

The Weekly Covid-19 Literature Round-Up

Edition 7: April 29, 2020

Collated by Emory ID (Adult and Pediatric) and Medical Microbiology Fellows

“Never doubt that a small group of thoughtful, committed citizens can change the world. Indeed, it’s the only thing that ever has.” -Margaret Mead

“By hook or by crook this peril too shall be something that we remember.” -Homer, *The Odyssey*

“We must accept finite disappointment, but never lose infinite hope.” -MLK, Jr.

Epidemiology

Brought to you by: Aaron Kofman, MD

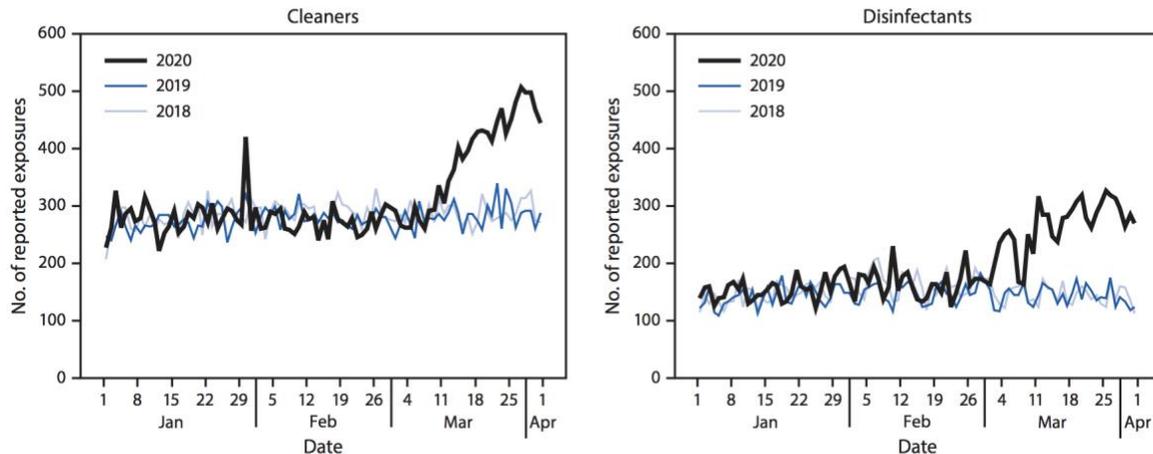
Arons, Melissa M. et al. “Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility.” *New England Journal of Medicine* (April 24, 2020): <https://doi.org/10.1056/NEJMoa2008457>.

- **Relevance:** Presymptomatic and asymptomatic transmission have been increasingly well-described features of SARS-CoV-2 epidemiology.
- **Findings:** Residents in two skilled nursing facilities in King County, WA were enrolled in two serial point-prevalence
 - Surveys conducted 1 week apart.
 - At time point 1, 27/48 (56%) of residents participating in the surveys that tested positive were asymptomatic, of whom 24 subsequently developed symptoms (would therefore be “presymptomatic”)
 - Presymptomatic individuals had a median rRT-PCR Ct value of 23.1 (at time of presymptomatic-ness), with viable virus recovered from 17/24 individuals
 - Of note, 26 symptomatic staff members who continued to work tested positive (19% of total)
- **What this study adds:** Transmission of SARS-CoV-2 is extremely efficient within nursing facilities, with presymptomatic spread accounting for a large portion of cases and likely contributing to transmission. Low Ct values at time of presymptomatic-ness and viable virus recovery from a majority of these patients adds further evidence to the picture.
- **Limitations/Conclusions:** The relative degree of transmission from facility residents (presymptomatic, asymptomatic or symptomatic) as compared to staff is difficult to know from this study. With 19% of study workers symptomatic and testing positive for SARS-CoV-2, this may have played a substantial role in transmission as well, and there are likely additional presymptomatic cases among this group that could also account for transmission. Regardless, the study adds important characterization to the extreme vulnerability of nursing facility residents to COVID-19.

Cleaning and Disinfectant Chemical Exposures and Temporal Associations with COVID-19 – National Poison Data System, United States, January 1, 2020 – March 31, 2020. Chang et al, *MMWR Morb Mortal Wkly Rep* 2020;69:477-481. [http://dx.doi.org/10.15585/mmwr.mm6915e6external icon](http://dx.doi.org/10.15585/mmwr.mm6915e6externalicon). Accessed April 27, 2020

- **Relevance:** The COVID-19 pandemic has resulted in new national guidance on cleaning recommendations. There may be an associated risk of chemical exposures.
- **Findings:** The authors compare the number of reported calls to national poison centers for exposures to cleaners and disinfectants during the period of January–March 2020, to the same period in 2018 and 2019.
 - The number of calls in 2020 was 45,550, representing a 20.4% and 16.4% increase (respectively) compared to 2019 (37,822 cases) and 2018 (39,122 cases). **Pictures are a thousand words:**

FIGURE. Number of daily exposures to cleaners and disinfectants reported to U.S. poison centers — United States, January–March 2018, 2019, and 2020*[†]



* Excluding February 29, 2020.

[†] Increase in exposures to cleaners on January 29, 2020, came from an unintentional exposure to a cleaning agent within a school.

- Largest number of calls among cleaners was for bleach and among disinfectants were nonalcohol disinfectants and hand sanitizers
- Largest percentage of exposure routes was inhalation (increase of 35.3% from 2019)
- Two case vignettes were provided: (1) an adult woman cleaning her groceries in a sink filled with 10% bleach, vinegar, and hot water who subsequently developed shortness of breath and mild hypoxemia improved with symptomatic treatment; (2) a preschool-aged child found unresponsive at home next to an open bottle of ethanol-based hand sanitizer and admitted with an elevated BAL
- **What this study adds:** Temporal data demonstrating a likely trend of increased chemical exposure during the COVID-19 pandemic
- **Interpretation/Limitations/Conclusion:** With much of the COVID-19 response appropriately focused on COVID-19-specific issues, this short analysis succinctly demonstrates one small but significant area of “collateral damage” of COVID-19. One important limitation of this study is that the authors do not parse out what percentage of reported exposures were identified as real. Even though there is a convincing spike in reports of exposure, it is unknown to what extent these reports are themselves truly representative of actual exposure events or to what extent they may be secondary to perceived exposure in a setting of significantly increased presence of these products in the public’s day-to-day lives. Another limitation is the lack of morbidity/mortality data aside from the case vignettes.

Transmission/Infection Control

Brought to you by: Nithin Gopalsamy, MD

Liu, Yuan et al. “Aerodynamic Analysis of SARS-CoV-2 in Two Wuhan Hospitals.” *Nature*, April 27, 2020, 1–6.
<https://doi.org/10.1038/s41586-020-2271-3>.

- Aerosol transmission of COVID-19 has been suggested though not well-characterized. Transmission is primarily thought to be via droplet and contact though retrospective study of SARS in 2003 suggested airborne spread may have also been present.
- Transmission is primarily thought to be via droplet and contact though retrospective study of SARS in 2003 suggested airborne spread may have also been present.
 - Airborne SARS-CoV-2 and its aerosol deposits were quantified using droplet digital PCR of the viral RNA
 - Samples obtained from 30 sites in units and public areas in 2 hospitals in Wuhan - one representing a tertiary hospital and the other representing the make-shift hospitals constructed
 - Among patient areas, very low or non-detectable concentrations of airborne SARS-CoV-2 inside the rooms, suggesting effective negative pressure isolation
 - Among patient areas, highest concentration noted on toilets; very low or non-detectable concentrations of airborne SARS-CoV-2 inside the rooms, suggesting effective negative pressure isolation
 - Among medical staff areas, highest concentration noted in PPE removal rooms
 - Among public areas, concentration generally low; most notable site near entrance of department store
 - With addition of disinfectant to high-risk areas, concentration reduced to undetectable levels
- Limitations: PCR-positivity does not infer infectivity (unknown if these quantified particles harbor live virus actually leading to new cases). Small number of samples.
- Conclusions: Decontamination should remain a high priority with particular attention now to patient room toilets, PPE before its removal (if feasible), and high volume public areas such as store entrances. COVID appears to aerosolize though remains unclear if these aerosol particles contain live virus leading to transmission.

Houghton, Catherine et al. "Barriers and Facilitators to Healthcare Workers' Adherence with Infection Prevention and Control (IPC) Guidelines for Respiratory Infectious Diseases: A Rapid Qualitative Evidence Synthesis." *Cochrane Database of Systematic Reviews*, no. 4 (2020).

<https://doi.org/10.1002/14651858.CD013582>.

- Infection prevention and control (IPC) strategies are extensive in an effort to reduce risk of transmission of COVID-19; though healthcare workers may wish to adhere to IPC guidelines, there are many challenges to doing so.
 - 36 studies focusing on the experiences and perceptions of HCW with IPC guidelines for respiratory infections and sampled 20 of them for the analysis
 - Summarized qualitative results with 26 findings found - 3 graded as high confidence (detailed as below), 18 as moderate, and 5 as low using GRADE-CERQual approach
 - Clear communication of IPC strategy key to its implementation
 - Lack of training about the specific infection and how to use PPE contributes to poor implementation
 - Discomfort of wearing PPE reduced adherence; ensuring proper fit could help overcome this barrier
- Limitations: Rapid review so not the comprehensive review usually associated with Cochran Library. Qualitative data by nature so detailed statistical analysis not feasible. Extrapolating data from prior respiratory infections though not necessarily in the setting of a pandemic with potentially associated resource limitations and increased HCW stress.

- **Conclusions:** Clearly outlining infection prevention and control strategy while tailoring it to the disease at hand may improve HCW adherence to guidelines. While PPE may be limited during this pandemic, prioritizing well-fitting and comfortable PPE may improve adherence.

Clinical Syndrome

Brought to you by: Divya Bhamidipati, MD

Auld, Sara et al. "ICU and Ventilator Mortality among Critically Ill Adults with COVID-19." *MedRxiv*, April 26, 2020, 2020.04.23.20076737. <https://doi.org/10.1101/2020.04.23.20076737>.

- Estimated 15-20% of COVID-19 infections require hospitalization with 3-5% requiring critical care. Reported mortality rates in those requiring mechanical ventilation have ranged between 50-97% based on literature from China, UK, and Italy. This has raised concern that mechanical ventilation should potentially be avoided in these patients.
- This study examined 217 patients admitted to 6 COVID designated ICUs across an academic healthcare center to help evaluate if mechanical ventilation was associated with high risk of death
- 75% (165) received mechanical ventilation, 65% (143) needed vasopressors, 29% (63) required renal replacement therapy; 59.4% (129) transferred alive from the ICU to the floors. Median ICU length of stay 12 days
- Mortality of 28.5% in those who were ventilated (47/165), and overall mortality 25.8% with 40% surviving to discharge
- Characteristics of those who died: median age 70 (older than those who survived), more likely to have CAD, higher SOFA scores on admission, and higher D-dimer and CRP
- Patients who died in the ICU were more likely to have respiratory failure requiring mechanical ventilation, shock requiring vasopressors and renal failure requiring CRRT/iHD
- **Conclusion:** Lower mortality than what has been previously reported in China, Italy, and the UK
- **Limitations:** Earlier intubation was part of the internal protocol, patients were placed in units already accustomed to caring for critically ill patients and those with acute respiratory failure. Will need further analysis of the impact of clinical interventions on survival.

Ye, Guangming et al. "Clinical Characteristics of Severe Acute Respiratory Syndrome Coronavirus 2 Reactivation." *The Journal of Infection* 80, no. 5 (2020): e14–17. <https://doi.org/10.1016/j.jinf.2020.03.001>.

- There has been little information thus far on reactivation in the literature about SARS-CoV-2
- This was a retrospective study of 55 patients diagnosed with COVID-19 pneumonia with 5 patients (9%) who were discharged from the hospital presenting with reactivation (negative \diamond positive PCR).
 - Patient characteristics: Age range 27-42, no underlying disease in any of these patients, other viral infections (influenza, H7 avian influenza) excluded upon presentation.
 - 4/5 had fever without chills, all had fatigue, normal LFTs, and typical CT findings of multiple patchy ground glass opacities on Chest CT. 1/5 with progressive lymphopenia and elevated neutrophilia.
 - Time from negative to positive PCR ranged from 4-17 days.

- **Conclusion:** None had severe pneumonia, 1 was asymptomatic – overall no specific clinical characteristics noted to help distinguish reactivation.
- **Limitations:** Unclear what parameters were used to define “reactivation” – no data given on previous clinical course and whether these were persistent symptoms or new symptoms; no information on previous PCR testing parameters; this may be just amplification of already present dead RNA rather than true “reactivation”; need more information on immune responses such as antibodies in those considered “reactivated”. Small sample size also makes this hard to draw conclusions from.

Therapeutics

Brought to you by: Boghuma Titanji, MD, PhD

Magagnoli, Joseph et al. “Outcomes of Hydroxychloroquine Usage in United States Veterans Hospitalized with Covid-19.” *MedRxiv*, April 23, 2020, 2020.04.16.20065920. <https://doi.org/10.1101/2020.04.16.20065920>.

- The hydroxychloroquine saga has dominated much of the COVID-19 treatment landscape. Prior to this study from the VA healthcare system, a controversial open label non randomized study from France (Raoult et.al) touted the merits of combining hydroxychloroquine with Azithromycin to treat COVID-19.
 - Following that initial study, the drug has gained popularity as the preferred off-label antiviral agent for COVID-19. Other studies have since emerged casting doubt on the safety and efficacy for hydroxychloroquine against SARS-CoV-2 most notably a recent study from Brazil which showed higher rates of deaths and adverse events in patients who received high dose hydroxychloroquine for treatment of COVID-19 and a lack of clinical improvement in treated patients.
- This was retrospective analysis of patients hospitalized for SARSCoV-2 infection in the Veterans Health System up until April 11, 2020. Patients were categorized based on treatment with hydroxychloroquine alone (HC), hydroxychloroquine plus azithromycin (Hc+AZ) or supportive care (no HC). A total of 368 patients were evaluated (HC, n=97; HC+AZ, n=113; no HC, n=158). Rates of death in the HC, HC+AZ, and no HC groups were 27.8%, 22.1%, 11.4%, respectively. Rates of ventilation in the HC, HC+AZ, and no HC groups were 13.3%, 6.9%, 14.1%, respectively. Compared to the no HC group, the risk of death from any cause was higher in the HC group (adjusted hazard ratio, 2.61, P=0.03) but not in the HC+AZ group (1.14; 95% CI, P=0.72)
- This study, though an observational retrospective cohort study by design, included a control group comparing the intervention (treatment with hydroxychloroquine) to supportive care. The lack of a control group has been a much-criticized feature of the previous cohort studies published on use of hydroxychloroquine to treat COVID-19.
 - Importantly this study highlighted the apparent lack of benefit for those treated and the higher rates of death associated with receiving hydroxychloroquine.
- **Interpretation/limitations/conclusions:** The main limitation of the study is the absence of randomization. The authors however make a decent attempt to adjust for COVID-19 related confounders. However, this does not fully rule out the possibility of selection bias or residual confounding. Also, the study included only men with median age of 65 and as such may not be generalizable to a more heterogenous population.
- **While we await randomized controlled studies assessing the usefulness of hydroxychloroquine in COVID-19, the data which are currently available suggest caution for its use given unclear benefit and possible harm.**

Diagnostics

Brought to you by: Ahmed Babiker, MBBS

Williams E et al. "Saliva as non-invasive specimen for detection of SARS-CoV-2."

<https://jcm.asm.org/content/jcm/early/2020/04/17/JCM.00776-20.full.pdf>

- **Background:** Prior small sample studies have revealed saliva as promising sample type for SARS-CoV-2 testing. This study expanded on previous evidence.
- **Findings:**
 - 522 patients were tested for COVID-19 by NP swab and saliva.
 - 39 patients tested positive by NP swabs, of which and 85% (33/39) had SARS-CoV-2 detected in saliva.
 - Ct value was significantly lower in NPS than saliva, suggestive of higher viral 42 loads in NP
- **Conclusion:** The authors demonstrate feasibility and sensitivity of collecting saliva as an alternative first-line. This may aid with ongoing swab and transport media shortages as well as decrease healthcare worker exposure and allow for conservation of personal protective equipment.

Rogers, Amy A. et al. "Evaluation of Transport Media and Specimen Transport Conditions for the Detection of SARS-CoV-2 Using Real Time Reverse Transcription PCR." *Journal of Clinical Microbiology*, April 27, 2020, JCM.00708-20, jcm;JCM.00708-20v1. <https://doi.org/10.1128/JCM.00708-20>.

- **Background:** Stability of SARS-CoV-2 in various storage conditions is unknown. Authors spiked high-titer SARS -CoV-2 remnant patient specimen into pooled SARS-CoV-2 RNA -negative specimen remnants for the various media types (VTM, UTM, RT-Eswab™, M4 and Saline)
- **Findings:**
 - Aliquots of samples were 36 stored at 18°C to 25°C, 2°C to 8°C and -10°C to -30°C and then tested at time points up to 14 days .
 - Specimens consistently yielded amplifiable RNA with mean Ct differences of < 3 over the various conditions assayed
- **Conclusions:** This provides additional data supporting alternative medias.

Xiao, Ai Tang et al. "Profile of RT-PCR for SARS-CoV-2: A Preliminary Study from 56 COVID-19 Patients."

Clinical Infectious Diseases. Accessed April 28, 2020. <https://doi.org/10.1093/cid/ciaa460>.

- **Background:** Studies examining duration of RT-PCR positivity have been limited by duration follow up.
- **Findings:** 56 patients were followed for 6 weeks after symptom onset
 - Median duration between onset of symptom to time to negative test was 24 days
 - All patients tested negative by 6 weeks
 - The positive rate of RT-PCR test results was highest at week 1 (100%), followed by week 2: 89.3%, week 3: 66.1%, week 4: 32.1%, week 5: 5.4%
 - 4 patients had 2 consecutive negative results followed by a positive result.
 - Patients with prolonged viral shedding (>24 days) were older and had higher rates of diabetes and hypertension

- **Limitations:** Only those with mild/moderate disease included, hence data cannot be extrapolated with those with severe disease. Furthermore, no viral culture data so unclear whether those with prolonged RT-PCR positivity were shedding infectious viral particles.

Vaccinology

Brought to you by: Amy Sherman, MD

Amanat, Fatima, and Florian Krammer. "SARS-CoV-2 Vaccines: Status Report." *Immunity* 52, no. 4 (April 2020): 583–89. <https://doi.org/10.1016/j.immuni.2020.03.007>.

- Within the last decade, vaccine technologies have rapidly evolved. A vaccine target for SARS-CoV-2 (the S protein) was identified early in the pandemic, and is now being integrated into different vaccine platforms. The authors review the current landscape for SARS-CoV-2 vaccines.
- Challenges in the development of an effective coronavirus vaccine:
 - Human coronavirus infections do not always induce long lived antibody responses. A durable response is needed for an efficacious vaccine.
 - The most severe disease from Covid-19 has been seen in older adults. Due to immune senescence, it is difficult to produce a robust immune response in this population to confer protection.
 - No clear animal model for early phase trials has been developed.
 - For a mostly naïve population, protection via vaccination will likely require a prime-boost vaccination regimen (e.g. at least 2 vaccines in a series).
 - Novel vaccine must be able to be mass-produced.
- Current pipeline of SARS-CoV-2 vaccine development:
 - Target the S protein: RNA, DNA, recombinant protein, viral vector-based (VSV) vaccine platforms.
 - Target the whole virion: Live attenuated and inactivated vaccines
- **Conclusions:** Developing safe and effective vaccines for humans usually takes years. With the rapid identification of the SARS-CoV-2 sequence, the process has been accelerated. However, since there are no current approved coronavirus vaccines, we must start from the beginning to build a viable vaccine, and also build the capacity for mass production. Even with new technologies and an accelerated process, SARS-CoV-2 vaccines will likely not be ready for at least 12-18 months.

Basic Science/Virology

Brought to you by: Sam Stampfer, MD, PhD

Wenhao Dai et al. "Structure-based design of antiviral drug candidates targeting the SARS-CoV-2 main protease." *Science*. DOI: 10.1126/science.abb4489. April 22, 2020.

- Of the currently-licensed drugs that are being repurposed to treat COVID-19, only remdesivir and protease inhibitors (most prominently lopinavir/ritonavir) have direct protein targets on SARS-CoV-2. Lopinavir/ritonavir was designed for the HIV protease, but has shown potential to treat SARS-COV 1 & 2 *in vitro*, Unfortunately, it has yet to show any clinical benefit in humans for COVID-19. Here, the authors explore creating a superior protease inhibitor to target SARS-CoV-2.

- The M^{pro} protease in SARS-CoV-2 is a 3C-like cysteine protease that cleaves the two large SARS-CoV-2 polyproteins into 16 non-structural proteins. The active site of this protein is highly conserved among all coronaviruses.
- The authors analyzed the SARS-CoV M^{pro} structure active site and rationally designed small molecule inhibitors against it. They attempted to design molecules with an aldehyde group that would hopefully directly target and form a covalent bond with the cysteine in the active site of the protease.
- They designed and produced two new protease inhibitors, 11a and 11b. They crystallized both with purified SARS-CoV-2 M^{pro} and demonstrated that both form a C-S bond between the drug's aldehyde group and the protease's active cysteine. Additionally, these compounds fit well in the active site and form multiple hydrogen bonds with active-site side chains, along with hydrophobic interactions and ring stacking.
- They expressed SARS-CoV-2 M^{pro} in E Coli, purified it, and tested its protease activity against a fluorogenic substrate. They used this system to evaluate the *in vitro* IC₅₀ values for their compounds, which were extremely potent. Inhibitor 11a had a 53 nanomolar (nm) IC₅₀ in this assay, while inhibitor 11b was 40 nanomolar.
- They then tested the compounds against SARS-CoV-2 virus in a plaque-reduction assay. 11a had an EC₅₀ of 530 nanomolar, and 11b of 720 nanomolar.
- They evaluated pharmacokinetics to determine whether these might be suitable treatment options *in vivo*. The half-life of 11a was longer than 11b when given IV and was pursued further. When given at 5 mg/kg, IV half lives were 4.4-7.6 hours depending on the animal. Drug levels up to 40 mg/kg were tolerated by rats and dogs, but one out of four rats died when 11a was used at 60 mg/kg.
- **Summary:** The authors used rational design principles to generate two potent inhibitors against the SARS-CoV-2 protease. These inhibitors have sub-micromolar EC₅₀ values, and inhibitor 11a has pharmacokinetic properties that make it suitable for therapeutic use. Further studies are needed to evaluate drug safety and efficacy *in vivo*.

Timothy Abbott et al. "Development of CRISPR as an Antiviral Strategy to Combat SARS-CoV-2 and Influenza." *Cell*. <https://doi.org/10.1016/j.cell.2020.04.020> April 29, 2020.

- CRISPR-Cas is a technology that mediates degradation of specific RNA sequences. A CRISPR-associated RNA (crRNA) binds to and targets a specific RNA sequence, and a Cas protein then degrades it. Here, the authors apply this technique to COVID-19 treatment, by using PAC-MAN (Prophylactic Antiviral CRISPR in human cells) to simultaneously degrade the SARS-CoV-2 RNA genome and viral mRNAs.
- They use a CRISPR system with a customizable 22 nucleotide sequence that allows very specific targeting. They use the Cas13d protein in conjunction with this, which has high catalytic activity in human cells.
- Using genomic analysis, the authors found that just six crRNAs would be required to target 91% of all sequenced coronaviruses, providing broad coverage against any current and future coronavirus to cause human infection.
 - The most conserved genes were the RNA-dependent RNA polymerase (RdRP) and the nucleocapsid (N).
- To test this, they generated a lung cell line (A549) expressing Cas13d along with their selected crRNAs. This was co-expressed with segments of the genome targets from SARS-CoV-2 fused to GFP. Successful CRISPR-mediated cleavage would thus result in decreased GFP production.

- Anti-RdRp crRNAs repressed GFP by up to 86%; anti-N by up to 71%. RNA quantification showed similar results.
- Similar but slightly inferior results were obtained when SARS-CoV-2 genomic material was introduced by lentiviral infection (done to closer mimic true infection conditions).
- The authors did not have access to SARS-CoV-2, so they applied the same techniques as above to generate crRNAs against different segments of the influenza genome, which they then tested with live influenza virus infecting Cas-13d-expressing A549 lung epithelial cells. They were able to reduce the MOI by up to 78%, with their most consistent results using crRNAs against influenza neuraminidase.
- **Summary:** The authors develop a system that can be used to specifically degrade SARS-CoV-2 RNA *in vitro* in lung epithelial cell lines. The system is extremely versatile, allowing for rapid generation of customized CRISPR sequences to target any viral RNA sequence, with potential applications for current and future pandemic viruses.
- **Limitations:** This is an initial proof of concept with many hurdles to overcome before clinical use. It was not tested against fully-infectious SARS-CoV-2 virus, but just against SARS-CoV-2 partial genomes. To make this work *in vivo*, there will need to be a method to deliver Cas13d plus the crRNA directly to SARS-CoV-2 infected cells. Additionally, they may need to optimize the system to improve its efficacy. Even in an idealized *in vitro* system with a cell line that stably expressed the Cas13d enzyme, there was still no more than 86% degradation of targeted SARS-CoV-2 sequences. It is unclear whether this would translate to a clinical benefit, particularly as the system likely becomes less efficient *in vivo*.

Pediatrics

Brought to you by: Satoshi Kamidani, MD

Castagnoli, Riccardo et al. "Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review." *JAMA Pediatrics*, April 22, 2020.

<https://doi.org/10.1001/jamapediatrics.2020.1467>.

- While data are available for adult patients with coronavirus disease 2019 (COVID-19), limited reports have analyzed pediatric patients infected with SARS-CoV-2.
- Designed to retrieve all articles published from December 1, 2019, to March 3, 2020. Retrospective cross-sectional and case-control studies, case series and case reports, bulletins, and national reports about the pediatric SARS-CoV-2 infection were included.
 - A total of 815 articles were identified. 18 studies with 1065 participants (444 patients were younger than 10 years, and 553 were aged 10 to 19 years) with confirmed SARS-CoV-2 infection were included.
 - All articles reflected research performed in China, except for 1 clinical case in Singapore.
 - Children at any age were mostly reported to have mild respiratory symptoms, fever, dry cough, and fatigue, or were asymptomatic.
 - Bronchial thickening and ground-glass opacities were the main radiologic features, and these findings were also reported in asymptomatic patients.

- Most pediatric patients were hospitalized, and symptomatic children received mainly supportive care. 1 infant presented with pneumonia, complicated by shock and kidney failure, and was successfully treated with intensive care.
- No deaths were reported in children aged 0 to 9 years whereas, 1 death was reported in the age range of 10 to 19 years.
- **Limitations:** A brief 3-month period reviewed. European and US studies in children with COVID-19 were not available. The included studies were only observational designs, and many were simple case series or case reports.
- **Conclusions:** Most children with COVID-19 presented with mild symptoms, if any, generally required supportive care only, and typically had a good prognosis.

Xie, Xinyan et al. "Mental Health Status Among Children in Home Confinement During the Coronavirus Disease 2019 Outbreak in Hubei Province, China." *JAMA Pediatrics*, April 24, 2020.

<https://doi.org/10.1001/jamapediatrics.2020.1619>.

- As the coronavirus disease 2019 (COVID-19) epidemic progressed in Wuhan, Hubei province, China, the Chinese government ordered a nationwide school closure and more than 180 million students in China were restricted to their homes.
- This study investigated depressive and anxiety symptoms among students in Hubei province, China, measured by the Children's Depression Inventory–Short Form (CDI-S) and the Screen for Child Anxiety Related Emotional Disorders.
- In Hubei province, students in Wuhan were restricted to home from Jan. 23, 2020 to Apr. 8, 2020, and those in Huangshi (a city about 52 mi from Wuhan) from Jan. 24, 2020 to Mar. 23, 2020.
 - Among a total of 2330 students in grades 2 through 6 in 2 primary schools in Hubei province, 1784 participants completed the survey (response rate of 76.6%)
 - Students had been restricted to home for a mean (SD) of 33.7 (2.1) days when they completed this survey.
 - A total of 403 students (22.6%) and 337 students (18.9%) reported depressive and anxiety symptoms, respectively. Students who were slightly or not worried about being affected by COVID-19 had significantly lower CDI-S scores than those who were quite worried (β , -0.184 [95%CI, -0.273 to -0.095]), with a decreased risk of depressive symptoms (odds ratio, 0.521 [95%CI, 0.400-0.679]).
- **Limitations:** No comparison and no assessment of their baseline feeling/moods. Could not evaluate whether these outcomes will be long-lasting after the COVID-19 outbreak.
- **Conclusions:** Higher rates of depressive and anxiety symptoms during COVID-19 outbreak as compared to historical national averages in China. A better understanding of how the epidemic affects students' mental health can help guide future interventions.

Immunocompromised Hosts

Brought to you by: Amy Sherman, MD

Pereira, Marcus R. et al. "COVID-19 in Solid Organ Transplant Recipients: Initial Report from the US Epicenter." *American Journal of Transplantation* n/a, no. n/a. Accessed April 28, 2020. <https://doi.org/10.1111/ajt.15941>.

- The role of chronic immunosuppression on outcomes for patients affected by Covid-19 is not known. The authors describe the characteristics of 90 solid organ transplant (SOT) recipients with Covid-19 at two large academic centers in NYC during the initial 3 weeks of the epidemic.
 - Transplant recipients: 46/90 renal, 17/90 lung, 13/90 liver, 9/90 heart, 3/90 heart-kidney, 1/90 liver-kidney, 1/90 kidney-pancreas.
 - Median time from transplant to Covid-19 diagnosis = 6.64 years
 - 24% with mild disease, 46% with moderate disease, and 30% with severe disease. Patients with severe disease tended to have hypertension, active cancer, and/or advanced age.
- For hospitalized patients (68/90), treatment strategies included reducing immunosuppression. Patients received a mix of hydroxychloroquine, azithromycin, and tocilizumab.
- Mortality: 16/90 died from Covid related complications. 37/90 discharged home. No cases of rejection or thromboembolic complications.
- Conclusions: Immunosuppressed patients presented with similar symptoms to those reported in the general population. Indications and optimal timing for treatment (esp immunomodulatory therapies) remains unknown for immunocompromised hosts. Severity of disease and mortality rates were high in this population.
- Limitations: The high mortality rate reported may reflect sampling bias (mostly hospitalized patients included), and does not take into account confounding factors (e.g. comorbidities and advanced age may have driven this conclusion, not immunosuppression itself).

Akalin, Enver et al. "Covid-19 and Kidney Transplantation." *New England Journal of Medicine* 0, no. 0 (April 24, 2020): null. <https://doi.org/10.1056/NEJMc2011117>.

- To investigate the clinical syndrome and risk factors of renal transplant recipients infected with SARS-CoV-2, a single center in NYC evaluated 36 consecutive patients between March 16 and April 1, 2020.
 - 72% were male, median age = 60 years old. 39% were black, 42% were Hispanic.
 - 94% had hypertension, 69% had DM2, 36% had a history of smoking, and 17% had heart disease.
 - Immunosuppression regimens included tacrolimus, prednisone, and/or mycophenolate mofetil.
- Most common symptom initially was fever, but only in 58% of patients. 39% required mechanical ventilation.
- Lab findings: lymphopenia, thrombocytopenia, low CD3, CD4, and CD8 counts. Elevated inflammatory markers.
 - Mortality: 10/36 patients (28%).
- Conclusions: As compared to the general population, kidney transplant-recipients with Covid-19 has less fever as a presenting symptom, lower CD3, CD4, CD8 counts, and more rapid clinical progression. The low CD3/CD4/CD8 counts support the need to decrease immunosuppressive therapies. Overall higher mortality reported in this population.
- Limitations: Single center study in NYC, may not be generalizable to other cities/transplant centers. Patients had significant comorbidities (e.g. HTN and DM2) that are known to be risk factors for severe Covid disease.

Disclaimer: The above references were selected and summarized by amazing Emory ID fellows. We have tried to put together an accurate list and summary, but please know that this is not intended to be 100% comprehensive! Also, it is impossible to keep completely up-to-date!