epub ahead of print]. | Shyam Desai (4/25) |
| | Greenland, J. R. et al. COVID-19 Infection Implications for Perioperative and Critical Care Physicians. Anesthesiology 2020 [Epub ahead of print]. | Beth Hall (4/27) |
| | L Meng et al. Intubation and ventilation amid the COVID-19 outbreak: Wuhan's experience. Anesthesiology 2020 [Epub ahead of print]. | Nick Sytsma (4/28) |
| | S Lie et al. Practical considerations for performing regional anesthesia: lessons learned from the COVID-19 pandemic. Can J Anaesth 2020 [Epub ahead of print]. | John Sweeney (4/28) |
| | Peng, Qian-Yi, et al. "Findings of lung ultrasonography of novel corona virus pneumonia during the 2019–2020 epidemic." Intensive care medicine (2020): 1. | Nick Sytsma (5/5) |
| | Liang W et al. Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19. JAMA Intern Med. Published online May 12, 2020. doi:10.1001/jamainternmed.2020.2033 | Nick Sytsma (5/21) |
| | Sommer, P et al., Initial Clinical Impressions of the Critical Care of COVID-19 Patients in Seattle, New York City, and Chicago., Anesthesia & Analgesia: March 25, 2020 - Volume Publish Ahead of Print - Issue - doi: 10.1213/ANE.0000000000004830 | Nick Sytsma (6/10) |
| | Jacobs, JP. et al. "Extracorporeal Membrane Oxygenation in the Treatment of Severe Pulmonary and Cardiac Compromise in Coronavirus Disease 2019: Experience with 32 Patients" ASAIO J. 2020;66(7):722-730. doi:10.1097/MAT.0000000000001185 | Reilly Frauchiger-Ankers (7/31) |
| | Nepal G. et al. "Neurological manifestations of COVID-19: a systematic review." Crit Care. 2020;24(1):421. Published 2020 Jul 13. doi:10.1186/s13054-020-03121-z | Javier Paulino (8/17) |
| | Heman-Ackah SM. et al. "Neurologically Devastating Intraparenchymal Hemorrhage in COVID-19 Patients on Extracorporeal Membrane Oxygenation: A Case Series" Neurosurgery. 2020;87(2):E147-E151. doi:10.1093/neuros/nyaa198 | Aliya Rodriguez (8/28) |
| | Aminnejad R. et al. "Lidocaine during intubation and extubation in patients with coronavirus disease (COVID-19)" Can J Anaesth. 2020;67(6):759. doi:10.1007/s12630-020-01627-2 | Carter Do (9/2) |

# Table of Contents: Critical Care (2/2)

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# Reviews from 2022

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| Diagnosis | Gans, Joshua S., et al. "False-Positive Results in Rapid Antigen Tests for SARS-CoV-2." JAMA (2022). | Sonia Mehra (2/27/22) |
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COVID-19
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# Reviews from 2022

| Section | Manuscript | Reviewer (Date Posted) |
|---|---|---|
| Vaccine Development | Fenioux C et al. SARS-CoV-2 Antibody Response to 2 or 3 Doses of the BNT162b2 Vaccine in Patients Treated With Anticancer Agents. JAMA Oncology. Published online January 07, 2022. | Natalie Maltby (2/23/22) |
| | Bar-On, Yinon M., et al. "Protection against Covid-19 by BNT162b2 booster across age groups." New England Journal of Medicine 385.26 (2021): 2421-2430. | Alex Hodakowski (2/28/22) |
| | Andrews, Nick, et al. "Duration of Protection against Mild and Severe Disease by Covid-19 Vaccines." New England Journal of Medicine (2022). | Natalie Maltby (2/23/22) |
| | Arbel, Ronen, et al. "BNT162b2 vaccine booster and mortality due to Covid-19." New England Journal of Medicine 385.26 (2021): 2413-2420. | Carter Do (2/23/22) |
| | Eliakim-Raz, Noa, et al. "Antibody titers before and after a third dose of the SARS-CoV-2 BNT162b2 vaccine in adults aged≥ 60 years." Jama 326.21 (2021): 2203-2204. | Chris Szewcyk (2/23/22) |
| | Hansen, Christian Holm, et al. "Vaccine effectiveness against SARS-CoV-2 infection with the Omicron or Delta variants following a two-dose or booster BNT162b2 or mRNA-1273 vaccination series: A Danish cohort study." medRxiv (2021). | Timothy Kuzel (2/23/22) |
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# DIAGNOSIS

# *SAA is a biomarker to distinguish the severity and prognosis of Coronavirus Disease 2019 (COVID-19)*

**Huan Li et al.**

*Journal of Infection*
*March 22, 2020*
*DOI: https://dx.doi.org/10.1016%2Fj.jinf.2020.03.035*

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| *Purpose* | To determine if serum amyloid A (SAA) is a marker for prognosis and severity of COVID19. |
| *Study design* | Case series (n = 132 patients) |
| *Level of evidence* | Level 4 |
| *Methods* | From January 18 - February 26 2020, 132 inpatients from Tianyou Hospital in Wuhan, China with positive PCR for SARS-CoV-2 were evaluated for lab data and clinical assessment. Time points included admission, 2-5 days of hospitalization, and at the composite endpoint (Feb 26 2020). The data evaluated included blood SAA, C Reactive Protein (CRP), procalcitonin (PCT), white blood cell count (WBC), lymphocytes (L), platelet count (PLT), CT imaging, and disease progression. At the study endpoint, patients status was assessed as discharged, still inpatient, or expired. |
| *Findings* | Patients showed high levels of SAA and CRP. Out of 132 patients, 123 had SAA above 10mg/L (<10mg/L set as normal clinical reference). The L count decreased in these patients. **As patients with COVID-19 became worse in clinical severity, the levels of SAA and CRP increased and the number of lymphocytes decreased.** Using a ROC curve, **the ratio of SAA/L was more sensitive in predicting the severity of COVID-19 clinical course than measuring SAA and L individually.** When comparing the CT scans to the SAA level, patients with a higher SAA were more likely to have worse CT findings. |
| *Clinical Implications* | **Levels of SAA and CRP increase significantly in patients with COVID-19 infections, and increased proportionally with respect to clinical severity.** Lymphocyte count (L) decreased in these patients as well. The ratio of SAA/L appears to be a more sensitive measure predicting severity of clinical manifestation as opposed to measuring SAA or L alone. **Using both SAA and CT scans can aid clinicians in predicting patient severity.** |
| *Limitations* | This study did not utilize a control group. Additionally, patients came from a single hospital, limiting generalizability of findings. |

# *Diagnosis of the Coronavirus disease (COVID-19): rRT-PCR or CT?*

**Chunqin Long et al.**

*European Journal of Radiology*
*March 25, 2020*
*DOI: https://doi.org/10.1016/j.ejrad.2020.108961*

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| *Purpose* | To evaluate the diagnostic value of computed tomography (CT) and real-time reverse-transcriptase-polymerase chain reaction (rRT-PCR) for COVID-19 pneumonia. |
| *Study design* | Retrospective chart review (n = 87 patients) |
| *Level of evidence* | Level 3 |
| *Methods* | Nasopharyngeal isolates and CT imaging were obtained on 87 patients among 204 patients suspected of having COVID-19. Nasopharyngeal swabs were collected and sent for reverse transcriptase polymerase chain reaction (rRT-PCR), and CT scans were examined retrospectively by two radiologists with 10 and 15 years of experience in chest imaging, respectively. In cases of disagreement, a consensus was reached. CT evaluations included the lobar location and pattern of the lesion. |
| *Findings* | **On CT imaging, peripheral distributions were observed more in the diseased group** (72.2%) vs more focal consolidation (52.0%) in the control group ($p<0.05$). Moreover, **ground-glass opacities were observed more frequently in the disease group.** Only one patient with COVID-19 had a normal chest CT. This yielded a sensitivity of 97.2% (35/36). In terms of the rRT-PCR testing, the test was initially positive in 30 patients, for a sensitivity of 83.3% (30/36). **However, of the six false-negative patients, three were positive with a second round of testing, and the final three were positive with a third round of testing.** |
| *Clinical Implications* | **CT imaging proved to be more sensitive than rRT-PCR in the initial diagnosis of COVID-19** in a cohort of patients in China. **This study recommends that patients with positive CT findings but negative rRT-PCR results still be placed in isolation** and have rRT-PCR testing repeated in the subsequent days of admission. |
| *Limitations* | The study has a small sample size, likely because it was conducted during the height of the pandemic in China. The number of rRT-PCR tests conducted were limited by supply, and only those with fever and a positive CT test were tested with rRT-PCR. |

# *COVID-19 infection among asymptomatic and symptomatic pregnant women: Two weeks of confirmed presentations to an affiliated pair of New York City hospitals.*

**Noelle Breslin et al.**

*American Journal of Obstetrics and Gynecology MFM*
*April 9, 2020*
*DOI: https://doi.org/10.1016/j.ajogmf.2020.100118*

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| *Purpose* | To present the clinical characteristics of confirmed COVID-19 cases presenting to an affiliated pair of NYC hospitals over 2 weeks between March 13 and March 27, 2020. |
| *Study design* | Case series (n = 43) |
| *Level of evidence* | Level 4 |
| *Methods* | Retrospective review of medical records over a 15-day period beginning with the first PCR-confirmed COVID-19 infection involving a pregnant patient on March 13, 2020. Clinical documentation for all pregnant women who tested positive for COVID-19 via PCR nasopharyngeal swab was reviewed. Records related to neonates born to COVID-19 positive women were also reviewed. |
| *Findings* | 43 pregnant women tested positive for COVID-19 infection during the study period. The mean maternal age was 26.9 ±5.9 years and median gestational age was 37 and 0/7 weeks. 86% of COVID-19 positive women showed mild disease, 9.3% exhibited severe disease and 2 developed critical disease presentations. 41.8% of women had an additional comorbid condition, with mild intermittent asthma as the most common. 14 (32.5%) of 43 patients initially presented without COVID-19 associated symptoms. No infants were found to be COVID-19 positive after birth. |
| *Clinical Implications* | **Universal testing among pregnant women upon admission for delivery can help with infection control**, and allows hospitals to preserve limited PPE supplies among women who are test-negative. There may also be implications in the management of neonates delivered to COVID positive women and it supports more restrictive visitor policies, strict hand and respiratory hygiene precautions, and masking of all patients and birth partners, as well as staff on the labor unit. **COVID-19 should also be considered on the differential diagnosis in women present with common perinatal and postoperative infectious or respiratory complications.** |
| *Limitations* | This study was the largest case series to date of pregnant women with COVID-19 infection, although the sample size still remains small. This cohort includes patients presenting for care at either a tertiary care center or a smaller community hospital in NYC, but these findings may be generalizable to other centers or regions with lower disease prevalence. |

# *Profiling early humoral response to diagnose novel coronavirus disease (COVID-19)*

**Li Guo et al.**

*Clinical Infectious Diseases*
*March 21, 2020*
*DOI: https://doi.org/10.1093/cid/ciaa310*

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| *Purpose* | To describe the timeline of antibody production against SARS-CoV-2 and to evaluate the efficacy of diagnostic testing for COVID-19. |
| *Study design* | Cross-sectional study |
| *Level of evidence* | Level 3 |
| *Methods* | Paired plasma samples and throat swabs were collected from 82 confirmed (via qPCR or deep sequencing) and 58 probable (qPCR and deep sequencing negative, but typical symptoms) COVID-19 cases from Beijing and Wuhan hospitals. 135 plasma samples collected from adults in 2018 with acute lower respiratory tract infections and 150 plasma samples collected from healthy adults in 2018 and 2019 were used as controls. Host response against SARS-CoV-2 was examined using ELISA on recombinant viral nucleocapsid protein. Cross-reactivity of anti-SARS-CoV-2 antibodies against nucleocapsid genes of CoV-229E, -NL63, -OC43, HKU1, SARS-CoV-1, and MERS-CoV were tested by Western Blotting. CLustalW program was utilized to align nucleocapsid gene sequences. |
| *Findings* | IgM, IgA, and IgG antibodies against SARS-CoV-2 were positively detected, respectively, in 90.4%, 93.3%, and 77.9% of the plasma samples collected from confirmed and suspected cases of COVID-19. The median time to IgM and IgA detection was 5 days after symptom onset, peaking between 8-14 days. The median time to IgG detection was 14 days after symptom onset, peaking between 15-21 days. The detection rate for a single PCR test is 51.9% with >90% positive detection 1-3 days after symptom onset. By day 5, PCR detection decreases to <80%, then <50% at 14 days. When comparing PCR to anti-SARS-CoV-2 IgM antibody detection, the detection rate was higher by qPCR within the first 5.5 days after symptom onset, and higher by IgM ELISA after 5.5 days of symptom onset. Performing IgM ELISA on qPCR negative samples, however, increased the detection rate to 98.6%. |
| *Clinical Implications* | **Testing for the presence of IgM on PCR negative samples in cases of suspected COVID-19 could improve sensitivity of testing and aid in early detection of subclinical patients**, helping to prevent spread of the virus with early and accurate diagnosis. |
| *Limitations* | This study used a cross-sectional sample. Due to individual variation in production of antibody development, longitudinal studies likely would have yielded more reliable data. A strong cross reactivity was found between SARS-CoV-2 recombinant N proteins with human plasma positive for IgG antibodies against SARS-CoV-1, but not NL63, 229E, OC43, and HKU1. It is unlikely, however, that these patients were pre-infected with SARS-CoV-1 during the last epidemic in 2002. |

# *Clinical Characteristics of Coronavirus Disease 2019 in China*

**W Guan et al.**

*New England Journal of Medicine*
*February 28, 2020*
*DOI: 10.1056/NEJMoa2002032*

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| *Purpose* | To identify the clinical characteristics of COVID-19 patients in China. |
| *Study design* | Case series (n = 1,099) |
| *Level of evidence* | Level 4 |
| *Methods* | The study included 1,099 COVID-19 patients from 552 hospitals across 30 provinces in mainland China from December 11, 2019 to January 29, 2020. Data included exposure history, clinical symptoms, and laboratory and radiologic findings. Cases were defined as severe vs. non-severe using the American Thoracic Society guidelines for community-acquired pneumonia. Incubation period was defined as time between earliest date of exposure and symptom onset. The primary composite end point was admission to ICU, mechanical ventilation, or death. |
| *Findings* | Most patients (43.9%) were Wuhan residents, and 72.3% of nonresidents reported contact with Wuhan residents. However, 25.9% of nonresidents denied recent travel or contact with Wuhan residents. Patient ages ranged from 0-14 (0.9%), 15-49 (55.1%), 50-64 (28.9%), and >65 (15.1%), with median age of 47 years. Most patients had never smoked (85.4%), and 12.6% were current smokers. The most common presenting symptom was cough (67.8%), followed by fever (43.8%). Admission to ICU, mechanical ventilation, or death occurred in 24.9% of patients with severe disease and 6.1% of all patients. Pneumonia was diagnosed in 91.1% of patients and acute respiratory distress syndrome (ARDS) in 3.4%. Most common CT findings were ground-glass opacity (56.4%) and bilateral patchy shadowing (51.8%). No radiographic or CT abnormality was found in 2.9% of severe patients. Notable laboratory findings of patients included lymphocytopenia (83.2%), thrombocytopenia (36.2%), and leukopenia (33.7%). |
| *Clinical Implications* | The clinical characteristics and conventional routes of transmission of COVID-19 mimic those of SARS-CoV. Absence of fever occurs more frequently in COVID-19 (56% on presentaton, 11% after hospitalization) than in SARS-CoV-1 (1%) and MERS-CoV (2%). **Using fever as a symptom for detection may not be reliable.** |
| *Limitations* | Some cases demonstrated incomplete documentation of exposure history and laboratory testing. The incubation period could only be estimated for 26.5% of patients, allowing recall bias to play a significant role. The studied population inevitably represents a more severe presentation of COVID-19, as asymptomatic individuals or those with mild symptoms would likely remain home, not requiring additional medical care. |

# *Relation between chest CT findings and clinical conditions of coronavirus disease (COVID-19) pneumonia: A multicenter study.*

**Wei Zhao et al.**

*American Journal of Roentgenology*
*date published*
*DOI: 10.2214/AJR.20.22976*

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| *Purpose* | To explore the relationship between chest CT findings and COVID-19 pneumonia. |
| *Study design* | Retrospective study (n = 101) |
| *Level of evidence* | Level 4 |
| *Methods* | Medical records were retrospectively collected for 101 patients with confirmed COVID-19 diagnosis in four cities of Hunan province in China. Patients were divided in two groups: non-emergent vs emergent type infections. All patients underwent CT upon admission and the extent of respiratory involvement was evaluated using a CT scoring system. Chest CT scans were blindly and independently reviewed by two radiologists with 5 and 15 years of experience, respectively. |
| *Findings* | Out of 101 patients in the study, 87 (86.1%) were in the non-emergent group, 14 (13.9%) were in the emergency group. Eighty-seven patients had ground glass opacities (GGO) on CT, 65 had mixed GGO and consolidations, 72 had vascular enlargement in the lesion and 53 had traction bronchiectasis. Lesions on CT were more likely to have peripheral distribution (n=88), bilateral involvement (n=83), have lower lung predominance (n=55), and be multifocal (n=55). Patients in emergency group were older than those in non-emergent group but the difference in the rate of underlying disease was not significant. |
| *Clinical Implications* | **CT is considered routine imaging for care of COVID-19 patients. Combination of chest CT and PCR screening is necessary for early diagnosis.** COVID-19 presents with typical CT features can be helpful in screening suspected cases and evaluating extent of disease. |
| *Limitations* | The study was limited by the number of patients included (n=101). Other viral infections and negative results were not included in the analysis limiting comprehensive exploration compared to other lung infections. Follow up CT findings were not evaluated limiting insight on progression. |

# *Comparison of throat swabs and sputum specimens for viral nucleic acid detection in 52 cases of novel coronavirus (SARS-Cov-2)-infected pneumonia (COVID-19).*

**Chenyao Lin et al.**

*Clinical Chemistry and Laboratory Medicine*
*April 16, 2020*
*DOI: https://doi.org/10.1515/cclm-2020-0187*

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| *Purpose* | To compare the accuracy and efficiency of throat vs sputum samples in diagnosing COVID-19. |
| *Study design* | Case series (n = 54) |
| *Level of evidence* | Level 4 |
| *Methods* | This was a retrospective study on 52 patients at Jinyintan Hospital in Wuhan, China from February 7-16, 2020. Patients were diagnosed using WHO interim guidance. Simultaneously, both a throat swab and sputum specimen were taken and tested for COVID-19 via reverse transcription polymerase chain reactio (RT-PCR). |
| *Findings* | The majority of patients tested were middle aged and elderly males (average age 57.3 years and 27/52 were men). The percent of patients that tested positive for COVID-19 via RT-PCR from a sputum sample was 76.9% (40 cases) vs. 44.2% (23 cases) from a throat swab. Authors reported that 51.9% of the patients had the same result on RT-PCR for throat and sputum samples, 40.4% showed positive sputum samples and negative throat swabs, and 7.7% showed negative sputum samples and positive throat swabs. |
| *Clinical Implications* | Proper collection of specimens is an important step in the diagnosis of infectious diseases. **Screening patients via sputum culture compared to throat swab via RT-PCR may increase the accuracy of diagnosing of COVID-19.** Considering that sputum is more sensitive than throat swabs for 2019-nCoV detection, patients should not be excluded from having COVID-19 if they have a negative RT-PCR result via throat swab. |
| *Limitations* | This study was a sample size of only 52 patients from a single hospital, thus evaluation of larger group of patients needed. Additionally, sputum has a high viscosity, which can make it difficult to test and there is no standardized pre-treatment procedure in order to test serum. Pre-treatment of sputum in this study used acetylcysteine, which can cause loss of some of the RNA. Also, the study did not include data on nasopharyngeal swabs or bronchoalveolar lavage fluid, which would be a useful comparison for diagnostic methods. Lastly, not all patients produce sputum with COVID-19, thus this could limit sputum RT-PCR testing. |

# *Evaluation of Nucleocapsid and Spike Protein-based ELISAs for detecting antibodies against SARS-CoV-2*

**Wanbing Liu et al.**

*Journal of Clinical Microbiology*
*March 30, 2020*
*DOI: 10.1128/JCM.00461-20*

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| *Purpose* | To look for the presence of IgM and IgG antibodies on two immunogenic portions of the SARS-CoV-2 virus in patients, the nucleocapsid protein (rN) and the spike protein (rS). |
| *Study design* | Observational laboratory analysis |
| *Level of evidence* | Level 3 |
| *Methods* | Blood samples of 214 patients with laboratory confirmed COVID-19 (and 100 healthy control samples) were run using enzyme-linked immunosorbent assay (ELISA) to detect both IgM and IgG antibodies against the rN and rS proteins of the SARS-CoV-2 viral structure. Patients were 0-55 days post onset (DPO) of disease, with median DPO of 15 days. |
| *Findings* | Of the 214 patients samples tested for presence of anti-rN IgM and IgG antibodies, 68.2% and 70.1% of patients displayed positive IgM and IgG antibodies, respectively. For anti-rS antibody presence, 77.1% and 74.3% of patients displayed positive IgM and IgG antibodies, respectively. The presence of IgM and/or IgG was looked at for both rN and rS, and patients displayed one or both of the antibodies in 80.4% and 82.2%, respectively. Regarding time course of serologic response, positive rates of both IgM and IgG for rN and rS assays were low at <10 DPO, although IgM increased at 6-10 DPO. IgM and/or IgG for patients at 16 DPO was 88.9% and 90.7% for rN and rS, respectively. None of the 100 healthy controls displayed positive IgM or IgG to either rN or rS. The detection of IgM was significantly higher using both kits (81.3%) vs. the rN kit alone (68.2%), but not using the rS kit alone (77.1%). For IgG, 80.4% were positive using both kits, significantly higher than the rN kit alone (70.1%) but not so for the rS kit alone (74.3%). When testing for presence of IgM and/or IgG, no significant difference was seen between both kits (86.9%) and either rN (80.4%) or rS (82.2%). |
| *Clinical Implications* | **The rS-based IgM antibody test is more sensitive for the detection of SARS-CoV-2** due to the earlier immune response against the S protein. Antibodies increased in a time-dependent manner, with IgM decreasing at >35 DPO. **Antibody tests should be considered as adjuvant testing to nasopharyngeal PCR swabs, especially in patients who are >10 DPO.** |
| *Limitations* | The study could not follow up with discharged patients to see the extent of the antibody decrease >35 DPO. Moreover, additional immunogenic proteins could have been tested using ELISA to observe antibody production to various parts of the protein. |

# *Imaging and clinical features of patients with 2019 novel coronavirus SARS-CoV-2: A systematic review and meta-analysis*

**Yinghao Cao et al.**

*Journal of Medical Virology*
*March 30, 2020*
*DOI: https://doi.org/10.1002/jmv.25822*

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| *Purpose* | To outline clinical characteristics of patients with novel coronavirus pneumonia (NCP). |
| *Study design* | Meta-analysis |
| *Level of evidence* | Level 5 |
| *Methods* | Authors executed a detailed search on PubMed, Cochrane Library, Embase, National Knowledge Infrastructure [CNKI], and China Biology Medicine disc [CBMdisc] using the keywords 2019 novel coronavirus pneumonia, COVID-19, Coronavirus, SARS-CoV-2, Wuhan Coronavirus, clinical features, 2019 novel coronavirus pneumonia, and imaging features. Inclusion criteria included cross-sectional studies, case studies, patients with confirmed NCP, and data on clinical characteristics, biochemical indicators, and imaging signs. Case reports were excluded. The quality of all included literature was assessed using the Institute of Health Economics (IHE) scale. After final review, 31 articles and 46,959 patients were included in the meta-analysis. |
| *Findings* | Mean age of patients with SARS-CoV-2 infection was 46.4 years old and 55.6% were male. About 35.6% of patients had comorbidities, including 18.3% with hypertension, 11.2% with cardiovascular disease, 10.3% with diabetes, 3.9% with chronic obstructive pulmonary disease, and 3.0% with chronic hepatonephropathy. The main symptoms were fever (87.3%) and cough (58.1%). Other presentations included dyspnea (38.3%), myalgia or weakness (35.5%) and chest tightness (31.2%). Most patients with NCP required hospitalizations, and 29.3% of those patients required intensive care. The main complications were respiratory failure, acute respiratory distress syndrome (ARDS), and multiple organ failure. In imaging results, 75.7% of patients had lesions involving both lungs, and 69.9% showed ground-glass shadows. A computerized tomography (CT) chest is highly sensitive to SARS-CoV-2 (97% in epidemic areas). |
| *Clinical Implications* | This study illustrates that COVID-19 causes bilateral pneumonia and lung function rapidly deteriorates. **Chest CT imaging has proved to be very sensitive to COVID-19 and serves as an important supplement to nucleic acid detection**. |
| *Limitations* | The study was limited to studies in England and China, but not from South Korea, Italy, Iran, and Japan where the pandemic is rapidly increasing and causing a catastrophic impact on the health of communities. |

# *Ultrastructural evidence for direct renal infection with SARS-CoV-2.*

**Evan Farkash et al.**

*Journal of the American Society of Nephrology*
*April 20, 2020*
*DOI: https://doi.org/10.1681/ASN.2020040432*

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| *Purpose* | To evaluate direct renal infection by SARS-CoV-2 as a proposed mechanism of renal failure in COVID-19 patients. |
| *Study design* | Case report |
| *Level of evidence* | Level 4 |
| *Methods* | An autopsy was performed on a single patient who died of COVID-19 following an open repair of an aortic dissection, complicated by hypoxic respiratory failure and oliguric renal failure. Renal tissues were examined with light and electron microscopy to detect for evidence of SARS-CoV-2 in renal cells. |
| *Findings* | Light microscopy analysis of tissue collected at autopsy from a patient with COVID-19 and acute renal failure showed focal tubular isometric vacuolization and mild to moderate necrosis and karyolysis. Ultrastructural analysis showed abundant viral forms, consistent in size and morphology with SARS-CoV-2, within tubular epithelial cells that correlated directly to areas of isometric vacuolization. Viral structures were organized into small arrays and predominantly found in the cytoplasm, indicative of intracellular manufacturing and assembly. Vacuoles contained double membrane vesicles suggestive of partially assembled virus. Viral detection, arrays, and assembly support direct infection of the kidney with SARS-CoV-2 as a proposed mechanism of renal failure. |
| *Clinical Implications* | **This study supports direct infection of kidney as the mechanism of renal injury in COVID-19 patients**. However, the cause of kidney injury in patients with COVID-19 remains unclear. |
| *Limitations* | This case report only evaluates renal tissue from a single patient. Additional studies are needed to further support direct infection as a proposed mechanism of renal failure in COVID-19 patients. Furthermore, evidence of direct renal infection does not preclude alternate mechanisms of kidney injury. |

# *A preliminary study on the ultrasonic manifestations of peripulmonary lesions of non-critical novel coronavirus pneumonia (COVID-19).*

**Yi Huang et al.**

*SSRN*

*February 28, 2020*

*DOI: http://dx.doi.org/10.2139/ssrn.3544750*

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| *Purpose* | To explore the ultrasonic manifestations of peripulmonary lesions of non-critical COVID-19 and provide reference for clinical diagnosis and efficacy evaluation. |
| *Study design* | Retrospective analysis |
| *Level of evidence* | Level 4 |
| *Methods* | The authors reviewed pulmonary ultrasonography studies performed on 20 non-critical patients with COVID-19. Each patient had direct ties to Wuhan in January and February, 2020. Studies included conventional two-dimensional ultrasound and color Doppler flow imaging ultrasonography (CDFI). Each study was reviewed independently by two physicians using the six-zone method of each lung, where the sum of all zone's scores represented the global lung ultrasound score. |
| *Findings* | COVID-19 foci are mainly observed in the posterior fields in both lungs, especially in the posterior lower fields. Fused B-lines and waterfall signs are visible under the pleura. The B lines, which are good indicators of alveolar interstitial syndrome, are fused and in fixed position. The pleural line is unsmooth, discontinuous, and interrupted. The subpleural lesions show patchy, strip, and nodule consolidation. Air bronchogram sign or air bronchiologram sign can be seen in the consolidation. The involved interstitial tissues have localized thickening and edema, and there is localized pleural effusion around the lesions. CDFI ultrasound shows insufficient blood supply in the lesions. **High frequency linear array probe is suggested to be used for minor subpleural lesions, as it can provide rich information and improve diagnostic accuracy.** |
| *Clinical Implications* | Chest CT is recommended for the diagnosis of COVID-19 since lung abnormalities may develop before clinical manifestations of SARS-CoV-2 infection. This study offers a brief overview of expected ultrasonic pulmonary findings in COVID-19 patients to understand the pathophysiology of the disease. **Ultrasound cannot replace CT scans, but is superior to CT in detecting small, peripulmonary lesions and effusions.** It can also produce real-time images and show dynamic changes such as blood flow. Additionally, ultrasound is available point-of care, radiation-free, and is repeatable, and machines are easily disinfected. Ultrasound may be a preferable imaging modality for some patients. |
| *Limitations* | The study sample size is small. There are no control studies or interventions. The study did not follow patients over time nor re-scan with symptom resolution. |

# *Diagnostic value and dynamic variance of serum antibody in coronavirus disease 2019.*

**Yujiao Jin et al.**

*International Journal of Infectious Diseases*
*April 3, 2020*
*DOI: 10.1016/j.ijid.2020.03.065*

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| *Purpose* | To evaluate diagnostic value of dynamic variance of serological testing in COVID-19. |
| *Study design* | Case control |
| *Level of evidence* | Level 4 |
| *Methods* | A retrospective study comparing the IgM and IgG titers of COVID-19 nucleocapsid and spike protein from 43 laboratory confirmed COVID-19 patients to titers from 33 patients with suspected COVID-19 who tested negative from January 2020 to March 4 2020 at Xi Hospital of Hangzhou, China. A positive COVID-19 diagnosis was determined using RT-PCR on patient sputum or oral swab samples. IgM and IgG titers were measured on patient serum samples using chemi¬luminescence immunoassay (CLIA) analysis and presented in arbitrary units/mL (AU/mL). |
| *Findings* | **Sensitivity of serum IgM and IgG antibodies was 48.1% and 88.9%, respectively. Specificity of serum IgM and IgG antibodies was 100% and 90.9%, respectively.** No control patients were positive for IgM antibodies and only 3/33 (9.1%) control patients were positive for IgG antibodies, however, their titers were low (less than 15 AU/mL). Of the RT-PCR confirmed COVID-19 group, 27 were tested for viral antibodies before becoming virus negative. In this group, 13/27 (48.1%) had IgM antibodies and 24/27 (88.9%) had IgG antibodies. The IgM positive predictive value was 100% (13/13) while the IgM negative predictive value was 70.2% (33/47). The IgG positive predictive value was 88.9% (24/27) while the IgG negative predictive value was 90.9% (30/33). Over the span of 32 days after RT-PCR confirmation, patients with COVID-19 had IgM titers that initially increased then declined, while IgG titers increased and then became stable. Only IgG had a significantly different median titer after patients converted to virus-negative with double the titer compared to when the patients were virus-positive. |
| *Clinical Implications* | This study suggests that serological testing may be helpful in the diagnosis of COVID-19 patients. |
| *Limitations* | Due to the small sample size used in this study, the reliability of the results should be questioned. Additionally, since serological testing kits were not readily available at the start of the study, the time between the onset of symp¬toms to serological testing was varied. Furthermore, this study does not attempt to correlate the serology results with severity of disease. |

# *Diagnostic Accuracy of an Automated Chemiluminescent Immunoassay for anti-SARS-CoV-2 IgM and IgG Antibodies: An Italian Experience*

**Maria Infantino et al.**

*Journal of Medical Virology*
*April 24, 2020*
*DOI: https://doi.org/10.1002/jmv.25932*

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| *Purpose* | To assess the diagnostic performance of a novel fully automated chemiluminescence immunoassay (CLIA) for quantitative detection of anti-SARS-CoV-2 IgM and IgG antibodies. |
| *Study design* | Case-control selection cross-sectional study (n=105) |
| *Level of evidence* | Level 3 |
| *Methods* | 61 COVID-19 positive patients (59 ± 23 years; 35 women, 26 men) hospitalized in San Giovanni di Dio Hospital (Florence, Italy) and 44 patients with rheumatic diseases (n=31) and infectious diseases (n=13) serving as a pre-COVID-19 (2018-2019) control group were tested for IgM and IgG anti-SARS CoV-2 antibodies via the iFlash1800 CLIA analyzer. All COVID-19 patients were confirmed to be infected with SARS-CoV-2 by performing RT-PCR using oropharyngeal and nasopharyngeal swabs (confirmed by two SARS-CoV-2 nucleic acid tests). Based on manufacturer recommendations, samples found to have IgM and IgG concentrations ≥10 AU/mL were considered positive (reactive). |
| *Findings* | At the manufacturer's recommended threshold of ≥10 AU/mL, sensitivity for IgM antibodies was 73.3% and specificity was 92.2%, IgG antibody sensitivity was 76.7% and specificity was 100%. Receiver Operating Characteristics (ROC) performance curves showed Area Under the Curve (AUC) values of 0.918 and 0.980 for anti-SARS-CoV-2 antibodies IgM and IgG, respectively. Among the COVID-19 patients 64.1% (41/64) demonstrated both IgM and IgG positive test results, while 4.7% (3/64) had only IgM positive results and 7.8% (5/64) had only IgG positive results. The average concentration of IgM antibodies in COVID-19 positive sera was 69.8 AU/mL versus 48.9 AU/mL for IgG antibodies. |
| *Clinical Implications* | Early and accurate diagnosis of COVID-19 plays a critical role in slowing it's spread. When serology testing is used for diagnostic purposes, detection of the patient's immune response (e.g., IgG, IgM, IgA, and total antibody counts) is the point if interest. This study demonstrates that COVID-19 patients produce both IgM and IgG antibodies, with few patients producing only IgG or IgM antibodies. This is one of the first studies on anti-SARS-CoV-2 IgM and IgG antibodies by CLIA method on an Italian population. |
| *Limitations* | The results of this single-center cohort study are limited by the varying lengths of time between the onset of symptoms in COVID-19 positive patients and the development of positive serum samples. In addition, patients in the early stages of the disease were not enrolled in this study and as such, the efficacy of this method as an early diagnostic tool is unclear. Due to the nature of the assay using antigens from different components of SARS-CoV-2, different levels of cross-reactivity with other coronavirus antibodies are possible; however, authors did not examine such cross-reactivity. |

# *False Positive Results in Rapid Antigen Tests for SARS-Co-V*

**Joshua S. Gans,PhD et al.**
*JAMA Network*
*January 7, 2022*
*DOI: https://doi.org/10.1001/jama.2021.24355*

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| *Purpose* | To investigate the incidence of false-positive COVID rapid antigen tests. |
| *Study design* | Retrospective, cohort study |
| *Level of evidence* | Level 3 |
| *Methods* | Asymptomatic employees were screened twice weekly using rapid antigen tests from January 11-October 13, 2021 to assess as a screening for asymptomatic workers. Participants testing positive were referred for a confirmatory polymerase chain reaction (PCR) test that was completed within 24 hours. Data was verified by an audit process by external participant organizations. |
| *Findings* | 903,408 rapid antigen tests were performed in over 537 workplaces. Of the 1,322 positive results, 1,103 patients received further evaluation by PCR. False positives, identified as a positive rapid antigen test followed by a negative confirmatory PCR test, was 426 (42%). Of the false positives, 278 (60%) occurred in two workplaces, which were drawn from a single batch of the "Abbott's Panbio COVID-19 Ag Rapid Test Device." |
| *Clinical Implications* | This study indicates that the false positive results from COVID rapid antigen tests are low. As many of the false positives were identified to be associated with one batch of tests, the false positives are more likely a result of manufacturing instead of an implementation issue. Therefore, it is important to identify faulty batches and to inform officials as well as manufacturing companies efficiency, to allow removal of defective tests and to return to employment. |
| *Limitations* | Limitations include convenience sampling for the different workplaces. Additionally, reporting the lot number and/or results of the confirmatory PCR tests were optional for the participants. Finally, this study was performed in Canada and therefore may not generalize to other parts of the world. |

# CRITICAL CARE

# *High-flow nasal-oxygenation-assisted fiberoptic tracheal intubation in critically ill patients with COVID-19 pneumonia: a prospective randomized controlled trial*

**Cai-Neng Wu et al.**

*British Journal of Anaesthesia*
*March 19, 2020*
*DOI: https://doi.org/10.1016/j.bja.2020.02.020*

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| *Purpose* | Examine efficacy and safety of high-flow nasal oxygenation (HFNO) versus standard bag-mask oxygenation (SMO) during fiberoptic bronchoscopic intubation in critically ill patients with COVID-19 pneumonia. |
| *Study design* | Prospective Randomized Controlled Trial (n= 60) |
| *Level of evidence* | Level 2 |
| *Methods* | 60 patients participated the study and randomly split into HFNO and SMO groups, each including 30 patients. Two patients from the HFNO ultimately dropped out of the study. Six anesthesiologists performed 10 consecutive intubations, five from each group. Patients were positioned supine with their heads up and were pre-oxygenated for a total of four minutes via HFNO or SMO prior to rapid sequence fiberoptic intubation. During intubation attempts, HFNO was maintained whereas no oxygen was administered to the SMO group. |
| *Findings* | **Intubation time was significantly shorter in the HFNO versus SMO group**. HFNO group had both greater minimum SpO2% and lower occurrence of rescue face-mask ventilation during intubation as compared to the SMO group. **There were no significant differences in 7-day mortality, incidence of SpO2<80%, or percentage of minimum SpO2 >95% during intubation**. |
| *Clinical Implications* | There was shorter intubation time and lower incidence of desaturation during intubations leading to rescue face-mask ventilation in patients who received preoxygenation with HFNO. The results of this study suggest a possible avenue for anesthesiologists to consider during intubation of COVID-19 patients to limit potential exposure to the virus. |
| *Limitations* | Six anesthesiologists participated in the study; however, it was not reported in the manuscript whether outcomes were similar between the six anesthesiologists or not. Smaller final sample size in HFNO vs SMO groups is also a concern. Authors did not mention breathing treatments or medications, such as steroids, prior to intubation, which could potentially impact ease of intubation and/or PaO2 percentage. |

# *COVID-19 Infection: Implications for Perioperative and Critical Care Physicians*

**John R. Greenland et al.**

*Anesthesiology*
*March 27, 2020*
*DOI: 10.1097/ALN.0000000000003303*

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| *Purpose* | To summarize the currently available evidence to guide management of critically ill patients with COVID-19. |
| *Study design* | Systematic review |
| *Level of evidence* | 4 |
| *Methods* | Literature review of 108 journals. |
| *Findings* | Critically ill patients tend to have high SARS-CoV-2 viral loads, increasing transmission risk to healthcare providers. Studies conducted in Hubei Province, China showed **5-25% of COVID-19 positive patients were admitted to the ICU, and of those in the ICU, 60-70% progressed to acute respiratory distress syndrome (ARDS). Although high-flow nasal cannula does not significantly decrease intubation rates, it has been shown to lower 90-day mortality in ARDS.** Noninvasive positive pressure ventilation in H1N1 and MERS had failure rates 50-90%. **After intubation, management of COVID-19 is similar to management of ARDS.** Guidelines recommend low tidal volume ventilation (4-8 ml/kg body weight) to maintain plateau pressures <30 cm H2O, with permissive hypercapnia. Guidelines also recommend prone positioning >12 hr/day in severe ARDS if there are sufficient personnel to ensure lines and endotracheal tube are not displaced. High positive end-expiratory pressure (PEEP) is cautiously recommended to increase lung recruitment, but some studies have shown increased mortality with high vs low PEEP. |
| *Clinical Implications* | While use of angiotensin-converting enzyme (ACE)-inhibitors and angiotensin-receptor blockers (ARBs) could lead to upregulation of ACE-2 receptors, major cardiology societies do not currently recommend altering therapy for patients on these medications. Impaired secretion clearance is thought to predispose respiratory failure, highlighting the importance of consistent bronchial hygiene in COVID-19 patients. Use of noninvasive positive pressure ventilation with close monitoring should only be used as an initial management strategy for mild COVID-19-associated ARDS, or if chronic obstructive pulmonary disease (COPD) exacerbation or heart failure is contributing to respiratory distress, as it had high failure rates in the prior H1N1 and MERS epidemics. |
| *Limitations* | The conclusions by the authors are drawn from review of clinical studies but need substantiation from further research. Due to limited data, many of the management guidelines illustrated in this paper are based off studies on MERS, SARS, and H1N1. Future research is also needed to address route of infection, and whether there are observed differences in clinical presentation based on transmission. |

# *Intubation and Ventilation Amid the COVID-19 Outbreak: Wuhan's Experience*

**Meng Lingzhong et al.**

*Anesthesiology*
*March 26, 2020*
*DOI: 10.1097/ALN.0000000000003296*

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| *Purpose* | To detail best practices regarding intubation and ventilation of critically ill COVID-19 patients. |
| *Study design* | Review article |
| *Level of evidence* | 4 |
| *Methods* | This is a summary of four webinars discussing preparedness, airway management, lung-protective ventilation, goal of oxygenation, and extracorporeal membrane oxygenation (ECMO). Information was based on firsthand experience from physicians treating critically ill patients in Wuhan. |
| *Findings* | This articles estimates percentage of patients requiring intubation at 3.2%.<br>-**Intubation Recs**: Any patients with cardiopulmonary arrest or jeopardized airway should be intubated. Any patient in respiratory distress (respiratory rate (RR) >30/min) or with hypoxemia (SpO2 < 93% on room air (RA); PaO2:FiO2 < 300 mmHg) is only intubated IF 1) the condition has progressively gotten worse or is expected to get worse AND 2) 2hr high-flow oxygen therapy or non-invasive ventilation is not expected to be effective.<br>-**Intubation Procedure Recs**: Infection Control: Two single-use filters placed in the inhalation and exhalation breathing circuits. Preoxygenation: If patient on high-flow oxygen, consider bag valve mask or tightly fitting facemask. If patient on bilevel positive airway pressure (BiPAP), continue for preoxygenation. Modified Rapid Sequence Induction: Goal is intubation within 60 secs of muscle relaxants to shorten the period of potentially ineffective ventilation, from losing consciousness to endotracheal tube (ETT) placement. Muscle relaxants are administered directly after loss of consciousness to facilitate speed.<br>- **Ventilation Recs**: In the absence of formal vent settings recs, the authors recommend acute respiratory distress syndrome (ARDS) ventilation guidelines emphasizing 1) Tidal volume (TV) less than 6 ml/kg predicted body weight; 2) RR less than 35 breaths/min; 3) plateau airway pressure less than 30 cm H2O; 4) positive end expiratory pressure (PEEP) greater than 5 cm H2O. |
| *Clinical Implications* | Anesthesia providers play a key role in the treatment of infected patients; critically ill patients with COVID-19 should be intubated and ventilated per the above recommendations. |
| *Limitations* | The authors are simply reporting what has (and has not) worked during their clinical experience treating COVID patients. There are no interventions, controls, or outcomes reported. The authors admit clinicians may reasonably dissent with their guidelines. |

# *Practical considerations for performing regional anesthesia: lessons learned from the COVID-19 pandemic*

**Sui An Lie et al.**

*Canadian Journal of Aneasthesia*
*March 24, 2020*
*DOI:10.1007/s12630-020-01637-0*

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| *Purpose* | To address logical advantages, practical considerations, and recommended measures in planning and performing surgeries using regional anesthesia (RA), as opposed to general anesthesia (GA), with respect to infection control in the setting of emerging infectious disease outbreaks. |
| *Study design* | Review article |
| *Level of evidence* | 5 |
| *Methods* | Narrative discussion and expert opinion. |
| *Findings* | -**Pre-operatively, fit the patient with a surgical face mask** for transfer to operating room (OR) with health care workers wearing appropriate personal protective equipment (PPE). **Transition from paper-based consent documentation to mobile electronic devices protected with single-use covers**. In preparation of the OR, minimize personnel present, and utilize single-use materials when possible. Fit OR equipment with single-use plastic covers. Reduce drugs and materials kept in drug trolleys wherever possible.<br>-Intra-operatively, sedation should be used with caution. **Use nasal canula under the patient's surgical mask if needed**.<br>-In the presence of respiratory disease, use alternatives to brachial plexus block such as interscalene, suprascapular, or infraclavicular blocks to minimize the risk of diaphragmatic paralysis.<br>-In the event of complications, anesthesiologists should be prepared to convert to GA or summon help for resuscitation.<br>-**Post-operatively, the patient should recover in the same OR to prevent contamination of other clinical areas**. OR equipment should be left for decontamination prior to use with another patient. |
| *Clinical Implications* | Having a well thought out plan for RA to manage infected patients may help to ensure the safety of both the patient and peri-operative team. |
| *Limitations* | This review lacks data to support its conclusions. Nuances of planning for surgeries using RA during infectious disease pandemics are largely left to individual institution. |

*Review by Nick Sytsma, MD*



# *Findings of lung ultrasonography of novel corona virus pneumonia during the 2019-2020 epidemic*

**Qian-Yi Peng et al.**

*Intensive Care Medicine*
*March 12, 2020*
*DOI: https://doi.org/10.1007/s00134-020-05996-6*

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| *Purpose* | To summarize lung ultrasonography findings for evaluation of COVID-19. |
| *Study design* | Case Series |
| *Level of evidence* | Level 4 |
| *Methods* | The authors performed lung ultrasonography on 20 patients with COVID-10 using a 12-zone method and aggregated typical pathological findings. |
| *Findings* | -Some providers have recommended early CT for screening suspected patients, but lung ultrasound may not be practical for critically ill patients; additionally, lung ultrasound has significant advantages in that there is ease of use at point of care, repeatability, absence of radiation exposure, and low cost.<br>-Characteristic findings in 20 confirmed COVID-19 pts include 1) thickening of the pleural line with pleural line irregularity; 2) B-lines in a variety of patterns including focal, multi-focal, and confluent; 3) consolidations in a variety of patterns including multifocal small, non-translobar, and translobar with occasional mobile air bronchograms; 4) appearance of A-lines during recovery phase; and 5) pleural effusions are uncommon.<br>- Focal B-lines are the main feature in the early stage and in mild infection; alveolar interstitial syndrome is the main feature in the progressive stage and in critically ill patients; A-lines can be found in the convalescence.<br>- Predominant pattern is of varying degrees of interstitial syndrome and alveolar consolidation, correlated with the severity of the lung injury. |
| *Clinical Implications* | This study offers a brief overview of expected lung ultrasound findings in COVID-19 patients. **Lung ultrasound is helpful for diagnosing pneumonia/ARDS at presentation, tracking the evolution of disease, monitor lung recruitment maneuvers, managing ECMO and/or prone positioning, and making decisions related to weaning ventilator support.** |
| *Limitations* | The study only includes scans from twenty patients. No demographic information included; authors assume the ultrasound findings are universal. These ultrasound findings are consistent with many different lung processes/types of pneumonia; therefore can likely help diagnose pneumonia but not specifically COVID pneumonia. |

# *Development and Validation of a Clinical Risk Score to Predict the Occurrence of Critical Illness in Hospitalized Patients With COVID-19*

**Wenhua Liang et al.**

*Journal of the American Medical Association Internal Medicine*
*May 12, 2020*
*DOI: 10.1001/jamainternmed.2020.2033*

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| *Purpose* | To develop and validate a clinical score assigned at hospital admission to assist in prediction of which patients with COVID-19 will develop critical illness. |
| *Study design* | Retrospective cohort (developmental cohort n=1590; validation cohort n=710) |
| *Level of evidence* | Level 3 |
| *Methods* | Researchers established a cohort of COVID-19 positive patients from 575 hospitals across 31 Chinese provinces. Patients were considered critical upon ICU admission, intubation, or death. Epidemiological, clinical, laboratory, and imaging variables ascertained at hospital admission were screened using Least Absolute Shrinkage and Selection Operator (LASSO) and logistic regression to identify predictive factors of critical illness. Independent predictive factors were then combined to form a risk score calculator (COVID-GRAM). The scoring system's accuracy was measured by the area under curve (AUC) method. The scoring system was subsequently validated using four additional Chinese cohorts. |
| *Findings* | The development cohort included 1590 patients. Mean age was 48.9 years and 57.3% of patients were male. The validation cohort included 710 patients with a mean age of 48.2 years. 53.8% of patients were male. From 72 potential predictors, 10 variables were independent predictive factors and included in the risk score: chest radiographic abnormality (odds ratio, OR: 3.39), age (OR: 1.03), hemoptysis (OR: 4.53), dyspnea (OR: 1.88), unconsciousness (OR: 4.71), number of comorbidities (OR: 1.60), history of cancer (OR: 4.07), neutrophil-to-lymphocyte ratio (OR: 1.06), lactate dehydrogenase (OR: 1.002), and direct bilirubin (OR: 1.15). Mean AUC in the development cohort was 0.88 and the AUC in the validation cohort was 0.88. The score has been translated into an online risk calculator that is freely available to the public at http://118.126.104.170/. |
| *Clinical Implications* | The authors have created an easily accessible, highly accurate scoring system (COVID-GRAM) for predicting a COVID-19 patient's risk of developing critical illness, therefore allowing staff to better prioritize patient care and optimize the use of resources. Early returns indicate this scoring system (using ten significant variables and factors including chest X-ray abnormality, age, hemoptysis, dyspnea, and the number of comorbidities) is more accurate than the CURB-6 system commonly used by emergency physicians. |
| *Limitations* | The populations used in both the developmental and validation cohorts were not enormous. All data originates from China, which may impact its generalizability to patients in other countries as it has been well documented that countries have varying incidences of comorbidities. |

# *Initial Clinical Impressions of the Critical Care of COVID-19 Patients in Seattle, New York City, and Chicago*

**Phillip Sommer et al.**

*Anesthesia & Analgesia*
*March 25, 2020*
*DOI: 10.1213/ANE.0000000000004830*

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| *Purpose* | To describe the clinical impressions of COVID-19 cases requiring intensive care. |
| *Study design* | Observational/Expert Opinion |
| *Level of evidence* | Level 4 |
| *Methods* | This study was observational, with no reported interventions or population data. The study mentions aggregating more than 300 clinical cases, 100 of which required intubation, from America's hardest hit cities: Seattle, New York City, and Chicago. |
| *Findings* | Patients present diverse and nonspecific initial symptoms of fever, malaise, fatigue, and cough in addition to chest pain, headache, altered mental status, and gastrointestinal changes. Younger patients were not exempt from severe presentation. Lab findings were notable for rarely elevated white blood cell (WBC) counts with lymphopenia being a common prognostic sign. Procalcitonin levels were typically somewhat low. C-reactive protein (CRP) was frequently elevated with a positive correlation to severity of illness. Troponin and liver biomarkers were also sometimes elevated. Coagulation abnormalities, including D-dimer elevations, were frequently observed. Bilateral patchy pulmonary opacities on chest x-ray were almost always present and severity was usually congruent with disease severity. Hypotension was common and treated with low-dose vasopressors. Concurrent myocardial infarction (MI) was also described. Severe cardiomyopathy presenting as respiratory symptoms was observed and appeared to dramatically increase mortality. Severe acute kidney injury (AKI) and refractory metabolic acidosis cases were not uncommon along with electrolyte abnormalities including hyperkalemia. Hypoxemia presented out of proportion to clinical presentation, frequently requiring noninvasive oxygenation which was associated with a high rate of intubation and low rate of successful extubation. Severe respiratory failure was reported to occur ~ 1 week after initial symptoms. Treatment of COVID-19 in the critical care setting was largely supportive. Antiviral therapies, hydroxychloroquine, and aminoquinolines have generated research interest, but there is no consensus on their use or the utility of administering steroids. |
| *Clinical Implications* | As rapidly-expanding COVID-19 infections continue to consume the US health care system's finite resources, this study, which summarizes the COVID-19 landscape in three US metropolitan areas, is useful for urban providers to preserve and augment their dwindling clinical and operational resources. It is also potentially useful for providers who have not encountered a COVID-19 surge to date, as it helps to establish clinical expectations. |
| *Limitations* | This article is limited by a lack of objective data, lack of interventions, and urban patient populations and therefore, the findings may not be generalized to a wide array of clinical settings. |

# *Extracorporeal Membrane Oxygenation in the Treatment of Severe Pulmonary and Cardiac Compromise in Coronavirus Disease 2019: Experience with 32 Patients*

**Jeffrey P. Jacobs et al.**

*ASAOI Journal*

*April 17, 2020*

*DOI: 10.1097/MAT.0000000000001185*

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| *Purpose* | To enhance the understanding of the use of extracorporeal membrane oxygenation (ECMO) in COVID-19 patients who are severely ill and develop acute respiratory and cardiac compromise refractory to conventional therapy. |
| *Study design* | Cohort Study (n=32) |
| *Level of evidence* | Level 3 |
| *Methods* | Authors used a multi-institutional database to collect and analyze data at 9 different hospitals from 32 patients with confirmed COVID-19 infection who were supported by ECMO therapy between March 17 and April 9, 2020. Collected metrics included pre-COVID-19 risk factors and comorbidities, features of ECMO support, specific medications utilized to treat COVID-19, and short-term outcomes through hospital discharge. |
| *Findings* | Of the 32 patients placed on ECMO, 5 (15.625%) survived and have been taken off ECMO, 10 (31.25%) died while on ECMO, and 17 (53.125%) were alive and still on ECMO upon completion of the study. Only 1 of the 5 patients taken off ECMO had been discharged at the conclusion of the study. All 5 patients who survived were on venous-venous ECMO, and patients requiring veno-arterial support appear to have a poorer prognosis. Of the 32 total patients on ECMO, 6 were given antiviral drugs (Remdesivir), 5 were given intravenous steroids, 6 were given anti-interleuken-6 receptor monoclonal antibodies (Tocilizumab or Sarilumab), and 1 was given Hydroxychloroquine. 3/6 of the patients given antivirals survived and were successfully weaned off ECMO. **4/5 of those patients given intravenous steroids survived and were successfully weaned of ECMO.** The patient given Hydroxychloroquine survived and was successfully weaned off ECMO. 2/6 of those patients given anti-interleuken-6 receptor monoclonal antibodies survived and were successfully weaned of ECMO. **None of the 5 patients who survived and were taken off ECMO had a previous history of heart disease, and surviving patients were younger on average than the patients who died on ECMO.** |
| *Clinical Implications* | There seems to be some effectiveness in using ECMO therapy along with other supportive care measures for some severely ill COVID-19 patients who may experience acute pulmonary and cardiac compromise. Intravenous steroid therapy showed positive results for survival and successful removal of ECMO. |
| *Limitations* | This study is limited by a short time span and a small sample size. In addition, over half of the sample was still on ECMO at the time of study conclusion, so many final outcomes are unaccounted for. More collaborative research on ECMO outcomes is needed, including follow ups on patient outcomes from this study. |

# *Neurological manifestations of COVID-19: a systematic review*

**Gaurav Nepal et al.**

*Critical Care*
*July 13, 2020*
*DOI: 10.1186/s13054-020-03121-z*

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| *Purpose* | To evaluate various neurological manifestations reported in COVID-19 patients and hypothesize their underlying pathophysiology. |
| *Study design* | Systematic review (n = 37 studies included) |
| *Level of evidence* | Level 1 |
| *Methods* | The authors performed a systemic review of all studies, published in any language, which reported neurological manifestations in patients infected by SARS-CoV-2. They reviewed pre-prints and published studies from PubMed, Google Scholar, China National Knowledge Infrastructure, Research square, medRxiv, SSRN, and ChinaXiv. After yielding 106 articles from their literature search, 37 articles met inclusion criteria. This included 12 retrospective studies, 2 prospective studies, and 23 case reports/series. |
| *Findings* | **The most common neurological manifestations of COVID-19 infection were peri- and post-infectious hyposmia and hypogeusia**, which were found in 59.45% and 56.48% of patients, respectively. This was hypothesized to result from direct viral-mediated damage to the olfactory nerve and/or apparatus. Also, inflammatory-mediated cerebral edema was a well-documented complication, which commonly presented as headache, confusion, delirium, loss of consciousness, seizure, and coma. In other cases, SARS-CoV-2 induced a cytokine storm syndrome, which created a hypercoagulable state leading to the presentation of an ischemic stroke. Additionally, the S protein of SARS-CoV-2 was hypothesized to reduce the expression and function of ACE2 proteins, leading to decreased ability to lower blood pressure and subsequent cerebral hemorrhage in some cases. Lastly, acute transverse myelitis, Guillain-barré syndrome, and Bell's palsy were also seen in some cases and was thought to be due to molecular mimicry between microbial and nerve antigens. |
| *Clinical Implications* | This systemic review sheds light on the spectrum of neurological conditions that can arise in patients with COVID-19. **In many of the included studies, the patient's neurological symptoms preceded their respiratory or gastrointestinal symptoms.** Having an awareness of the possible neurological manifestations of SARS-CoV-2 infection may allow health care workers to detect impending infections earlier, resulting in earlier interventions and improved outcomes. |
| *Limitations* | Most of the studies included were case reports/series and retrospective observational studies. Also, this systematic review only included studies released prior to May 20, 2020, which could contribute to premature analysis of data trends that may not be up to date with the current literature. |

# *Neurologically Devastating Intraparenchymal Hemorrhage in COVID-19 Patients on Extracorporeal Membrane Oxygenation: A Case Series*

**Sabrina M Heman-Ackah et al.**

*Neurosurgery*
*May 19, 2020*
*DOI: https://doi.org/10.1093/neuros/nyaa198*

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| *Purpose* | To describe cases of intracranial hemorrhage in patients on veno-venous (VV) ECMO for the treatment of COVID-19, and to propose the use of head CT screenings in patients on ECMO for COVID-19. |
| *Study design* | Case Series |
| *Level of evidence* | Level 4 |
| *Methods* | A retrospective analysis was performed on two cases of neurologically devastating intraparenchymal hemorrhage (IPH) in patients on VV ECMO for the treatment of COVID-19. Patient's clinical history, laboratory results, treatment, and available imaging were examined. Both patients lacked the classical risk factors for ECMO-related intracranial hemorrhage. |
| *Findings* | There were two patients who required ECMO for refractory hypoxia secondary to COVID-19. The first patient was a 58-year-old female with a history of diabetes and lupus, and the second patient was a 46-year-old male with a history of hypertension and obstructive sleep apnea. Both patients presented with cough, fever, and shortness of breath. The female and male patients were both found to have a nonreactive pupil after being on ECMO for 19 days and 7 days, respectively. Head CTs from both patients showed a left frontal IPH. Patients were extubated and expired. Both patients were heparinized since the initiation of ECMO. Laboratory results from these patients showed no dysfunction in the clotting cascade while on ECMO. |
| *Clinical Implications* | This study suggested that in patients with COVID-19 on ECMO, there is poor reliability on coagulation markers as a clinical predictor of hemorrhage, and an inability to perform neurological evaluations due to paralysis and sedation. Therefore, it was argued that head CT screenings in this patient cohort could be useful in more quickly identifying patients who have suffered a brain injury. These screenings would reduce the amount of time ventilators and ECMO machines are used, increasing their availability to patients with a higher probability of recovery. |
| *Limitations* | There were only two patients analyzed in this study, and there was no comparison group, therefore these findings are not generalizable to a large patient population. Additionally, this study relied on medical records to obtain data, which are susceptible to being inaccurate. Furthermore, this retrospective analysis is subject to selection bias because researchers self-selected these cases. |

# *Lidocaine During Intubation and Extubation in Patients with Coronavirus Disease (COVID-19)*

**Reza Aminnejad, et al.**

*Canadian Journal of Anaesthesia*
*March 16, 2020*
*DOI: doi:10.1007/s12630-020-01627-2*

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| *Purpose* | To suggest the usage of lidocaine to prevent possible coughing during intubation and extubation for COVID-19 infected patients. |
| *Study design* | Systematic Review |
| *Level of evidence* | Level 5 |
| *Methods* | The authors reviewed and summarized the findings from five published papers to summarize recommendations for critical care and anesthesiology teams caring for COVID-19. They focused on the usage of lidocaine for reducing coughing and preventing postoperative airway complications. |
| *Findings* | Coughing, and the subsequent ejection of infected droplets into the atmosphere, is a well-established mechanism of spread for COVID-19. The introduction of any airway instrument can exacerbate coughing, so coughing is a common symptom during intubation or extubation. Thus, the goal of reducing coughing during these procedures is to ultimately reduce the transmission of COVID-19. The studies found that IV use of lidocaine has the potential to reduce coughing, if given before intubation/extubation, without causing any other significant side effects. The authors suggest IV lidocaine is preferable to opioids, such as fentanyl, as these medicines cause coughing to occur before anesthesia and procedures. |
| *Clinical Implications* | Lidocaine may be a safe and effective way to reduce the spread of COVID-19 during intubation and extubation procedures, and should be considered when these procedures are performed on patients infected with COVID-19. |
| *Limitations* | There are relatively few studies addressing the prevention of coughing by using lidocaine. More studies are needed on the usage of lidocaine versus other medications preceding intubation and extubation of COVID-19 infected patients. |

# *Rapid Progression to Acute Respiratory Distress Syndrome: Review of Current Understanding of Critical Illness from Coronavirus Disease 2019*

**Ken J Goh et al.**
*Annals Academy of Medicine Singapore*
*March 16, 2020*
*PMID: https://pubmed.ncbi.nlm.nih.gov/32200400/*

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| *Purpose* | To describe the presentation of a patient with COVID-19 and identify clinical features and risk factors associated with severe illness, such as acute respiratory distress syndrome (ARDS). |
| *Study design* | Case report |
| *Level of evidence* | Level 5 |
| *Methods* | The authors described the presentation of a patient with COVID-19. |
| *Findings* | A 64-year-old previously healthy Chinese man presented with a fall preceded by dizziness, one week of fever, and one day of dyspnea. On presentation, he was febrile (102.2 F) and hypoxic (92% on room air) requiring 3 L/min flow of oxygen. Labs were significant for lymphopenia (0.23 x 109/L), thrombocytopenia (147 x 109/L), and elevated C-reactive protein (87.9 mg/L). Chest radiographs showed lower zone ground glass opacities and atelectasis in the left lower zone. Within 48 hours, the patient went into severe hypoxemic respiratory failure requiring high flow oxygen supplementation. Chest radiograph showed bilateral diffuse ground glass opacities. Arterial blood gas showed moderate to severe ARDS with a partial pressure of 80 mmHg, fraction of inspired oxygen of 0.7, and positive end-expiratory pressure of 10 cm H2O. On day 8 of admission,CT showed ground glass opacities and consolidation in both lungs consistent with ARDS. In addition to his age, this patient's **lymphopenia, neutrophilia, hypoalbuminemia, elevated lactate dehydrogenase (LDH), and elevated D-dimer are potential risk factors for worse outcomes**. A peak in viral load was seen shortly after symptom onset and then it declined; however, i**t remains unknown whether viral loads can be used to predict recovery.** Despite this patient having pathology on chest CT, there have been reports of critically ill patients with normal chest CTs. **Therefore, the presence of consolidation or opacities cannot be used as a risk factor.** |
| *Clinical Implications* | This case report helps identify risk factors that allow patients to be rapidly identified and closely monitored: age, lymphopenia, neutrophilia, hypoalbuminemia, elevated LDH, and elevated D-dimer. Since this case report shows how patients with COVID-19 can deteriorate rapidly, more studies are needed to identify early predictive markers of the more severe form of disease |
| *Limitations* | This case report has limited generalizability since it features only 1 patient. In addition, this patient has no comorbid illnesses, which affect a significant number of COVID patients. |

# *Cardiovascular Implications of Fatal Outcomes of Patients with Coronavirus Disease 2019 (COVID-19)*

**Tao Guo et al.**

*JAMA Cardiology*
*March 27, 2020*
*DOI: https://doi.org/10.1001/jamacardio.2020.1017*

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| *Purpose* | To evaluate the association of underlying cardiovascular disease (CVD) and myocardial injury with fatal outcomes in patients with COVID-19. |
| *Study design* | Retrospective Case Series |
| *Level of evidence* | Level 2 |
| *Methods* | Retrospective analysis of 187 COVID-19 patients hospitalized at the Seventh Hospital of Wuhan City, China from January 23, 2020 to February 23, 2020, including 144 discharged individuals and 43 individuals who died. Primary endpoint was incidence of COVID-19-associated death. Patient data included demographics, medical history, clinical lab values, comorbidities, complications, treatment measures, and outcomes. |
| *Findings* | **A total of 66 patients (35.3%) had underlying CVD** including hypertension, coronary heart disease, and cardiomyopathy, whereas **52 patients (27.8%) exhibited myocardial injury** as indicated by elevated Troponin T (TnT) levels. **Mortality was markedly increased in patients with elevated plasma TnT than in patients with normal TnT (31 [59.6%] vs 12 [8.9%]). Mortality was decreased in patients with underlying CVD and normal plasma TnT (13.33%, 4 of 30) when compared to patients with elevated TnT but no underlying CVD (37.5%, 6 of 16).** Patients with elevated TnT had significantly higher rates of common comorbidities, including hypertension, coronary heart disease, cardiomyopathy, diabetes, COPD, and CKD. Common inflammatory biomarkers (CRP, procalcitonin, and globulin) were all significantly higher in patients with elevated TnT. Patients with elevated TnT had significantly different indices of organ dysfunction as compared to patients with normal TnT**: elevated cardiac (CK-MB, myoglobin, NT-proBNP), kidney (creatinine), and liver (AST) biomarkers as well as decreased respiratory function (PaO2, FiO2).** |
| *Clinical Implications* | Myocardial injury is significantly associated with increased mortality in COVID-19. Myocardial biomarkers should be evaluated in patients with CVD who develop COVID-19 infection to best determine care plans and possible early and aggressive intervention. |
| *Limitations* | Those are early data from hospitalized patients at the epicenter of the coronavirus pandemic and the complete cardiac data (such as electrocardiography, echocardiography, coronary angiography, and magnetic resonance imaging) are missing due to the urgency of containing COVID-19. A larger cohort study is necessary in order to verify the conclusions from this project. Data was incomplete for portions of the study given the increased threshold of testing in the COVID-19 isolation ward. The impact of myocardial injury on mortality could be exaggerated as COVID-19 patient deaths may be caused by multiple organ dysfunctions. |

# *Successful COVID-19 rescue therapy by extra-corporeal membrane oxygenation (ECMO) for respiratory failure: a case report*

**Michael S. Firstenberg et al.**

*Patient Safety in Surgery*
*May 8, 2020*
*DOI: https://doi.org/10.1186/s13037-020-00245-7*

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| *Purpose* | Discuss the role of ECMO for rescue therapy of respiratory failure in critically ill COVID-19 patients and develop a decision-making algorithm for ECMO consideration. |
| *Study design* | Case Report |
| *Level of evidence* | Level 4 |
| *Methods* | Followed the hospital course of a patient who developed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) bilateral pneumonia. Since her respiratory status continued to deteriorate despite maximized critical care, veno-venous ECMO was initiated 7 days after hospitalization in conjunction with a 10-day course of compassionate use antiviral treatment with remdesivir. |
| *Findings* | The patient's pulmonary compliance, oxygenation, and ventilation gradually improved, and the patient was successfully decannulated at the bedside on ECMO day 11. The patient was discharged to a rehabilitation facility on hospital day 28. Researchers developed a decision-making algorithm for ECMO consideration that takes into consideration the ELSO (Extracorporeal Life Support Organization) guidelines as well as the RESP (Respiratory ECMO Survival Prediction) score developed by ELSO . Indications for veno-venous ECMO are profound and include respiratory failure refractory to conventional medical and ventilator management, including inhaled nitric oxide, prone positioning ventilation, and judicious use of paralytic agents. **Other than taking into account SAVE and RESP scores, due to limited resources, researchers advocate potentially limiting ECMO to patients with best predicted outcomes**—i.e. relatively young and otherwise hemodynamically stable candidates with isolated pulmonary dysfunction, few co-morbidities, and limited acute end-organ dysfunction. **ECMO should be used as a lung-protective adjuvant modality to support a patient's viral clearance by an antiviral therapy (remdesivir). ECMO should never be considered a primary therapy for any form of acute lung injury.** |
| *Clinical Implications* | This case report demonstrates a positive outcome in a 51-year-odl female patient with COVID-19 treated by the judicious application of ECMO in conjunction with compassionate use of antiviral treatment (remdesivir). From a patient safety perspective, physicians should consider the early referral of patients with respiratory failure from SARS-CoV-2 pneumonia to a designated ECMO center. |

# *Initial ELSO Guidance Document: ECMO for COVID-19 Patients with Severe Cardiopulmonary Failure*

**Robert H. Bartlett et al.**

*ASAIO Journal*
*May 2020*
*DOI: https://doi.org/10.1097/mat.0000000000001173*

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| *Purpose* | To outline indications for extracorporeal membrane oxygenation (ECMO) in COVID-19 patients. |
| *Study design* | International guidelines |
| *Level of evidence* | N/A |
| *Methods* | Guidelines for ECMO were compiled by the Extracorporeal Life Support Organization (ELSO) and all ELSO chapters worldwide. |
| *Findings* | ECMO may be a life-saving therapy for COVID-19 patients with severe or refractory cardiopulmonary failure and has been proven effective in initial trials in Japan and South Korea. **ECMO should be considered on a case-by-case basis for COVID-19 patients, with highest priority given to younger patients with minimal to no comorbidities**. Older patients, those with significant comorbidities, and patients on mechanical ventilation for more than 7 days should be excluded given the poor prognosis of disease. **Timely echocardiographic assessment in suspected cardiac dysfunction or circulatory compromise is critical to the initiation and success of ECMO in these patients.** |
| *Clinical Implications* | The ELSO guidelines (including patient selection criterion, vascular access strategies, transport, and staff protection strategies) promote ECMO as a promising therapy for a subgroup of COVID-19 patients in cardiopulmonary failure. In young patients with a favorable prognosis, ECMO is a valuable option in the arsenal of treatment options for COVID-19. When ECMO no longer provides a benefit clinicans should return to conventional management. |
| *Limitations* | ECMO is a resource-intensive therapy requiring experienced centers with the capacity to effectively provide treatment. The pandemic has overwhelmed healthcare resources worldwide, and therefore ECMO may not be a viable option for many healthcare systems. Further limitations exist from the equity perspective in providing this complex treatment to COVID-19 patients when resources are limited. |

# *COVID-19 Pandemic: What Every Otolaryngologist-Head and Neck Surgeon Needs to Know for Safe Airway Management*

**Karthik Balakrishnan et al.**

*Otolaryngology – Head and Neck Surgery*
*April 14th, 2020*
*DOI: 10.1177/0194599820919751*

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| *Purpose* | To inform otolaryngologists about airway management to maintain patient and health care staff safety during the COVID-19 pandemic. |
| *Study design* | Commentary |
| *Level of evidence* | Level 4 |
| *Methods* | The authors of this paper reviewed COVID-19 and discussed appropriate methods for otolaryngologists to treat patients while maintaining the safety of all parties involved. |
| *Findings* | Application of lessons garnered from the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) outbreaks may limit the spread of COVID-19.<br>Aerosolized COVID-19 particles may stay airborne for 3 hours and even longer on surfaces.<br>**Otolaryngologists are recommended to limit procedures to urgent cases, optimize personnel, preferably use closed circuits (such as intubation with cuffed tube) and rapid sequence induction, minimize bag-masking, and avoid awake intubations to reduce coughing.**<br>Surgical staff are to properly learn how to utilize N95 masks/powered respirators and personal protective equipment (PPE). This involves using respiratory droplet precautions, wearing and removing PPE, confirming visibility, communicating through PPE, assessing fidelity of procedures, having patients wear a loop mask, and staying alert for asymptomatic carriers.<br>Otolaryngologists should remember certain considerations: indications of invasive ventilation for COVID-19 patients, viral shedding can exceed 20 days, decisions on whether to operate in the intensive care unit or operating room, patient factors that may impact surgical decisions, keeping a small yet efficient team to limit transmission, and carefully preparing equipment.<br>To prevent healthcare worker transmission, it is recommended to adapt from Hong Kong's tactics during the SARS outbreak. This includes learning from past outbreaks, having a rapid response team, monitoring staff, having PPE "buddy" checks, dedicated shoe and apparel storage, gowning as well as procedural sites, and dedicated personal for certain procedures. |
| *Clinical Implications* | To minimize aerosol generation and COVID-19 transmission, otolaryngologists (and surgical staff) are highly recommended to observe these guidelines since they are at higher risk of being exposed to aerosolized droplets by asymptomatic carriers. |
| *Limitations* | This study was published in April and new guidelines may have been implemented. This is also a commentary and requires further research to elucidate better guidelines. |

# *Guillain-Barré syndrome in SARS-CoV- 2 infection: an instant systematic review of the first six months of pandemic*

**Antonino Uncini et al.**

*Journal of Neurology, Neurosurgery and Psychiatry*
*August 27, 2020*
*DOI: http://dx.doi.org/10.1136/jnnp-2020-324491*

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| *Purpose* | To clarify the clinical characteristics and potential implications of Guillain-Barré syndrome (GBS) in SARS-CoV- 2 infection. |
| *Study design* | Systematic Review (n = 33 studies) |
| *Level of evidence* | Level 4 |
| *Methods* | The authors conducted a PubMed search of cases involving GBS and SARS-CoV- 2 infection between 1/30/20 and 6/30/20. A total of 33 papers (28 case reports and 5 case series) were found, and 42 patients were included in the systematic review. The authors documented key aspects of these cases including clinical characteristics, age, and time between infectious and neuropathic symptoms. |
| *Findings* | From January 30, 2020 to June 30, 2020, there was a 5.41-fold increase in the monthly incidence of GBS in Friuli Venezia-Giulia, Italy compared to the same months of previous years. Most patients (71.4%) had the classic form of GBS characterized by reduced or absent tendon reflexes, symmetrical weakness of the limbs, and sensory symptoms. The mean interval between onset of COVID-19 infection and GBS symptoms was 11.5 days (range: 3–28 days). Respiratory failure occurred in about one-third of patients with GBS. 50% of this group experienced hypercapnia, paradox respiration, and acidosis, which suggests neuromuscular respiratory failure due to GBS contributed significantly to their respiratory failure. Patients were treated mainly with IVIG and 62% showed definite improvement or recovered completely at short time follow-up. |
| *Clinical Implications* | Increased case reports of GBS coinciding with COVID-19 infection may suggest a possible pathogenic link between SARS-CoV- 2 and GBS. Future work should be done to examine the contribution of GBS to respiratory failure. Having an awareness of this increasingly common post-infection complication of SARS-CoV-2 infection may result in earlier interventions and improved outcomes. |
| *Limitations* | Overall, the patients that were included in the study were mostly from Europe (79.4%) and Italy (30.9%). Also, the incidence of GBS during the pandemic was only analyzed in Friuli Venezia-Giulia, Italy. These limitations decrease the external validity of the author's results. Since this systematic review had a small sample size and exclusively used case reports, future studies seeking to determine if there is a true association between SARS-CoV- 2 and GBS will likely require a prospective standardized cohort study with a case-control design. |

# *Novel Approach to Reduce Transmission of COVID-19 During Tracheostomy*

**Peter Foster et al.**

*Journal of the American College of Surgeons*
*April 10, 2020*
*DOI: 10.1016/j.jamcollsurg.2020.04.014*

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| *Purpose* | To propose a novel protocol for performing a tracheostomy on COVID-19 patients that reduces the risk of infecting hospital staff. |
| *Study design* | Case Report |
| *Level of evidence* | Level 5 |
| *Methods* | The surgery department at Berkshire Medical Center, a 307-bed community hospital in Pittsfield, MA, developed a protocol for performing tracheostomies on COVID-19 patients who require mechanical ventilation. First, operating room staff put on PPE, consisting of boot covers, sterile gown, under gloves, surgical mask, powered air-purifying respirators, and sterile gloves, in an anteroom. The patient is accompanied by an anesthesia provider in full PPE during the transfer from the ICU to the operating room. Once in the operating room, the patient is placed in the supine position on the operating table, draped in a sterile manner with a thyroid drape, and a magnetic instrument mat is placed over the patient's upper chest. Next, an Omni-Tract retractor is mounted to the operating table at the level of mid-abdomen, opposite the surgeon, and the retractor arms are placed in a wide-V configuration over the upper body. A Bookwalter or Thompson retractor set may also be used. Then, an Ecolab Scope Pillow Warmer drape, a clear plastic material, is stretched over the retractor arms to form a barrier between the operative field and the surgeon. The drape is secured with snaps to the retractor. Finally, Buffalo Filter smoke evacuator tubing is connected to two heat moisture exchange filters and placed under the drape to provide further air filtration. The surgeon and assistant perform the procedure with hands underneath the drape. Numerous rehearsals of the protocol were performed to analyze mechanics, ease of use and set-up, and visibility of the surgical site. |
| *Findings* | This protocol was successfully used on 1 patient who was intubated for 28 days. |
| *Clinical Implications* | The COVID-19 pandemic has increased the use of mechanical ventilation for patients who develop prolonged respiratory failure. This feasible protocol allows hospitals to perform tracheostomies in a manner that reduces droplet and aerosol exposure to hospital staff, decreasing the spread of the disease. |
| *Limitations* | The rate of COVID-19 transmission among hospital staff who use this protocol was not evaluated. A study that analyzes this variable using a large data set would be helpful in determining the efficacy of this protocol. |

# *Pediatric Airway Management in COVID-19 patients - Consensus Guidelines from the Society for Pediatric Anesthesia's Pediatric Difficult Intubation Collaborative and the Canadian Pediatric Anesthesia Society.*

**Clyde T. Matava et al.**

*Anesthesia & Analgesia*
*July 13, 2020*
*DOI: 10.1213/ANE.0000000000004872*

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| *Purpose* | To identify overarching goals during airway management and intubation of pediatric patients suspected or confirmed to have COVID-19. |
| *Study design* | Nominal Group Technique (NGT) case review and digital forum |
| *Level of evidence* | N/A |
| *Methods* | The Pediatric Difficult Intubation Collaborative (PeDI-C), comprised of 35 hospitals from 6 countries, used expert opinion, early data about COVID-19, and existing guidelines to create a set of consensus guidelines for pediatric intubation procedures. Protocols were crafted with emphasis on practitioner safety and prevention of contamination or exposure while intubating or managing the airway of pediatric COVID-19 patients. |
| *Findings* | GENERAL: Contact surfaces, (keys, badges, phones) must be removed during procedures. Negative pressure rooms and complete air exchange should be utilized whenever possible<br>INTUBATION RECOMMENDATIONS: Premedication of patients should be performed to avoid coughing and dispersal of droplets. Avoidance of nasal administration will decrease patient stress and possibility of droplet aerosolization upon exhale. Rapid Sequence Intubation (RSI) with limited mask/bag air administration and with plastic barrier is the most effective way to prevent droplet aerosolization. Cuffed tracheal tube, video laryngoscopy, and in-line closed suctioning preferred. Nasal cannula and BVM not advised. Viral filters should be in place for transport of intubated patients.<br>EXTUBATION RECOMMENDATIONS: Patients should be pre-medicated to minimize coughing and droplet expulsion. Extubation should be done in an operating room with plastic coverings and in-line suction, not in patient recovery areas or ED. |
| *Clinical Implications* | Research indicates that minimization of trauma, stress, and surface contact during the intubation, airway management, and extubation of pediatric patients is critical in protecting providers from COVID-19 exposure and contraction. Novel protocols developed though NGT have created a temporary set of guidelines for providers to follow when approaching these situations. These guidelines significantly reduce contact with patient and also propose higher premedication of patients. |
| *Limitations* | These findings are based on alterations of pre-existing protocols for airway management providers throughout the United States. Due to the rapid nature of the expanding COVID-19 pandemic, randomized clinical trials to determine efficacy of these protocols have not yet occurred. As such, these novel protocols are the adaptation of existing protocols based on expert opinions as opposed to formal clinical results. |

# *Neurological Manifestations of Patients Infected with the SARS-CoV-2: A Systematic Review of the Literature*

**Federico Cagnazzo et al.**

*Journal of Neurology*
*October 30, 2020*
*DOI: 10.1007/s00415-020-10285-9*

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| *Purpose* | To perform an updated review of the literature on neurological manifestations of COVID-19 infected patients. |
| *Study design* | Systematic review |
| *Level of evidence* | Level 1 |
| *Methods* | PRISMA-guideline-based systematic review of studies reporting neurological manifestations of COVID-19 patients totaling 39 studies and 68,361 laboratory-confirmed COVID-19 patients. |
| *Findings* | Consistent with other studies, 79% of patients presented with fever, 60.1% had dry cough, 31.7% fatigue, and 19.6% dyspnea.<br>Neurological manifestations were present in 21.3% of COVID-19 hospitalized patients, with headache (5.4%), myalgia/elevated creatine kinase (5.1%), and psychiatric disorders (4.6%) the most commonly reported.<br>The proportion of patients with impaired consciousness ($p = 0.0001$) and acute cerebrovascular events ($p = 0.02$) were significantly higher among those with severe COVID-19 infection.<br>Acute ischemic stroke presented with mean delay of $14 \pm 5$ days from COVID-19 symptom onset. Admission to the intensive care unit (ICU) was required for 63% of patients with acute ischemic stroke with intra-hospital mortality rate of 22.8%. |
| *Clinical Implications* | A substantial number of COVID-19 infected patients have neurological manifestations, and those with severe disease are more likely to have impaired consciousness and acute cerebrovascular events. |
| *Limitations* | Initial studies have not been designed to collect data on neurologic events with COVID-19, and thus data is missing and/or incomplete in a number of reports. Thus, exclusion of a higher frequency of benign neurologic symptoms (i.e. headache, anosmia) in patients with more mild disease not necessitating hospitalization cannot be included. Additionally, the mortality of patients among those with neurologic events in tandem with infection is in its reporting infancy. |

# *Cerebral Ischemic and Hemorrhagic Complications of Coronavirus Disease 2019*

**Ahmad Sweid, et al.**

*International Journal of Stroke*
*June 26, 2020*
*DOI: 10.1177/1747493020937189*

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| *Purpose* | To present a comprehensive summary of the SARS-CoV-2-induced factors that are associated with acute cerebrovascular pathologies |
| *Study design* | Case series and literature review |
| *Level of evidence* | Level 4 |
| *Methods* | A retrospective study of 22 patients with diagnosis of acute cerebrovascular disease and COVID-19 infection from 2 institutions in the USA was performed. A PubMed literature search and pooled analysis was performed for acute cerebrovascular disease in conjunction with COVID-19 infection. |
| *Findings* | Pathologies included acute ischemic stroke (n=17), aneurysm rupture (n=3), and sinus thrombosis (n=2) with mean age of 59.5 years. Stroke and thrombosis patients had mean initial NIH Stroke Scale of 13.8 ± 8.0. Cerebrovascular incident was the initial manifestation of COVID-19 in 45.5% of cases. Duration from COVID-19 symptom onset to neurologic manifestation was 8.8 ± 4.4 days.<br><br>Among stroke and thrombus patients, mechanical thrombectomy was performed in 84.2% cases, with 100% achieving Thrombolysis in Cerebral Infarction score ≥2B/3 compared to 77.1% in the pooled analysis. Mortality in the present series was 33.3% compared to 45.9% in the pooled analysis.<br><br>Total mortality was 36.4%, and 50% of patients had poor functional status (modified Rankin Score 3-6) upon discharge. |
| *Clinical Implications* | This study provides preliminary data on the acute management and outcomes of cerebrovascular disease in COVID-19 infection, including incidence of acute neurologic symptoms as an initial presentation and time from symptoms to neurologic insult. |
| *Limitations* | A small (n=22), retrospective cohort study without longitudinal follow-up and outcomes is presented. This study presents early information on the presenting demography and treatment of cerebrovascular disease related to COVID-19 infection. The heterogeneity and paucity of large studies precludes analysis and extrapolation of these reports on the impact of COVID-19 incidence in acute cerebrovascular disease. |

# VACCINE DEVELOPMENT

# *SARS-CoV-2 and SARS-CoV Spike-RBD Structure and Receptor Binding Comparison and Potential Implications on Neutralizing Antibody Vaccine Development*

**Chunyun Sun et al.**

*bioRxiv*

*February 20, 2020*

*DOI: https://doi.org/10.1101/2020.02.16.951723*

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| *Purpose* | To investigate whether SARS-CoV neutralizing antibodies (nAbs) possess cross-reactivity to SARS-CoV-2. |
| *Study design* | Observational study |
| *Level of evidence* | Level 4 |
| *Methods* | Sequence, macro, and microstructures were evaluated with computer analysis softwares. Binding kinetics, antibody cross-reactivity, and neutralization efficiency were measured by ELISA. SARS-CoV nAbs were generated by immunizing rodents with SARS-CoV S1 or RBD protein; two SARS-CoV S-protein rabbit polyclonal antibodies and four monoclonal antibodies were analyzed for cross reactivity using ELISA. Non-Ace2-blocking antibodies were also screened for cross-reactivity using ELISA. |
| *Findings* | **Within the receptor binding domains (RBDs) of SARS-CoV and SARS-CoV-2, significant differences were found in the receptor binding motifs (RBMs).** SARS-CoV nAbs demonstrated little cross-reactivity with SARS-CoV-2 S1 protein, indicating a **low probability of identifying efficacious cross-reactive nABs to SARS-CoV-2 from SARS-CoV antibodies or antibody libraries.** However, three ACE2-non-blocking monoclonal antibodies were found to cross-bind the SARS-CoV-2 S1 protein and cross neutralize the SARS-CoV-2 pseudovirus at high concentrations. Based on the two viruses' RBD structural similarities, targets for cross-reactive and neutralizing antibodies may be found. |
| *Clinical Implications* | There is a potential trade-off between the efficacy and spectrum of therapeutic antibodies to different coronaviruses. This paper underscores the challenges in developing broadly protecting antibodies and vaccines against SARS-CoV-2 and its future mutants or SARs-CoV, should it re-emerge. |
| *Limitations* | Types of antibodies obtained in this study were limited. Future research needs to explore mechanism of neutralization for non-blocking RBD antibodies. |

# *Potential Rapid Diagnostics, Vaccine and Therapeutics for 2019 Novel Coronavirus (2019-nCoV): A Systematic Review*

**Junxiong Pang et al.**

*Journal of Clinical Medicine*
*February 26, 2020*
*DOI: https://doi.org/10.3390/jcm9030623*

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| *Purpose* | To provide guidance to policymakers on the most effective distribution of resources for research and development surrounding (2019-nCoV). |
| *Study design* | Systematic Review |
| *Level of evidence* | Level 1 |
| *Methods* | Authors compiled the findings of 27 human studies examining the diagnostics, vaccines, and therapeutic drugs for Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and the 2019 novel coronavirus (2019-nCoV). |
| *Findings* | Nucleic acid based tests are useful for diagnosing active 2019-nCoV (a.k.a. SARS-CoV-2) infection and serological testing may be effective for determining the extent of infection, including asymptomatic infection and attack rate in populations. Potential vaccines and antiviral treatment modalities for SARS-CoV-2 infection are presented based on data from trials for other corona viruses, including MERS-CoV and SARS-CoV. |
| *Clinical Implications* | Nucleic acid testing is useful for diagnosing SARS-CoV-2 infection At the time of publishing of this study, there was **only one vaccine that has received emergency approval, and is currently being used in clinical and surveillance centers in China.** Other vaccine candidates will take roughly one year to start phase 1 clinical trials. Given the absence of a vaccine and a long interval before one is available, **clinicians should consult literature for optimizing treatment protocols with pre-existing or available medications.** |
| *Limitations* | Inferences of vaccine effect on 2019-nCoV are largely based on the behavior of SARS and MERS. Most of the studies on vaccines for SARS and MERS were excluded by reviewers for being performed in cell or animal models, so only four studies were ultimately included. No vaccine studies in any population type were available for 2019-nCoV specifically. In addition, no completed trials on 2019-nCoV therapeutics had been completed at the time of the review. |

# *The COVID-19 vaccine development landscape*

**Tung Thanh Le et al.**

*Nature Reviews, Drug Discovery*
*April 8, 2020*
*DOI: 10.1038/d41573-020-00073-5*

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| *Purpose* | To contribute to the global efforts for the development of vaccines against COVID-19 by providing an overview of current vaccine development activity. |
| *Study design* | Narrative Review |
| *Level of evidence* | Level 5 |
| *Methods* | Since February of 2020, reviewers have continually monitored and reported on the COVID-19 vaccine development landscape using sources such as the World Health Organization, clinical trial databases, publicly available literature, press releases, and information from product developers. |
| *Findings* | There are currently 115 vaccine candidates for COVID-19 globally, 78 of which were confirmed to be in active development. Of these, **73 vaccines are in exploratory stages and the remaining five are in clinical development**. In clinical development, there are two vaccines using a non-replicating viral vector, one using recombinant protein, one using RNA, and one using DNA. **In addition, at least 10 projects are investigating the use of adjuvants, which would make lower doses possible and allow more people to get vaccinated without compromising efficacy.** |
| *Clinical Implications* | The high number of vaccine technology platforms being tested to fight COVID-19 offer hope for a safe, effective, and quickly available vaccine. In addition, it is possible that multiple platforms will be successful, which would allow different patient populations to receive different vaccines depending on their age and medical conditions. |
| *Limitations* | Many of the technology platforms being used for development are not currently used in any licensed vaccines, raising questions about safety and efficacy in an already accelerated development landscape. In addition, these platforms may not be able to use existing production equipment to manufacture vaccines on the massive scale that may be necessary. |

# *An effective CTL peptide vaccine for Ebola Zaire based on survivors' CD8+ targeting of a particular nucleocapsid protein epitope with potential implications for COVID-19 vaccine design*

**CV Herst et al.**

*BioRxIV/Vaccine*
*March 9, 2020*
*DOI: https://doi.org/10.1101/2020.02.25.963546*

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| *Purpose* | Develop a CTL (cytotoxic T lymphocyte) peptide vaccine producing a T-cell response against EBOV (Zaire ebolavirus); determine if CTL expansion can be driven by NP43-53, an EBOV nucleoprotein (NP) peptide shown to provide protective CTL-mediated immunity against EBOV in previous mouse studies; and see if this peptide is protective in an in-vivo EBOV murine challenge model. A similar approach to a CTL vaccine design may be possible for SARS-CoV-2. |
| *Study design* | Basic science/translational mouse study |
| *Level of evidence* | Level 5 |
| *Methods* | An established microsphere-based, synthetic vaccine platform was used to immunize C57BL/6 mice with NP43-53 or 9mer sub-sequences of NP43-53. Splenocytes were harvested 14 days after immunization and analyzed for IFN-γ release after simulation with peptide used in vaccination. Mice were then vaccinated with NP44-52 (a subsequence of NP43-53) or a control and challenged 14 days later with mouse-adapted EBOV. |
| *Findings* | **For the splenocyte restimulation experiments, there was no significant difference in IFN-γ production between NP43-53 vaccinated mice and control-treated mice**. **NP44-52-vaccination induced greater IFN-γ release than NP43-54 and was used for subsequent experiments**. In the in vivo EBOV challenge model, **control-treated mice showed increasing mortality compared to vaccinated mice, which survived and showed no morbidity.** Low levels of IL-6, MCP-1, IL-9, and GM-CSF and increased IFN-γ were found in surviving mice. |
| *Clinical Implications* | As a single dose of the peptide vaccine protected mice from EBOV morbidity and mortality, a CTL-mediated peptide vaccine may be feasible and efficacious for SARS-CoV-2. |
| *Limitations* | This is a murine study, so there is a limitation to how these findings can be applied to humans. For example, the NP43-53 peptide is a mouse peptide, and a human HLA-restricted peptide would need to be determined for an effective vaccine. |

# *COVID-19, an emerging coronavirus infection: advances and prospects in designing and developing vaccines, immunotherapeutics, and therapeutics.*

**Kuldeep Dhama et al.**

*Human Vaccines & Immunotherapeutics*
*March 18, 2020*
*DOI: https://doi.org/10.1080/21645515.2020.1735227*

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| *Purpose* | Highlight the ongoing advances in designing vaccines to counter COVID-19 (SARS-CoV-2), and focus on earlier efforts to develop a vaccine to fight human coronavirus (CoV) infections, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). |
| *Study design* | Review article |
| *Level of evidence* | Level 5 |
| *Methods* | This paper served as a brief review to highlight ongoing advances in COVID-19 vaccine development and compare them with prior efforts made in history. |
| *Findings* | Most COVID-19 vaccine strategies target the surface-exposed spike (S) glycoprotein as the major inducer of neutralizing antibodies. The possibility of developing a universal COVID-19 vaccine was assessed based on the similarity in T-cell epitopes of SARS-CoV and SARS-CoV-2. **SARS-CoV-2 shares genetic similarity with SARS-CoV, making it possible that vaccines developed for SARS-CoV can exhibit cross-reactivity to SARS-CoV-2**. Direct administration of monoclonal antibodies can help play a role in COVID-19 control. Studies have shown that patients recovering from SARS display potent neutralizing antibody responses. Studies have also shown that passive immunization with neutralizing antibodies induces substantial protection in mice subjected to lethal MERS-CoV challenge. |
| *Clinical Implications* | This study describes various designs of COVID-19 vaccine development: the S glycoprotein (recognizing the human ACE2 cellular receptor), the similarity in T-cell epitopes of SARS-CoV and SARS-CoV-2, and the direct administration of monoclonal antibodies. |
| *Limitations* | This study was limited by its lack of including suitable animal models for analyzing replication, transmission, and pathogenesis. |

# *Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic*

**Eakachai Prompetchara et al.**

*Asian Pacific Journal of Allergy and Immunology*
*March 2020*
*DOI: 10.12932/AP-200220-0772*

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| *Purpose* | Utilize historical data from SARS-CoV and MERS-CoV to compare past with the present SARS-CoV-2 outbreak. Aim to understand viral pathogenesis, host immune responses, and evasion strategies in order to inform therapeutic vaccine strategies moving forward. |
| *Study design* | Review article |
| *Level of evidence* | N/A |
| *Methods* | SARS-CoV, MERS-CoV, and SARS-CoV-2 were compared using viral comparisons using demographic data, characteristics, and immunopathogenesis as a foundation to inform discussion of various vaccine platforms. Delivery mechinisms range from DNA, viral vector, subunit, virus-like particles, inactivated and live-attenuated virus vaccines. |
| *Findings* | SARS-CoV-2 shares 79% genomic similarity with SARS-CoV and 50% with MERSCoV. SARS-CoV-2 and SARS-CoV also share the same entry receptor of ACE2, expressed on type 2 alveolar cells. **Nucleic acid-based vaccines showed promise in Phase I and II of trials for SARS-CoV and MERS-CoV (SARS-CoV-2 was not presented in this review); similar vaccines were trialed in less than one year after the Zika outbreak, depicting a hopeful timeline to therapeutic intervention.** This platform yields advantages of rapid production, simple design, and induction of both B and T cell responses. Yet this delivery modality has disadvantages of efficient delivery system requirement and lower immune response induction compared to live vaccines. |
| *Clinical Implications* | This paper highlights the robust and rapid response to SARS-CoV-2 vaccine development globally and suggests the pivotal role of international collaboration, preclinical studies performed in parallel with clinical trials to expediate therapuutic timeline. |

# *Multiple-epitope vaccine design using an immunoinformatics approach for 2019 novel coronavirus in China (SARS-CoV-2)*

**Ye Feng et al.**

*bioRxiv*
*March 3, 2020*
*DOI: https://doi.org/10.1101/2020.03.03.962332*

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| *Purpose* | Identify surface-exposed peptides of SARS-CoV-2 to design multiple-epitope vaccines. |
| *Study design* | Basic Science Study |
| *Level of evidence* | N/A |
| *Methods* | Based on the genome sequence of SARS-CoV-2 isolate Wuhan-Hu-1 retrieved from the NCBI database, candidate B-cell epitopes were analyzed from an online tool in the Immune-Epitope-Database And Analysis-Resource. Prediction of linear B-cell epitopes and surface accessible epitopes were performed through Bepipred software and Emini tool. Prediction of T-cell epitope binding affinity to specific HLA alleles were performed through netMHCpan and prediction software iNeo-Pred. Based on B-cell and T-cell epitopes, vaccine peptides were optimized for high epitope count and HLA score, then designed by an in-house tool iNeo-Design. In addition, an online server swiss-model was used to the predict the 3D protein structures and HLA molecules. |
| *Findings* | Based on 19 B-cell epitopes and 121 adjacent T-cell epitopes, 17 candidate vaccine peptides that contained both B-cell and T-cell epitopes were generated. 499 core T-cell epitopes were analyzed to generate 13 T-cell epitopes-only vaccine peptides. **All in all, a total of 30 peptide vaccine candidates were designed to potentially cause an immune response against SARS-CoV-2. 26 of them were from the spike protein, 2 were from the membrane protein, and 2 were from the envelope protein.** 5 peptides were located in the receptor binding domain region, suggesting that they were likely to induce production of neutralizing antibody. |
| *Clinical Implications* | This study recommends multiple vaccine peptides involving B-cell and T-cell epitopes to use as potential vaccines against SARS-CoV-2 |
| *Limitations* | The study was limited in that these multiple-epitope vaccine designs require in vitro and in vivo trials to determine effectiveness of these vaccine peptides. In addition, this study is a preliminary report that has not been peer-reviewed. |

# *Self-amplifying RNA SARS-CoV-2 lipid nanoparticle vaccine induces equivalent preclinical antibody titers and viral neutralization to recovered COVID-19 patients*

**Paul McKay et al.**

*bioRxiv preprint*
*April 25, 2020*
*DOI: https://doi.org/10.1101/2020.04.22.055608*

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| *Purpose* | To observe the IgG response to a self-amplifying RNA SARS-CoV-2 lipid nanoparticle vaccine generated in a murine model compared to antibody titers from recovered COVID-19 patients. |
| *Study design* | Randomized controlled animal trial |
| *Level of evidence* | N/A |
| *Methods* | Mice were randomly assigned to one of three groups. The treatment group was immunized with self-amplifying RNA (saRNA) for the SARS-CoV-2 spike protein encapsulated in lipid nanoparticles (LNP) in doses ranging from 0.01 µg to 10 µg. The positive control group received electroporated plasmid DNA, and the negative control group received saRNA encoding the rabies glycoprotein. Each group received two vaccines, one month apart. Serum samples from each group and from recovered SARS-CoV-2 human patients were collected. These samples were analyzed to measure SARS-CoV-2-specific IgG antibody levels and ability to neutralize a pseudotyped virus. |
| *Findings* | High quantities of IgG against SARS-CoV-2 were found in the mouse treatment group in a dose-responsive manner. Viral neutralization was significantly more effective in the treatment group than in the positive control group. At all vaccine doses, the treatment group demonstrated significantly higher quantities of SARS-CoV-2 specific IgG and significantly more viral neutralization than serum derived from natural infection in humans. A positive correlation between antibody levels and levels of viral neutralization was observed in both humans and mice. |
| *Clinical Implications* | **A vaccine using saRNA encapsulated in LNP has the potential to provide protection against SARS-CoV-2 infection. This vaccine formulation was effective at stimulating a robust cytokine response in mice, suggesting that the LNP enhances the immunogenicity of the saRNA.** In addition, the cellular immune response favored Th1 cells, which increases the likelihood that the results are translatable to humans. RNA therapeutics formulated with LNP are already in clinical use and require lower doses than messenger RNA drugs, easing some concerns about clinical safety. |
| *Limitations* | This was a mouse model and the results may not be generalizable to humans. The sample size was small, with n=7 or 8 for each group, and mice within the treatment group did not all receive the same vaccine dose. This study still has to undergo peer review. |

# *In silico Design of novel Multi-epitope recombinant 1 Vaccine based on Coronavirus surface glycoprotein*

**Mandana Behbahani**

*bioRxiv preprint*
*April 21, 2020*
*DOI: https://doi.org/10.1101/2020.03.10.985499*

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| *Purpose* | To perform an in silico design a vaccine for Coronavirus based on surface glycoproteins. |
| *Study design* | In Silico |
| *Level of evidence* | N/A |
| *Methods* | A multi-epitope vaccine based on surface glycoprotein was designed through application of bioinformatics methods. NCBI resources were used to gather relevant protein sequences and to determine sequence alignment. Antigenicity of the coronavirus surface glycoprotein was evaluated using VaxiJen 2.0 server. B-cell epitopes were predicted using ElliPro and IEDB analysis resource. T-cell epitope prediction was performed using ProPred-1 server. 17 potent linear B-cell and T-cell binding epitopes from surface glycoprotein were predicted in silico. Then, the epitopes were joined via different linkers. The ability of selected epitopes to induce interferon-gamma was then evaluated using IFNepitope web server. |
| *Findings* | A final vaccine was constructed, which composed of 398 amino acids and attached to 50S ribosomal protein L7/L12. Physicochemical properties and antigenicity in the proposed vaccine demonstrated that the vaccine was stable. Molecular docking studies confirmed that the vaccine interacted with MHC-I and MHC-II molecules as expected. Interferon-gamma analysis showed that 16/17 epitopes had the potential to produce interferon-gamma. |
| *Clinical Implications* | This study introduced a novel multi epitope vaccine design against Coronavirus. The multi-epitope vaccine with 50S ribosomal protein L7/L12 as adjuvant was a stable construct with high aliphatic content and high antigenicity. |
| *Limitations* | This was an in silico study; the proposed virus must still be followed by in vitro and in vivo studies before proceeding. Also, this study still has to undergo peer review. |

# *Potent neutralizing antibodies in the sera of convalescent COVID-19 patients are directed against conserved linear epitopes on the SARS-CoV-2 spike protein*

**Chek Meng Poh et al.**

*bioRxiv preprint*
*March 31, 2020*
*DOI: https://doi.org/10.1101/2020.03.30.015461*

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| *Purpose* | Identify potential immunodominant linear B-cell epitopes on SARS-CoV-2 virus spike glycoprotein for vaccine development. |
| *Study design* | Basic Science Investigational Study |
| *Level of evidence* | N/A |
| *Methods* | Convalescent serum samples were collected from 25 patients in Singapore during the COVID-19 outbreak. Pseudotyped lentivirus expressing SARS-CoV-2 spike (S) glycoprotein tagged with luciferase reporter was used to assess neutralizing activity of sera. Antigenic targets of sera were determined using liner B-cell peptide library for entire S protein of either SARS-CoV or SARS-CoV-2 and peptide-based ELISA and antibody depletion assays. Sera from recovered SARS patients and healthy patients were used as comparisons and control groups, respectively. |
| *Findings* | - Six of the 25 sera samples demonstrated good neutralizing capability with IC50 scores ranging between 694-836 (one outlier; IC50 = 1603). COVID-19 patient sera strongly detected peptide pools S14 and S21. **The individual peptides detected within these pools were S14P5 and S21P2. Importantly, both peptides are localized in proximity to functionally important regions of the S protein: peptide S14P5 is localized in proximity to the RBD and S21P2 contains part of the fusion peptide sequence.** Antibody-depletion assays demonstrated reduced neutralization of SARS-CoV-2 pseudovirus infection when antibodies against the aforementioned peptides were depleted in the sera. Sera from COVID-19 patients demonstrated detection against SARS-CoV pool S51 which overlaps with SARS-CoV-2 pool S21, raising the potential of a pan-coronavirus epitope. |
| *Clinical Implications* | This study identifies two immunodominant B cell linear epitopes (S14P5 and S21P2) that are recognized by neutralizing antibodies and may serve as immunogenic targets for vaccine. |
| *Limitations* | The study was limited by its small sample size, with only six patient samples demonstrating good neutralization capacity. Further development is necessary to create a vaccine based on this work. Also, this study still has to undergo peer review. |

# *If a coronavirus vaccine arrives, can the world make enough?*

**Roxanne Khamsi**

*Nature*
*April 9, 2020*
*DOI: 10.1038/d41586-020-01063-8*

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| *Purpose* | Biomedical companies around the world are working on formulating a SARS-CoV-2 vaccine. Most research to date has compared the numerous platforms available and their respective advantages and disadvantages. Optimistic timelines project a vaccine will be available within the next 12 to 18 months. This article seeks to address the question that follows: once a vaccine is formulated, how is the world to go about its production and equitable distribution? |
| *Study design* | News, review article |
| *Level of evidence* | 5 |
| *Methods* | Quantitative and narrative data collection from reputable sources including: World Health Organization (WHO), Coalition for Epidemic Preparedness Innovations (CEPI), US Pharmacopeia (USP), and several others. |
| *Findings* | **How vaccine distribution looks will depend heavily on the delivery mechanism, which range from inactivated form to subunit to RNA/DNA based, with each formulation bearing its own challenges and rewards.** Regardless of the platform chosen, CEPI describes a gap that needs to be unpacked: a fair allocation system. In response to pandemics of the past, the World Health Organization (WHO) adopted the Pandemic Influenza Preparedness (PIP) Framework to coordinate the supply-demand of vaccines, diagnostics, and drugs but due to its specificity for influenza, PIP does not apply to SARS-CoV-2. The article advocates for a rapid response mimicking this framework yet addresses time to devise as a limiting factor in addition to the retroactive obtainment of samples posing a logistical threat to its success. |
| *Clinical Implications* | This article allows for greater understanding of the vast limitations of vaccine development beyond delivery type; touching on production costs, resource scarcity, politics, and upholding the justice pillar of medical ethics. It calls on global governments and private funders to be proactive in their response to this knowledge; the Coalition for Epidemic Preparedness Innovations (CEPI) estimates minimum $3 billion USD are needed to develop, trial, and manufacture, and distribute a vaccine for the world (not including estimated billions needed to fuel manufacturing plants). |
| *Limitations* | The inevitable limitation in our current stage of the SARS-CoV-2 vaccine development lies in the careful balance of efficiency and efficacy. This article seeks to predict future challenges in this realm based on past patterns and present predicaments. |

# *Computers and viral diseases. Preliminary bioinformatics studies on the design of a synthetic vaccine and a preventative peptidomimetic antagonist against the SARS-CoV-2 (2019-nCoV, COVID-19) coronavirus*

**Barry Robson**

*Computers in Biology and Medicine*
*February 26, 2020*
*DOI: https://doi.org/10.1016/j.compbiomed.2020.103670*

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| *Purpose* | To find a short section or sections of SARS-CoV-2 viral protein sequence suitable for preliminary design proposal for a peptide synthetic vaccine and a peptidomimetic therapeutic, and to explore some design possibilities. |
| *Study design* | Bioinformatics |
| *Level of evidence* | Level 5 |
| *Methods* | The use of Q-UEL (an involved automatic surfing of the world wide web to speed access to information) systems to access relevant emerging literature, and to interact with standard publicly available bioinformatics tools on the internet. Additionally, the use of MARPLE/HDNstudent with XTRACTOR allows for specific search queries that bypass "autosurfing" of the internet. |
| *Findings* | The sequence of amino acids KRSFIEDLLFNKV was found to be particularly well conserved across many coronaviruses (including 2019-nCoV) and corresponds to the region around one of the known cleavage sites of the SARS virus believed to be required for virus activation for cell entry. Many conventions in diagnostic and vaccine design are not significant in coronavirus matches, however an exposed loop in the SARS coronavirus is an important target for creating antibodies and a carrier protein is necessary to promote immunogenicity. The addition of C-terminal and N-terminal linkage sequences resulted in the proposed L-amino sequence of GPSKRSFIEDLLFNKVTLAC as a B-epitope to be synthesized and attached to a carrier. |
| *Clinical Implications* | KRSFIEDLLFNKV protein subsequence is seen as a potential Achilles' heel because it is exposed or potentially exposable, being required for proteolytic activation cleavage, and is also a well conserved feature on the virus. This motif seems a likely primary target for synthetic vaccines and a basis for drug discovery. |
| *Limitations* | One must be aware of coincidental matches that are not truly significant unless one can see that the proteins being compared are essentially of the same function or family, with the order of similar sections preserved, and that the correspondences make sense. This was an in silico study; the proposed sequence must still be followed by in vitro and in vivo studies before proceeding. |

# *Insights into Cross-species Evolution of Novel Human Coronavirus 2019-nCoV and Defining Immune Determinants for Vaccine Development*

**Arunachalam Ramaiah, et al.**

*bioRxiv preprint*
*February 04, 2020*
*DOI: https://doi.org/10.1101/2020.01.29.925867*

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| *Purpose* | To analyze the genomic evolution of 2019 novel coronavirus (2019-nCov) and identify potential high binding affinity (HBA) CD4 T-cell epitopes (TCEs) for subunit vaccine development. |
| *Study design* | Basic Science Investigational Study |
| *Level of evidence* | N/A |
| *Methods* | Genome sequences of 2019-nCoV (n=48) were obtained on January 29th, 2020 from GSAID and GenBank, along with genomic sequences for SARS-CoV, SARS-like-CoV, and MERS-CoV strains (n=8,2,10, respectively). One alphacoronavirus sequence was used as an outgroup control. To identify potential target peptides for vaccine design, TCEs were predicted using structural protein sequences of highly conserved and representative 2019-nCoV strain Wuhan-Hu-1 (MN908947.3).. |
| *Findings* | Phylogenic analysis showed 2019-nCoV to be genetically and evolutionary related to bat CoVs. A large clade was formed by these viruses with both 2019-nCoV and bat-CoV virus clusters sharing a common ancestor (92% bootstrap support). Additionally, there was a 96% sequence similarity between the 2019-nCoV Wuhan-Hu-1 and bat/Yunnan/RaTG13/2013 strains. 2019-nCoV and bat/Yunnan/RaTG13/2013 sequences differed in the structural proteins spike (S) and membrane (M), but envelope (E) and nucleocapsid (N) were highly conserved. The binding affinity for all possible 15-mer peptides from the 2019-nCoV structural proteins against the predominant HLA-DR alleles in the ethnic populations of China, Thailand, Japan, and Asia-Pacific Region were assessed. There were eight common epitopes recognized by all HLA-DR alleles across the ethnic populations distributed among S, E, and M proteins (n=2, 3,3, respectively). |
| *Clinical Implications* | **This study suggests the current 2019-nCoV likely evolved from bat CoVs through a series of recombinant events that enabled it to adapt to humans.** Additionally, 8 epitopes recognized by HLA alleles common to different ethnic populations were identified; creating a subunit vaccine containing these eight epitopes may induce effective antiviral T-cell and antibody responses in different ethnic populations. |
| *Limitations* | This study only identified high-binding affinity TCEs against HLA-DR alleles predominant in Asia and Asia Pacific Region. As the 2019-nCoV is now classified as a pandemic and has spread to various countries globally, this decision may limit the generality of the predicted epitopes. Additionally, further in vitro and in vivo studies are needed to validate the predicted epitopes and whether they can produce a robust immune response. Lastly, this study has not been peer-reviewed. |

# *Preliminary Identification of Potential Vaccine Targets for COVID-19 Coronavirus (SARS-CoV-2) Based on SARS-CoV Immunological Studies*

**Syed Faraz Ahmed et al.**

*Viruses*
*March 2020*
*DOI: https://doi.org/10.3390/v12030254*

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| *Purpose* | To identify identical epitopes between SARS-CoV-2, SARS-CoV (responsible for the 2003 endemic), and MERS-CoV (responsible for the 2012 outbreaks) to find potential targets for an effective vaccine. |
| *Study design* | Laboratory Study |
| *Level of evidence* | N/A |
| *Methods* | The investigators obtained reference protein sequences for SARS-CoV-2, SARS-CoV, and MERS-CoV, along with SARS-CoV B- and T-cell epitopes. They estimated a population coverage for the T cell epitopes to represent the population likely to elicit an immune response for at least 1 T-cell epitope. Lastly, the investigators constructed a phylogenetic tree of the structural protein of SARS-CoV, MERS-CoV, and SARS-CoV-2, as well as the Zaria Bat coronavirus strain. |
| *Findings* | **The M (membrane), N (nucleocapsid), and E (envelope) proteins of SARS-CoV and SARS-CoV-2 have over 90% genetic similarity while the S (spike) protein has 76% similarity. The similarity between SARS-CoV-2 and MERS-CoV is substantially lower.** From previous studies, S and N proteins are known to induce immune responses. 27/115 T-cell epitopes are identical between SARS-CoV and SARS-CoV-2 (all in N or S proteins). MHC binding assays suggested 5 distinct MHC alleles for 19 of these epitopes. The population coverage for these epitopes is 59.76% globally and 32.36% in the Chinese population. To identify potential T cell targets that would cover a larger percentage of the population, additional T cell epitopes were considered that have not yet been experimentally tested for SARS-CoV. Of these, 229 epitope sequences had an identical match in SARS-CoV-2 with MHC allele information available and 102 of these were S or N proteins. Population coverage estimates for these sequences showed 96.29% with 20 distinct MHC alleles. 49 B-cell epitopes from SARS-CoV had an identical match in SARSCoV-2 (45 from N or S protein). |
| *Clinical Implications* | The study demonstrates similarities and differences between the novel coronavirus of 2020 and past coronavirus outbreaks. The study also determines important structural aspects of the SARS-CoV-2 epitope that may be used to develop an immune response. We may be able to extrapolate the data from previous immune responses to try to find ways to create a positive immune response against SARS-CoV-2. |
| *Limitations* | Despite the similarities between SARS-CoV and SARS-CoV-2, there is still significant genetic variation between the two and it is not obvious that immune responses will be elicited against both viruses. Additionally, as the virus continues to evolve, it is expected that more mutations will be observed, and as long as they occur outside of the epitope regions identified, they may not affect this analysis. Further T and B cell assays are important to identify the potential of the epitopes to induce a positive immune response against SARS-CoV-2. |

# *Strategies for vaccine design for corona virus using Immunoinformatics techniques*

**Anamika Basu et al.**

*bioRxiv preprint*
*March 2, 2020*
*DOI: https://doi.org/10.1101/2020.02.27.967422*

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| *Purpose* | To evaluate potential B cell and T cell epitopes present in non-structural protein 4 of beta coronavirus as a strategy for vaccine design against coronavirus. |
| *Study design* | Genome sequencing and analysis |
| *Level of evidence* | N/A |
| *Methods* | Based on the non-structural protein NS4 in Beta coronavirus HKU24 obtained from the InterPro database (accession number A0A0A7UXD8), potential B and T cell epitopes were predicted using various methods, such as the Kalaskar and Tongaonkar antigenicity scale, Stabilized matrix method, and a consensus approach which combines NN-align, SMM-align, and combinatorial library methods. Then, population coverage was assessed, and molecular docking studies were performed for identified T cell epitopes. |
| *Findings* | -**The peptide sequence IRNTTNPSAR and PTDTYTSVYLGKFRG were considered as the most potential B cell and T cell epitopes respectively. These epitopes may be considered as potential peptides for a peptide-based vaccine for coronavirus.**<br>-The predicted T cell epitopes PTDTYTSVY and PTDTYTSVYLGKFRG perfectly fitted into the epitope binding grooves of alpha helix of MHC I molecule and MHC II molecule. The epitope PTDTYTSVY was present in 58.87% of the Chinese population and 50.16% of the world population. |
| *Clinical Implications* | This study recommends potential B-cell and T-cell epitopes to use in a peptide-based vaccine for coronavirus. |
| *Limitations* | The study was limited in that this study requires in vitro and in vivo trials to determine effectiveness of these vaccine peptides. In addition, this study is a preliminary report that has not been peer-reviewed. |

# *Epitope-based peptide vaccine design and target site characterization against novel coronavirus disease caused by SARS-CoV-2*

**Lin Li et al.**

*bioRxiv preprint*
*February 27, 2020*
*DOI: https://doi.org/10.1101/2020.02.25.965434*

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| *Purpose* | To identify B- and T-cell epitopes for surface glycoprotein (S) of SARS-CoV-2 as possible targets for vaccine development by using immunoinformatics approach. |
| *Study design* | De novo bioinformatics analysis |
| *Level of evidence* | N/A |
| *Methods* | The SARS-CoV-2 protein sequence and all 3D structures were found in the National Center for Biotechnology Information (NCBI) database and Protein Data Bank (PDB). Several programs were used to analyze the protein chemical and physical properties (e.g., half-life, molecular weight, etc.), including Protparam, TMHMM v2.0, DIANNA v1.1. B-cell epitopes, and the MHC-I and MHC-II binding T-cell epitopes, were predicted and identified using the Immune-Epitope-Database and Analysis-Resource (IEDB), BcePred, and VaxiJen v2.0. There was a focus on antigenicity, exposed surface, flexibility, hydrophilicity, polarity, and turns. Protein allergenicity, toxicity, and enzyme digestion was evaluated using Allergen FP 1.0, ToxinPred, and a protein digest server. Protein-epitope interactions were evaluated using PepSite. Global conservation of the S protein structure utilized the NGDC database's 138 SARS-CoV-2 virus strains from 38 worldwide locations. |
| *Findings* | - After evaluation, **four B-cell epitopes are predicted to be non-allergenic and non-toxic, and identified as potential targets for vaccine research**. None of them can be digested by multiple enzymes.<br>- **Two MHC-I and nine MHC-II binding T-cell epitopes are predicted to have high antigenicity and to interact with various HLA alleles.**<br>- All identified epitopes were found in all the global SARS-CoV-2 samples. None of the identified epitopes are susceptible to digestion by multiple enzymes, which suggests that these epitopes would be stable. |
| *Clinical Implications* | **This study provides a basis for the development of peptide-based vaccines against the current SARS-CoV-2 pandemic**. A vaccine would increase prognosis, lower infection rate, and subsequently lower strain on healthcare systems and workers globally. |
| *Limitations* | The study was limited to computational analysis and a de novo analysis; the epitopes identified require further in vitro and in vivo studies to demonstrate efficacy. SARS-CoV-2 seems to have a high potential for mutation so information gathered here might be obsolete within the next year. This study has not been peer-reviewed. |

# *Vaccines for SARS-CoV-2: Lessons from other Coronavirus Strains*

**Eriko Padron-Regalado**

*Infectious Diseases and Therapy*
*April 23, 2020*
*DOI: https://doi.org/10.1007/s40121-020-00300-x*

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| *Purpose* | To review the pertinent information about COVID-19 to help create a vaccine |
| *Study design* | Review |
| *Level of evidence* | Level 5 |
| *Methods* | Review the past and ongoing vaccine development efforts for clinically relevant coronavirus strains in order to help develop safe and effective vaccines for COVID-19. |
| *Findings* | - No vaccine is currently available for SARS-CoV-2.<br>- While we want to develop safe and efficient vaccines, we should worry about adverse drug events as animal models and vaccination regimens have demonstrated the possibility of this occurring.<br>- We need to address the possibility of short-term immunogenicity, which would happen if the virus induces production of neutralizing antibodies.<br>- Exploiting T cell responses for coronavirus vaccination should also be considered (along with B cell responses) as they are persistent and protective in animal models.<br>- Employing the N protein of coronavirus for vaccination has the potential of providing long-term cross-protection. |
| *Clinical Implications* | **As of April 2020, no vaccine is commercially available for coronavirus.** Moving forward, we can study the MERS and SARS vaccine development processes to learn more about SARS-CoV-2. While creating a vaccine is of utmost importance, we must also realize the potential side effects of vaccines and should not be oblivious to this. **The N protein of coronavirus has the potential for providing long term cross-protection.** |
| *Limitations* | Coronavirus is highly infectious, which limits the progress of creating a vaccine. Furthermore, it is difficult to find adequate animals or individuals to start vaccine trials. |

# *Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody*

**Xiaolong Tian et al.**

*Emerging Microbes & Infections*
*February 17, 2020*
*DOI: https://doi.org/10.1080/22221751.2020.1729069*

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| *Purpose* | To experimentally determine the cross-reactivity of several anti SARS-CoV antibodies with 2019-nCoV spike protein. |
| *Study design* | Basic Science Investigational Research |
| *Level of evidence* | N/A |
| *Methods* | 2019-nCoV receptor binding domain (RBD) protein was expressed and purified. Its conformation with its human receptor, angiotensin converting enzyme 2 (ACE2), was predicted. Biolayer interferometry binding (BLI) assay was utilized to determine the binding affinity of SARS-CoV spike protein and 2019-nCoV RBD to human ACE2. Lastly, ELISA (utilizing high binding assay plates coated with purified 2019-nCoV RBD) and BLI (utilizing streptavidin-coated biosensors) assays were employed to measure the binding affinities of a series of representative SARS-CoV-specific antibodies reported to target RBD and possess neutralizing activity: m396, CR3014, CR3022, and MERS-CoV-specific human monoclonal antibody m366. Anti-CD40 antibody was used as a negative control. |
| *Findings* | **2019-nCoV RBD bound potently to human ACE2 as determined by BLI, with an affinity comparable to that of SARS-CoV spike protein with human ACE2** (15.2 and 15.0 nM, respectively). Of the antibodies tested, only SARS-CoV specific antibody CR3022 was found to bind potently with 2019-nCoV RBD. No competition in binding for 2019-nCoV RBD was found between CR3022 and ACE2 as determined by BLI. This suggests CR3022 recognizes an epitope that does not overlap with the ACE2 binding site of 2019-nCoV. Protein sequence alignment of 2019-nCoV and SARS-CoV RBD demonstrates they differ at the C-terminus residues. |
| *Clinical Implications* | This study points to CR3022 as a potential therapeutic for the treatment and prevention of 2019-nCoV. The lack of cross-reactivity from the other RBD targeting SARS-CoV-specific antibodies may have resulted as a consequence of the structural differences between 2019-nCoV and SARS-CoV RBD. This study raises the possibility that a vaccine developed from epitopes outside the ACE2 binding site may be a more promising in inducing cross-reactive neutralizing antibodies. |
| *Limitations* | The study was limited by the small number of antibodies utilized and none of the tested antibodies showed cross-reactivity with the ACE2 binding site of 2019-nCoV, which is essential for the virus replication. Also, virus neutralization tests were not performed. More work will be needed for the development of novel monoclonal antibodies, which specifically binds to 2019-nCoV spike protein. |

# *DNA vaccine protection against SARS-CoV-2 in rhesus macaques*

**Jingyou Yu et al.**

*Science*
*May 20, 2020*
*DOI: 10.1126/science.abc6284*

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| *Purpose* | To evaluate pre-clinical DNA vaccine candidates for the prevention of COVID-19 using a rhesus macaque model of SARS-CoV-2 infection. |
| *Study design* | Animal Trial |
| *Level of evidence* | Level 3 |
| *Methods* | Twenty-five adult rhesus macaques received one of six prototype DNA vaccines expressing variants of the SARS-CoV-2 S protein, and 10 macaques received a sham control. The animals each received two doses, one at week 0 and one at week 3. At week 5, S-specific binding antibodies and neutralizing antibodies (NAbs) were measured. At week 6, all animals were challenged with SARS-CoV-2. The 6 vaccine variants were (1) full-length spike protein (S), (2) deletion of the cytoplasmic tail (S.dCT), (3) deletion of the transmembrane domain and cytoplasmic tail reflecting the soluble ectodomain (S.dTM), (4) S1 domain with a foldon trimerization tag (S1), (5) receptor-binding domain with a foldon trimerization tag (RBD), and (6) a prefusion stabilized ectodomain with deletion of the furin cleavage site, two proline mutations, and a foldon trimerization tag (S.dTM. PP). |
| *Findings* | Before challenge with SARS-CoV-2, vaccinated macaques exhibited NAb levels comparable to those of humans and macaques who had recovered from SARS-CoV-2 infection. S-specific and RBD-specific antibodies in vaccinated macaques functioned in neutrophil phagocytosis, complement deposition, monocyte cellular phagocytosis, and NK cell activation. **Vaccinated animals had markedly lower levels of subgenomic mRNA (sgmRNA) as compared to sham controls in all groups except for S.dTM.** Less immunogenic vaccines, such as S.dTM, showed partial protection in the lower respiratory tract but no protection in the upper respiratory tract, suggesting that it may be easier to protect against lower respiratory tract disease compared with upper respiratory tract disease. |
| *Clinical Implications* | NAb, S-specific and RBD-specific titers at week 5 inversely correlated with peak sgmRNA levels, suggesting that high levels of all three antibodies are protective against SARS-CoV-2 infection. NAb titers correlated with all antibody effector functions except for antibody-mediated NK cell activation, suggesting a primary role of NAbs in protecting against SARS-CoV2 infection.The S vaccine was found to be the most effective in both the upper and lower respiratory tracts, and protection in both anatomic compartments is likely necessary for pandemic control. |
| *Limitations* | This study does not address the expected length of protection from any of the six vaccines. It also does not address the issue of antibody-dependent enhancement of respiratory disease, which could be a significant safety concern. As an animal study, the results may not be generalizable to humans. |

# *ChAdOxl nCoV-19 vaccination prevents SARS-CoV-2 pneumonia in rhesus macaques*

**Neeltje Van Doremalen et al.**

*bioRxiv*

*May 13, 2020*

*DOI: https://doi.org/10.1101/2020.05.13.093195*

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| *Purpose* | To determine the immunogenicity of an adenovirus-vectored vaccine against the spike protein of SARS-CoV-2 in mice and rhesus macaques. |
| *Study design* | Animal Trial |
| *Level of evidence* | Level 3 |
| *Methods* | Thirteen mice were vaccinated with either an experimental adenovirus-vectored vaccine against the spike protein of SARS-CoV-2 (ChAdOx1 nCoV-19) or an adenovirus-vectored control expressing green fluorescent protein (ChAdOx1 GFP). The following markers of humoral and cellular immunity were measured 9-14 days later: IgG titers against spike protein subunits S1 and S2, virus-specific neutralizing antibodies, IFN-γ ELISpot responses in splenocytes toward peptides spanning the spike protein, and spike-specific CD4+ or CD8+ T cells. The ChAdOx1 nCoV-19 vaccine was then injected into 6 rhesus macaques, while the ChAdOx1 GFP control was injected into 3. The same immune markers measured in the mice were measured in the macaques. In addition, the macaques were challenged with the SARS-CoV-2 virus 28 days post vaccination. After challenge, clinical symptoms and respiratory signs were monitored, and bronchoalveolar lavage (BAL) fluid and lung tissue samples were measured for viral genomic RNA (gRNA) and viral subgenomic RNA (sgRNA). |
| *Findings* | **A single ChAdOx1 nCoV-19 vaccination in mice and rhesus macaques produced robust humoral and cell-mediated immune responses.** Prior to challenge with SARS-CoV-2, vaccinated animals had significantly higher levels of all measured immune markers as compared to controls. The immune response was predominately Th1 dominated. **After challenge with SARS-CoV-2, vaccinated macaques had significantly reduced viral load in BAL fluid and respiratory tract tissue as compared to controls.** None of the vaccinated macaques developed pneumonia. |
| *Clinical Implications* | The significant immune responses measured in vaccinated animals, along with the markedly healthier clinical and histological presentation of vaccinated and challenged macaques suggest that the ChAdOx1 nCoV-19 vaccine is effective at inducing protection against SARS-CoV-2. Importantly, there was no evidence of immune-enhanced disease in vaccinated animals. Taken together, the findings suggest that an adenovirus-vectored vaccine against SARS-CoV-2 may be safe and effective in humans. |
| *Limitations* | Samples sizes were very small, with only 13 mice and 9 macaques included. All macaques were euthanized 7 days post-inoculation, so this study cannot provide insight into long-term side effects. As an animal study, the results may not be applicable to humans. |

# *An mRNA Vaccine against SARS-CoV-2 – Preliminary Report*

**L.A Jackson et. al**

*The New England Journal of Medicine*
*July 14, 2020*
*DOI: 10.1056/NEJMoa2022483*

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| *Purpose* | To determine the effectiveness of the candidate vaccine mRNA-1273 in generating an antibody response to SARS-CoV-2. |
| *Study design* | Open-Label Randomized Trial |
| *Level of evidence* | Level 2 |
| *Methods* | A phase 1, dose escalation open-label trail was conducted on 45 healthy adults ranging in age between 18-55 years. Participants were divided into three groups of 15 participants each and received doses of 25ug, 100ug or 250ug. Participants received two vaccines 28 days apart with mRNA-1273, which encodes the stabilized perfusion SARS-CoV-2 spike protein. Antibody response was measured after each subsequent dose as were systemic adverse events. |
| *Findings* | After receiving the first vaccination, antibody responses were found to be higher with a higher dose. Antibody titers were measured as geometric mean titer (GMT), and found to be 40,227 in the 25ug group, 109,209 in the 100ug group, and 213,526 in the 250ug group. **After the second round of vaccination, serum-neutralizing activity was detected in all three groups with values in the upper half of what was measured in SARS-CoV-2 infection.** Systemic adverse effects of the vaccine were found in over 50% of participants which included fatigue, chills, headache, myalgia, and pain at the injection site. Adverse effects were more common after the second dose of the vaccination, and were higher in the 250ug dose group. 21% of the 250ug dose group reported one or more severe adverse effects (ex: urticaria in bilateral legs). **Of the three doses, the 100ug dose elicited a high neutralizing reposes coupled with a reactogenicity profile that is more favorable than that of the 250ug dose.** |
| *Clinical Implications* | The mRNA-1273 vaccine against the SARS-CoV-2 spike protein did induce an anti-SARS-CoV2 immune response in all participants. Only mild-moderate systemic adverse effects were reported and no trial-ending adverse events were identified. Thus, continuation with a phase 2 trail of mRNA-1273 in 600 healthy adults should be encouraged. |
| *Limitations* | As with all phase 1 trails, this vaccine was only studied in the context of healthy patients, thus limiting the generalizability of the study to the broader population which includes patients impacted by comorbidities. Additionally, this study did not examine the effect of vaccination of pregnant patients or children, limiting the ability to determine the safety profile and effectiveness in these subgroups. |

# *Speed, Evidence, and Safety Characteristics of Vaccine Approvals by the US Food and Drug Administration*

**Jeremy Pthumana et al.**

*JAMA Internal Medicine*
*November 10, 2020*
*DOI: 10.1001/jamainternmed.2020.7472*

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| *Purpose* | To review the typical FDA approval process for vaccines developed over the last decade. |
| *Study design* | Literature Review |
| *Level of evidence* | Level 2 |
| *Methods* | All original biologics licensing applications (BLAs) for new to market vaccines approved by the FDA between January 2010 and June 2020 were identified and reviewed using publicly available regulatory documents. Three key regulatory dates for each vaccine were used, including: investigational new drug submission (beginning of human testing), BLA submission, and FDA approval. Vaccine trials were reviewed for safety and efficacy evidence for approval. |
| *Findings* | Over the last decade, the FDA has approved 21 new vaccines, 4 of which received accelerated approval. The median clinical development period (i.e., from investigational new drug submission to FDA approval) was 8.1 years. Each vaccine approval was supported by evidence from a median of 7 clinical trials, with a median of 4961 patients enrolled in efficacy trials and 6710 patients included in the prelicensure safety data, where participants received follow up for serious adverse events for at least 6 months. The median vaccine efficacy among all approved vaccines over the last decade was 91.9%. |
| *Clinical Implications* | There is an ever-increasing need to develop a safe and effective COVID-19 vaccine. Yet, according to recent national surveys, over 50% of Americans are hesitant to receive a COVID-19 vaccine due to concerns of adverse side effects and lack of effectiveness. Given the urgency of not only developing a vaccine, but having a receptive public willing to accept it, COVID-19 vaccine clinical trials will need be significantly larger and include adequate follow up time for the emergence of adverse events. |
| *Limitations* | Specific data on the 4 vaccines that received accelerated approval was not elaborated on, despite the fact that this might be relevant to the current public health, economic, and social environment. |

# *Ad26 vaccine protects against SARS-CoV-2 severe clinical disease in hamsters*

**Lisa H. Tostanoski et al.**

*Nature*
*September 3, 2020*
*DOI: https://doi.org/10.1038/s41591-020-1070-6*

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| *Purpose* | To demonstrate the efficacy of an adenovirus vector-based vaccine in eliciting a neutralizing antibody response against SARS-CoV-2 and protection against adverse symptoms such as weight loss, pneumonia and decreasing mortality. |
| *Study design* | Experimental Research |
| *Level of evidence* | Level 1 |
| *Methods* | Twenty Syrian golden hamsters were challenged with 5 x 104 50% tissue culture infective dose of SARS-CoV-2 (TCID50; low dose = 6 x 107 viral particles; n=4) or 5 x 105 TCID50 (high dose = 6 x 108 viral particles; n =16). Of the high dose group, four animals were necropsied for tissue viral loads and histopathology and the other 8 hamsters were followed longitudinally and necropsied after morbidity. To test the efficacy of vaccination 50 male and female hamsters were randomly separated, and inoculated with 1010 or 109 viral particles of Ad26 vector with SARS-CoV-2 S soluble ecodomain (S.dTM.PP), full-length S (S.PP) with mutation of furin cleavage sites, and sham control (n = 10 per group). At 4 weeks, all animals were challenged with low and high doses of SARS-CoV-2 and necrorpsied on day 4 (n=3) for viral loads and histopathology and the remaining animals were followed through day 14 before necropsied and analysis. |
| *Findings* | In animals challenged with SARS-CoV-2, viral loads of SARS-CoV-2 (vRNA) and SARS-CoV-2-N protein (SARS-CoV-2-N) were highest at day 2, and declined to minimal levels by day 7. Inflammatory infiltrate was observed at day 2 with markers of inflammation peaking at day 7 coinciding with pneumonia, maximal weight loss, and mortality. In vaccination groups, S.dTM.PP elicited a 4.0-4.7-fold increase in median NAb titers while S.PP elicited 1.8-2.6-fold increases in median NAb titer versus control. Following SARS-CoV-2 challenge, control mice demonstrated 19.6% reduction in body weight, with 43% (3/7) of animals meeting euthanasia criteria by day 7 compared to an 8.7% and 4.0% reduction in body weight in S.dTM.PP and S.PP vaccinated mice, respectively. Additionally, vaccination protected against mortality. |
| *Clinical Implications* | **COVID-19 vaccine candidate showed robust protection against high-dose SARS-CoV-2 infection in hamsters. SARS-CoV-2 viral load in the lungs decreased from day 2 to day 7 and this is the first report published at this stage of the disease.** Generation of a neutralizing antibody response also protected hamsters against massive inflammatory activation and accumulation of lymphatic cells in infected tissues. Ultimately, single inoculation of SARS-CoV-2 S protects hamsters against severe clinical disease, such as pneumonia and mortality. |
| *Limitations* | Hamsters were removed from the study according to humane euthanization criteria and may not reflect the true mortality rate of control hamsters. In addition, although hamsters provide a useful disease model, understanding the efficacy of mechanisms of SARS-CoV-2 vaccination in humans must be evaluated. |

# *Reports of anaphylaxis after receipt of mRNA COVID-19 vaccines in the US – December 14, 2020 – January 18, 2021*

**Tom T. Shimabukuro et al.**

*JAMA*

*February 12, 2021*

*DOI: https://www.doi.org/10.1001/jama.2021.1967*

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| *Purpose* | To update early estimates regarding the reported rates of anaphylaxis following administration of the Pfizer-BioNTech or Moderna vaccines. |
| *Study design* | Chart Review |
| *Level of evidence* | Level 5 |
| *Methods* | Data from the Vaccine Adverse Event Reporting System (VAERS), which documents reports of suspected anaphylaxis, were reviewed by phsyicians at the CDC. Physicians applied the Brighton Collaboration case definition for anaphylaxis to classify the 66 case reports of anaphylaxis in the VAERS of nearly 10 million doses of vaccine administered to Americans between December 14, 2020-January 18, 2021. |
| *Findings* | Of individuals who received the Pfizer-BioNTech vaccine, 47 reports were identified in VAERS, whearase 19 reports were identified in VAERS for the Moderna vaccine amounting to 4.7 administered and 2.5 cases/million doses administered, respectively. Clinical characteristics of anaphylaxis were determined to be similar between both vaccines with symptom onset within 30 minutes of administration with generalized urticaria, diffuse erythematous rash, angioedema, respiratory and airway obstruction symptoms, and nausea. Of the 66 patients who were reported to experience anaphylaxis, 21 individuals (32%) had previous episodes of anaphylaxis from other exposures, including other vaaccinations. In response to anaphylaxis, 61 individuals (92%) received epinephrine in either the emergency department or were hospitalized. Another interesting finding was that the vast majority of cases of anaphylaxis occurred in women; however, it is still unclear exactly why side effects could be different between sexes. |
| *Clinical Implications* | **As new vaccines are introduced to market it is important to understand adverse effects of these vaccines. One concern after COVID-19 vaccination is the potential allergic reactions, including anaphylaxis. Anaphylaxis with eitherr Pfizer-BioNTech or Moderna vaccines is a rare occurrence with the benefits of vaccination greatly outweighing the risk of morbidity and mortality from SARS-CoV-2 infection**. Immediate epinephrine administration is recommended in all cases of anaphylaxis following COVID-19 vaccination and healthcare workers should be prepared to respond to an anaphylactic reaction. |
| *Limitations* | The dataset primarily captures individuals who require medical attention in a hospital setting and may underestimate the rate of anaphylaxis, as it does not account for mild reactions to the vaccine. It is important to identify what components of the vaccine are triggering anaphylaxis in order to formulate an even safer iteration of these vaccines. |

# *SARS-CoV-2 Antibody Response to 2 or 3 Doses of the BNT162b2 Vaccine in Patients Treated With Anticancer Agents*

**Charlotte Fenioux, MD et al.**

*JAMA Oncology*
*January 7, 2022*
*DOI: https://doi.org/10.1001/jamaoncol.2021.7777*

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| *Purpose* | To assess the humoral response to 2 or 3 doses of the BNT162b2 (BioNTech; Pfizer) vaccine in patients treated with anticancer agents. |
| *Study design* | Prospective observational cohort study (n= 163) |
| *Level of evidence* | 3 |
| *Methods* | 163 patients (median age, 66 [27-89] years; 53% men; 47% women) with solid tumors (digestive, urologic, breast, and other) receiving oncologic treatment and who had no history of COVID-19 were enrolled. 122 received chemotherapy (75%), 26 received targeted oral therapy (16%), and 15 received immunotherapy (9%). The humoral response to the BNT162b2 vaccine was evaluated with quantitative serologic testing for the anti–SARS-CoV-2 spike protein antibody. The primary end point of the study was sufficient humoral response which was set at a threshold of 1000 arbitrary units (AU)/mL. |
| *Findings* | Anti-S immunoglobulin G titer greater than 1000 AU/mL was found in 22 of the 145 (15%) at the time of the second vaccine administration and 92 of 142 (65%) 28 days after the second vaccination. 36 patients received a third dose due to poor antibody response and 75% (27 of 36) had an anti-S titer greater than 1000 AU/mL after the third dose. Humoral response was decreased 3 months after the second dose with 27 of 64 (42%) having titers less than 1000 AU/mL. Age, sex, cancer type, cancer category (neoadjuvant, adjuvant,metastatic first, or >1 line), lymphopenia, and use of corticosteroids before the vaccine were not associated with degree of humoral response. Chemotherapy schedule and timing of vaccine administration were not associated with lower humoral response. Lower anti-S were seen in patients treated with chemotherapy or targeted therapy compared to immunotherapy (odds ratio, 5.4; 95% CI, 1.5-20.2; P=.02). |
| *Clinical Implications* | Sufficient antibody response after 2 or 3 vaccine doses is seen in patients receiving oncologic treatment for solid tumors. There is evidence to use a third vaccine dose one month after the second dose for adequate antibody response. There was no relationship with the timing of vaccine administration and chemotherapy cycle. |
| *Limitations* | The study is limited by a small sample size which prevented comparative analysis between solid tumor types after the third dose of the vaccine. |

# *Protection against Covid-19 by BNT162b2 Booster across Age Groups*

**Yinon M. Bar-On et al.**

*The New England Journal of Medicine*
*December 8th, 2021*
*DOI: 10.1056/NEJMoa2115926*

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| *Purpose* | To compare the rates of confirmed COVID-19, severe illness and death between individuals that received the COVID-19 booster and those that did not |
| *Study design* | Case Control Trial |
| *Level of evidence* | Level 3 |
| *Methods* | The Israel Ministry of Health database was queried on October 12, 2021 to include fully vaccinated individuals 16 and older at least 5 months prior to the study, have been fully vaccinated after January 16, 2021, and did not have a past positive PCR test for COVID-19. 4,696,865 individuals met the inclusion criteria. Primary analysis compared those that received the COVID-19 booster (at least 12 days earlier) versus those who did not, whereas secondary analysis compared the rates in the COVID-19 booster group versus those in the early booster group (patients that received the booster 3-7 days earlier). Confirmed infection, development of severe illness, and death were chosen for periods of 2, 7 and 35 days prior to the data query. |
| *Findings* | The rate of confirmed COVID-19 infection was lower in the booster group by 9-17.2 when compared to the non-boosted group, and 4.9-10.8 when compared to the early-boosted group across all age groups studied. **The rate of severe illness and COVID-19 associated death was also significantly lowered in the boosted group when compared to both the non-boosted group and early-boosted groups.** In all age groups, the rate of confirmed infection was lower in the early booster group than in the non booster group. |
| *Clinical Implications* | **The booster dose reduced the rate of confirmed COVID-19 infection and severe illness across each different age group studied.** Across all age groups, the booster is effective against the delta variant in at least the short term, offering protection for individuals against COVID-19. |
| *Limitations* | This study focused on a time period that did not include the Omicron COVID-19 variant, potentially limiting the current applicability to the current stage of the COVID-19 pandemic. |

# *Duration of Protection against Mild and Severe Disease by Covid-19 Vaccines*

**Nick Andrews et al.**

*New England Journal of Medicine*
*January 12, 2022*
*Doi: https://doi.org/10.1056/NEJMoa2115481*

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| *Purpose* | To determine the effectiveness of 2 doses of the ChAdOx1-S, BNT162b2, and mRNA-1273 vaccines against symptomatic COVID19 infection, hospitalization, and death. |
| *Study design* | Case Control |
| *Level of evidence* | Level 4 |
| *Methods* | Vaccination status was compared between adults with COVID symptoms and PCR confirmed infection, hospitalization within 14 days and death within 28 days of confirmed PCR testing. The control group was made up of adults with symptoms of COVID-19 but had a negative PCR test. Analysis was stratified to determine vaccine effectiveness against the alpha and delta variants. Analysis was adjusted for age, sex, socioeconomic status, race, care home residence status, geographic region, healthcare worker status , and status of being in a high risk group or a clinically vulnerable group. |
| *Findings* | Vaccine effectiveness against the delta variant decreased to 44.3% by 20 weeks with the ChAdOx1-S and to 66.3% with the BNT162b2 vaccine. Vaccine effectiveness decreased more significantly in those greater than 65 years old compared to 40-64. After 20 weeks, effectiveness against hospitalization decreased to 80% and 91.7% and effectiveness against death was decreased to 84.8% and 91.9% with the ChAdOx1-S and BNT162b2 vaccines. Vaccine effectiveness at prevention of hospitalization decreased more significantly in those greater than 65 years old and those 40-64 with underlying medical conditions compared to healthy adults. The mRNA vaccines were more effective than the ChAdOx1-S vaccine at preventing more severe outcomes, against the alpha variant, and among younger persons as compared with older persons. |
| *Clinical Implications* | **Vaccine effectiveness decreases after 20 weeks with the most significant decline those over the age of 65 years old or with underlying medical conditions.** |
| *Limitations* | They were only able to successfully match 85.2% of PCR tests to the vaccination database. Exclusion of those participants may have skewed the data. A higher proportion of non-White compared to White persons were not able to be matched to the vaccination database and exclusion of them may have led to results not representative of the population. Participants had to declare symptoms in order to obtain a test and some asymptomatic persons may have declared symptoms in order to access a test. |

# *BNT162b2 Vaccine Booster and Mortality Due to Covid-19*

**Ronen Arbel et al.**

*The New England Journal of Medicine*
*December 23rd, 2021*
*DOI: 10.1056/NEJMoa2115624*

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| *Purpose* | To assess the decrease in mortality rate associated with the BNT162b2 booster vs individuals who did not receive the booster |
| *Study design* | Case Control Trial |
| *Level of evidence* | Level 3 |
| *Methods* | The Clalit Health Service (CHS) electronic medical records was queried on October 3, 2021 for members > 50 years of age that had received two doses of BNT162b2 booster > 5 months between the date of August, 6th, 2021 to September 29th, 2021. Participants were excluded if they received the booster before the start date and if they were infected with COVID-19 within 3 days before the effective booster date. 843,208 participants met the inclusion criteria. 758,118 participants (90%) received the booster within the study period. Primary analysis compared mortality rates of those who received the booster (at least 7 days earlier) versus those who did not. Secondary analysis compared COVID-19 infection rates of those in the booster group versus the non-booster group. |
| *Findings* | Mortality due to COVID-19 was much lower in the booster group (n= 65; 0.16 per 100,000 persons per day) compared to the non-booster group (n= 137; 2.97 per 100,000 persons per day). COVID-19 infection was lower in the booster group (n= 2888) compared to the non-booster group (n= 11,108). **Mortality and infection rates associated with COVID-19 were significantly lower in the boosted group when compared to non-boosted groups.** |
| *Clinical Implications* | The booster drastically reduces the mortality and infection rates of COVID-19 in the patients >50 who were fully vaccinated >5 months earlier. **The boosted group had a 90% lower mortality rate compared to those who did not receive it.** |
| *Limitations* | A longer study period is necessary to determine the long-term efficacy and safety profile of the vaccine. |

# *Antibody Titers Before and After a Third Dose of the SARS-CoV-2 BNT 162b2 Vaccine in Adults ≥ 60 Years*

**Noa Eliakim-Raz, et al.**

*Journal of the American Medical Association*
*November 5, 2021*
*DOI: https://doi.org/10.1001/jama.2021.19885*

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| *Purpose* | To compare antibody titers before and after receiving a third dose of the SARS-CoV-2 BNT162b2 vaccine in adults who are at least 60 years of age. |
| *Study design* | Case series (n = 97) |
| *Level of evidence* | Level IV |
| *Methods* | Researchers utilized data from healthcare workers and their family members who were at least 60 years of age and were going to receive a third dose of the SARS-CoV-2 BNT162b2 vaccine. There were a total of 97 participants. It's been demonstrated that healthcare workers had waning immunity after 6 months from the 2nd vaccine administration, so they sought to compare titers before and after a third vaccination in this specific age population of healthcare workers. The exclusion criteria included prior known SARS-CoV-2 infection and malignancy. Anti-S IgG titers were determined between August 4-12 2021 and were reassessed 10-19 after receiving the third vaccination. A Quant assay was used to measure titers; they defined seropositivity as at least 50 arbitrary units (Au)/mL. The difference in titers before and after the third vaccine administration was evaluated utilizing the Wilcoxon signed rank test. A Spearman correlation was then used to assess the correlation between titer values and age. A multivariable analysis on a linear model of log IgG value was used with age, days from first vaccination, and other demographic/comorbidity data. |
| *Findings* | Median age of all participants was 70 years. 94/97 participants (97%) were seropositive prior to receiving the third vaccination. After receiving the third dose, and at 10-19 days after receiving it, all participants were seropositive with a median titer increase of 440 AU/mL ( $P < 0.001$). No correlation between ages were found ( $R = - 0.075$ ; $P < 0.47$). None of the other variables played a role in titer levels. |
| *Clinical Implications* | Given the waning immunity with the SARS-CoV-2 BNT162b2 vaccine, especially after 6 months from the 2nd dose, it was sought to see how titer levels would change. **The evidence suggests that receiving a third dose significantly increases titers**. This is extremely important to healthcare workers on the frontlines. |
| *Limitations* | The sample size was relatively small ( < 100) and there was a lack of testing cellular immunity and neutralizing antibodies. Additionally, the follow-up time was short. |

# *Vaccine effectiveness against SARS-CoV-2 Infection with the Omicron or Delta variants following a two-dose or booster BNT162b2 or*

**Christian Holm Hansen et**

*medRxiv*
*December 20, 2021*
*DOI: https://doi.org/10.1101/2021.12.20.21267966*

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| *Purpose* | To estimate vaccine effectiveness (VE) against the novel SARS-COV-2 Omicron variant up to five months after a primary vaccination series with BNT162b2 or mRNA-1273 vaccines. |
| *Study design* | Cohort Study |
| *Level of evidence* | Level 3 |
| *Methods* | Data consisting of "complete residency", COVID-19 PCR test and vaccination data were studied. Whole genome sequencing or a novel variant specific PCR test were utilized to test for Omicron in all positive PCR cases. Results that were negative for Omicron were assumed to be Delta. The Vaccine Effectiveness (VE) was determined by comparing the rate of infection in unvaccinated to vaccinated individuals with two-does of BNT162b2 or mRNA-127s vaccine series. Previously SARS-Cov-2-PCR-positive individuals were excluded. Participants were studied at intervals of 30 days after full protection, 31-60 days, 61-90 days, and 91-150 days. VE was calculated as 1-Hazard Ratio (HR) using a Cox regression model adjusted for age, sex, geographical region and calendar time. |
| *Findings* | 5,767 omicron cases were identified by December 12, 2021. VE against Omicron was 55.2% and 36.7% for the BNT162b2 and mRNA-1273 vaccines respectively for participants who completed primary vaccination. Participants 60 years and older and who received a booster dose 14 to 44 days earlier had a VE of 54.6% when compared to those with only a primary vaccination. After 3-5 months, VE against Omicron was shown to be -76.5% and -39.3% for BNT162b2 and mRNA-1273 respectively. VE against Delta remained positive after 3-5 months for both vaccines. |
| *Clinical Implications* | **Providers should be offering boosters only during seasonal peaks due to a limited window of VE against Omicron with the current BNT162b2 and mRNA-1273 vaccines to ensure maximal protection for their patients**. The medical community should be wary that the current vaccines may not provide adequate protection to emerging strains of SARS-Cov-2. |
| *Limitations* | This study is a preprint and has not undergone the peer-review process, limiting its ability to be used to guide clinical practice. Additionally, the study was performed in Denmark so findings may not be generalizable to other areas of the world. Furthermore, the study does not look at hospitalization and death statistics and does not measure behaviors amongst the groups studied. |