

The Weekly Covid-19 Literature Round-Up

Edition 5: April 15, 2020

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

“It would be better if there were but one inhabitant to a square mile, as where I live.”

-Henry David Thoreau, Walden

“How did we end up here? Two ways. Gradually, then suddenly.” -Ernest Hemingway

Epidemiology

Brought to you by: Jessica Howard-Anderson, MD

Garg, Shikha. “Hospitalization Rates and Characteristics of Patients Hospitalized with Laboratory-Confirmed Coronavirus Disease 2019 — COVID-NET, 14 States, March 1–30, 2020.” *MMWR. Morbidity and Mortality Weekly Report* 69 (2020). <https://doi.org/10.15585/mmwr.mm6915e3>.

- Population-based surveillance for COVID-19-Associated hospitalizations in the US is now being performed by CDC and Emerging Infections Program (EIP) using existing influenza and RSV surveillance infrastructure.
 - Surveillance data from 14 states (GA is a participant) ~ 10% of US population
- COVID-NET hospitalization rates are being published each week at https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html
 - Can look at GA specific rates as well
- From 3/1- 3/30, COVID-19 hospitalization rate was ~ 4.6/100,000 population
 - Rates were highest in adults > 65 (~13.8/100,000 population); 54.4% males, 33% black
- 89% had 1 or more underlying condition
 - 50% had HTN, 48% were obese (most common underlying condition in age 18 -49), 35% had chronic lung disease
- Limitations: Data is preliminary, only 12% had data on underlying conditions, testing (and therefore surveillance) may be dependent on local resources/testing protocols.

Pan, An et al. “Association of Public Health Interventions With the Epidemiology of the COVID-19 Outbreak in Wuhan, China.” *JAMA*, April 10, 2020. <https://doi.org/10.1001/jama.2020.6130>.

- Cohort study of 32,583 patients with lab-confirmed COVID-19 in Wuhan from 12/8 – 3/8/20
- Epidemic was broken into 5 phases: 1) no interventions 2) massive human movement due to Chinese New Year 3) city lockdown, traffic restrictions, home confinement 4) central quarantine and treatment, 5) universal symptom survey (Figure 1)
 - The daily case rate peaked in phase 3 and the proportion of severe/critical cases decreased over time
- The public health interventions (**phases 3-5**) were temporally associated with decreasing case numbers and decrease in reproduction number (R_t from > 3 to < 1 in phases 4 and 5)

- Daily case rate in healthcare workers (HCWs) was higher than general population (130.5 v. 41.5/million people) but decreased in phases 4 and 5 with comprehensive PPE used
 - There was no difference in clinical severity for HCWs
- **Conclusion:** Aggressive, multifaceted measures of containment, mitigation, and suppression were temporally associated with improved control of COVID-19 in Wuhan.

Transmission/Infection Control

Brought to you by: Daniel Graciaa, MD, MPH

Heinzerling, Amy. "Transmission of COVID-19 to Health Care Personnel During Exposures to a Hospitalized Patient — Solano County, California, February 2020." *MMWR. Morbidity and Mortality Weekly Report* 69 (2020). <https://doi.org/10.15585/mmwr.mm6915e5>.

- Limited data are available on transmission of COVID-19 in health care settings despite evidence that health care personnel (HCP) are at increased risk of infection
- A patient with unrecognized COVID-19 was admitted in mid-February and transferred to a second hospital. Of 121 HCP at hospital A exposed to the patient, 43 were tested (nasopharynx and oropharynx) after developing symptoms within 14 days, and 3 were positive. All 3 positive HCP had unprotected exposure to the patient. Of 146 HCP at hospital B, 8 were symptomatic, and none tested positive.
- HCP who developed COVID-19 had higher estimated duration of both overall exposure and of exposure during aerosol-generating procedures (2 of 3), which included nebulizer treatments, BiPAP, and intubation for this patient. They were also more likely to have performed a physical exam.
- **Interpretation/limitations:** This report provides evidence of transmission of COVID-19 to healthcare personnel. Limitations include self-report of frequency/duration of HCP exposure and low case numbers precluding more than descriptive analysis. However, this reinforces the need for infection control measures including early recognition of cases, appropriate isolation, and adequate PPE.

Kissler, Stephen M., Christine Tedijanto, Edward Goldstein, Yonatan H. Grad, and Marc Lipsitch. "Projecting the Transmission Dynamics of SARS-CoV-2 through the Postpandemic Period." *Science*, April 14, 2020. <https://doi.org/10.1126/science.abb5793>.

- Transmission of SARS-CoV-2 after the initial pandemic wave is unknown but critical to long-term surveillance and control measures including non-pharmaceutical interventions such as physical distancing.
- Using estimates from US data for other betacoronaviruses (OC43 and HKU1) including seasonality, immunity, and cross-immunity, a model of SARS-CoV-2 transmission projects seasonal outbreaks in winter.
 - If immunity to SARS-CoV-2 is not permanent, regular circulation is projected with either annual outbreaks, if duration of immunity is similar to OC43 and HKU1 (approximately 40 weeks), or biennial outbreaks if duration is closer to two years.
- Assuming no cross-immunity, one-time physical distancing could push the epidemic peak into the fall and still exceed critical care capacity, but intermittent physical distancing into 2021, a treatment that reduces hospitalization by half, or increasing critical care capacity could prevent this. Cross-immunity from other betacoronaviruses could cause an apparent elimination of SARS-CoV-2 with a recurrent outbreak in 2024.

- Interpretation/limitations: This model is consistent with the expectation that seasonal transmission is likely, especially in the absence of immunity or a vaccine. Assumptions for the model include major unknowns such as duration of immunity to SARS-CoV-2 or cross-immunity from other betacoronaviruses.

Clinical Syndrome

Brought to you by: Alfonso Hernandez, MD, MPH

Thachil, Jecko et al. "ISTH Interim Guidance on Recognition and Management of Coagulopathy in COVID-19." *Journal of Thrombosis and Haemostasis* n/a, no. n/a. Accessed April 15, 2020.

<https://doi.org/10.1111/jth.14810>.

- Coagulopathy is one of the key and persistent features associated with poor outcomes in patients with COVID-19.
- Aims to provide a risk stratification at admission for COVID-19 patients as well as the management of coagulopathy.
- Coagulation markers on admission
 - D-dimer is an independent risk factor for severe disease: increases 3-4 times normal should be considered prognostic for possible severe disease even in the absence of respiratory symptoms and oxygen requirements and should prompt admission
 - PT and thrombocytopenia may be also poor prognostic signs but correlation is weaker than D-dimer
- Recommend measuring D-dimer, PT, and platelets in all patients with COVID-19 infection and in critically ill patients measuring fibrinogen
- Prophylactic dose low molecular weight heparin should be considered in all COVID-19 patients, regardless of severity of disease, in the absence of contraindications
 - Based on unpublished study of 449 patients with severe COVID-19 where heparin resulted in decreased mortality among those with a sepsis-induced coagulopathy score ≥ 4 or a D-dimer $>6x$ ULN.

Mao, Ling et al. "Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China." *JAMA Neurology*, April 10, 2020. <https://doi.org/10.1001/jamaneurol.2020.1127>.

- Retrospective chart review of 214 patients of whom 78 (36.4%) had neurologic manifestations
- Relied on subjective symptoms and physical examination – limited neuroimaging due to isolation requirements
- Categorized as:
 - Central (53, 24.8%) – dizziness (36), headache (28), impaired consciousness, acute cerebrovascular disease, ataxia, and seizure
 - Peripheral (19, 8.9%) - taste impairment (12), smell impairment (11), vision impairment, and nerve pain
 - Skeletal muscle injury (23, 10.7%) – pain or creatine kinase level >200 U/L
- More common in severe (45.5%) than non-severe (30.2%) disease
- Most manifestations occurred early in the disease – 1-2 days after symptoms onset

- Six patients had acute cerebrovascular disease and two presented with sudden onset hemiplegia without other symptoms and were diagnosed after CT showed pulmonary pattern consistent with COVID-19
- Fever and headache without other respiratory symptoms were the initial presentations of some patients (Total N unknown) who tested negative initially and were subsequently retested after they developed typical COVID-19 symptoms
- Limitations: Based on EMR review and likely incomplete, limited by lack of neurological imaging
- Conclusion: Continue to expand your illness script for COVID-19 as patients can present with stroke or headache/fever without respiratory symptoms. Patients with neurological manifestations may also have more severe disease during their hospitalizations.

Kim, David et al. "Rates of Co-Infection Between SARS-CoV-2 and Other Respiratory Pathogens." *JAMA*, April 15, 2020. <https://doi.org/10.1001/jama.2020.6266>.

- Performed nasopharyngeal swabs for SARS-CoV-2 and other respiratory pathogens from March 3rd to 25th 2020 on patients with symptoms at Stanford University.
 - Compared proportions of other respiratory pathogens between SARS-CoV-2 positive and negative patients.
- Tested 1217 specimens for SARS-CoV-2 from 1206 patients
 - 116 (9.5%) were positive for SARS-CoV-2
 - 24 (20.7%) were positive for 1 or more non-SARS-CoV-2 pathogen
 - Rhinovirus/enterovirus (6.9%)
 - RSV (5.2%)
 - Non-SARS-CoV-2 coronaviridae (4.3%)
 - Among those that tested negative for SARS-CoV-2 the proportion of co-infection with non-SARS-CoV-2 was 26.7%
 - 318 (26.1%) were positive for 1 or more non-SARS-CoV-2 pathogens
 - 24 (7.5%) were also positive for SARS-CoV-2
 - Among those that tested negative for non-SARS-CoV-2 the proportion of co-infection with SARS-CoV-2 was 10.2%
- Limitations: Single-center study, limited sample size and variations in spatiotemporal trends
- Conclusion: Up to 1 in 5 patients with SARS-CoV-2 positive samples also tested positive for other respiratory pathogens. Co-infections do not appear to be more common in patients who have SARS-CoV-2.

Ji, Dong et al. "Prediction for Progression Risk in Patients with COVID-19 Pneumonia: The CALL Score." *Clinical Infectious Diseases*. Accessed April 15, 2020. <https://doi.org/10.1093/cid/ciaa414>.

- Objective: To develop a scoring prediction model for severe COVID-19 disease
- Severe COVID-19 was classified as any of: RR >29, PaO₂ <94, PaO₂/FiO₂ <301 mmHg or requirement of mechanical ventilation
 - Progression to severe COVID-19 was development of any severe COVID-19 elements or worsening of lung CT findings
- Used Cox proportional hazards model to identify independent risk factors for severity and developed a nomogram whose predictive performance was measured by a concordance index and performance was assessed using ROC curves

- 208 patients were included: mean age 44 SD 16.3 (14.9% were >60y), mean hospitalization time was 17.5 SD 8.2, 40 (19.2%) of patients developed severe disease
- Comorbidity (hypertension, diabetes, cardiovascular disease, liver disease, asthma, chronic lung disease, HIV infections and malignancy for at least 6 months), age >60y, lymphocyte count <1,000 and LDH were independent risk factors for progression
- CURB-65 of 208 patients were from 0-2 points even among those with progression to severe disease
- CALL score was created (comorbidity, age, lymphocyte, and LDH) ranging from 4-13 points
 - Comorbidity: without = 1 point, with = 4 points
 - Age: ≤60 = 1 point, >60 = 3 points
 - Lymphocyte: >1,000 = 1 point, ≤1,000 = 3 points
 - LDH
 - <250 = 1 point; 250-500 = 2 points; >500 = 3 points
- AUROC was 0.91
 - Cut-off of 6 points: +LR 4.31 (3.2-5.8), -LR 0.06 (0.02-0.20)
 - Cut-off of 9 points: +LR 15.1 (6.0, 38.3), -LR 0.57 (0.40-0.80)
 - Three classes
 - 4-6 points: <10% progressed to severe disease; 7-9 points: 10-40% progressed to severe disease; 10-13 points >50% progressed to severe disease
- Limitations: Requires external validation prior to use. Did not present distribution of severity variables which limits interpretation.
- Conclusion: This may be a useful score to use when admitting patients to prognosticate whether they will develop severe disease. The low negative LR of a score 6 points or less makes it useful to triage patients especially when hospital census is high. Notable is the lack of predictive ability of the CURB-65 score for COVID-19.

Therapeutics

Brought to you by: Amy Sherman, MD

Grein, Jonathan, Norio Ohmagari, Daniel Shin, George Diaz, Erika Asperges, Antonella Castagna, Torsten Feldt, et al. "Compassionate Use of Remdesivir for Patients with Severe Covid-19." *New England Journal of Medicine* 0, no. 0 (April 10, 2020): null. <https://doi.org/10.1056/NEJMoa2007016>.

- Remdesivir is an antiviral (nucleotide analogue) that inhibits viral RNA polymerases. While remdesivir has shown *in vitro* activity against SARS-CoV-2, the clinical safety and outcomes for patients with Covid-19 is not known.
- Open-label program: Compassionate-use remdesivir was provided to patients hospitalized with Covid-19 for up to 10 days. 53 patients were included in the analysis (8 patients were excluded). Sponsored by Gilead Sciences.
 - No specific endpoints, number of patients, number of sites, or duration time points were predetermined.
 - Data collected: oxygen-support requirements, adverse events, laboratory values through day 10 of therapy. Follow-up information obtained through day 28.
- 36/53 patients (68%) showed improvement of oxygen requirements by median 18 days post-first dose, with 17 (of 30 intubated patients) extubated. Mortality: 7/53 (13%) died after completion of therapy.

Safety: 32 patients reported adverse events, including increased hepatic enzymes, diarrhea, renal impairment, rash, hypotension (more common in those receiving mechanical ventilation).

- **Limitations:** Not placebo controlled, missing data on several of the patients, not powered to analyze efficacy or safety, no predetermined endpoints. Furthermore, remdesivir was given at a median of 12 days after symptom onset; patients may have been improving via natural course of infection, not because of the drug.
- A **double-blinded RCT** is currently evaluating remdesivir v. placebo (1:1) in over 400 patients at 75 different sites. Let's wait to see the results from this trial!

“No Evidence of Clinical Efficacy of Hydroxychloroquine in Patients Hospitalized for COVID-19 Infection with Oxygen Requirement: Results of a Study Using Routinely Collected Data to Emulate a Target Trial | MedRxiv.” Accessed April 15, 2020. <https://www.medrxiv.org/content/10.1101/2020.04.10.20060699v1>. Preprint.

- Prior small studies (e.g. Gautret et al) have indicated that hydroxychloroquine (HCQ) may have a benefit in the treatment of Covid-19; however no large, placebo-controlled, randomized controlled trials have addressed this question.
- The authors collected data from 181 hospitalized and hypoxic patients with confirmed SARS-CoV-2 infection from 4 centers in France, with 84/181 who received HCQ within 48h of admission, and 97/181 who did not.
 - Primary aim: Transfer to ICU within 7 days from inclusion and/or death from any cause.
 - Secondary aim: Assess effectiveness of HCQ in preventing ARDS.
- Although this was not a RCT, the authors used an inverse probability of treatment weighting (IPTW) approach to “emulate” randomization, and balance potential confounders in the baseline variables between the 2 groups.
 - Transferred to the ICU or died within 7 days: 20.2% patients in HCQ group and 22.1% in no-HCQ group (RR 0.91, 95% CI 0.47-1.80).
 - Developed ARDS within 7 days: 27.4% in HCQ group and 24.1% in the non-HCQ group (RR 1.14, 95% CI 0.65-2.00).
 - Safety concerns: 8 patients in the HCQ group had ECG changes, resulting in discontinuation of HCQ.
- **Limitations:** Treatment was not randomly assigned, potential unmeasured confounders, number of patients treated with HCQ not balanced per center, did not measure serial PCR to evaluate differences in viral shedding.
- **Conclusions:** HCQ **not** supported for use in hospitalized patients with Covid-19, since HCQ was **not** associated with a reduction of ICU transfers, death, or ARDS development.

Sheahan, Timothy P. et al. “An Orally Bioavailable Broad-Spectrum Antiviral Inhibits SARS-CoV-2 in Human Airway Epithelial Cell Cultures and Multiple Coronaviruses in Mice.” *Science Translational Medicine*, April 6, 2020. <https://doi.org/10.1126/scitranslmed.abb5883>.

- An orally available antiviral drug, a ribonucleoside analog β -D-N⁴-hydroxycytidine (NHC, EIDD-1931), and its prodrug (EIDD-2801) were investigated for the treatment of Covid-19. NHC has been shown to have antiviral activity against influenza, Ebola, CoV, and Venezuelan equine encephalitis virus.
 - The compounds were discovered by the Emory Institute for Drug Development (EIDD).
- In a human airway epithelial cell culture model, NHC and EIDD-2801 were active against SARS-CoV-2, with dose dependent reduction in SARS-CoV-2 virus production. NHC was also active against remdesivir-resistant virus strains.

- EIDD-2801 was evaluated in the mouse model. Both prophylactic and therapeutic EIDD-2801 doses significantly reduced lung viral loads and improved pulmonary function for SARS and MERS-CoV.
- **Limitations:** No *in vivo* efficacy testing for EIDD-2801 for SARS-CoV-2. Unclear if the mouse model is the best animal model for SARS-CoV-2 and/or correlates to human pathogenicity.
- **Conclusions:** NHC, EIDD-1931 and EIDD-2801 are novel therapeutics that have potency against SARS-CoV-2, and clinically desirable with good oral bioavailability. Future trials are needed to investigate efficacy and safety in humans. The [FDA has approved an IND to begin human trials](#).

Diagnosics

Brought to you by: Ahmed Babiker, MBBS

Wehrhahn, Michael C. et al. "Self-Collection: An Appropriate Alternative during the SARS-CoV-2 Pandemic." *MedRxiv*, April 11, 2020, 2020.04.09.20057901. <https://doi.org/10.1101/2020.04.09.20057901>.

- Self-collection has been previously employed with high sensitivity/specificity in other respiratory virus testing and may mitigate PPE use and healthcare worker exposure.
- The study showed high concordance between self-collected (SC) and healthcare worker collected (HC) samples, and high sensitivity of SC samples tested by RT-PCR.
 - Among patients positive for SARS-Cov-2 (n=25)
 - 24/25 were detected by HC
 - 25/25 by SC
 - Sensitivity: 1.0 (95% CI: 0.86-1)
- High patient acceptance:
 - 74% of patients preferred self-collection over trained HC
- **Conclusions:** Initial data and validation of this method sample collection for SARS-CoV-2. Self-collection of throat and nasal swabs for SARS-CoV-2 offers an acceptable and reliable alternative to health care worker collected samples.

"Diagnosis of Acute Respiratory Syndrome Coronavirus 2 Infection by Detection of Nucleocapsid Protein | *MedRxiv*." Accessed April 15, 2020. <https://www.medrxiv.org/content/10.1101/2020.03.07.20032524v2>.

- Antigen detection test can allow for rapid identification and spare scarce PCR consumables and reagents.
- The authors describe the characteristics of an antigen detection test:
 - Fluorescence immunochromatographic assay which utilizes mouse anti-nucleocapsid protein monoclonal antibodies was used to detect nucleocapsid protein antigen
 - Turnaround time: 10 minutes
 - Among SARS-CoV PCR positive patients (n=208), 141 (68%) were N antigen positive
 - Sensitivity: 68%.
 - Among SARS-CoV PCR negative (n= 31) patients all (100%) were N antigen negative
 - Specificity: 100%.
 - Better performance among higher viral load samples (CT value<30)
 - 73.6% had a nucleocapsid antigen in urine on the same day
- **Limitations/Conclusion:** The specificity and turnaround time show that this test maybe a promising tool and utilized as part of a diagnostic algorithm, especially among those with higher VL (earlier in disease course?). Missing data on time of testing relative to symptom onset is a limitation.

Wölfel, Roman et al. "Virological Assessment of Hospitalized Patients with COVID-2019." *Nature*, April 1, 2020, 1–10. <https://doi.org/10.1038/s41586-020-2196-x>.

- Viral load and detection rates of SARS-CoV-2 differs across body sites.
- This study described: Viral load and detection rates across a variety of body sites
 - Swab viral load and detection rate declined after day 5 of symptoms, but patients remained positive (sometimes intermittently so) by RT-PCR for many days after resolution of symptoms.
 - The majority of paired swabs (5/9) and sputum samples taken between day 2-4 had equivalent viral load
 - No isolates were recovered by culture in samples taken after day 8, despite ongoing high viral loads.
 - Prolonged shedding/PCR positivity past symptom resolution (especially in sputum and stool) and seroconversion
 - Evidence of active virus replication in upper respiratory tract tissues and stool through identification of viral subgenomic messenger RNAs (sgRNA), which indicates the presence of actively-infected cells
- Limitations/Conclusion: This is a small sample (n=9) of relatively healthy patients. Moreover, patients were only followed up to 28 days out. Data emerging shows that patients can remain intermittently PCR positive for up to 6 weeks, however correlation with virus recovery is lacking, as is the case here.

Sutton, Desmond, Karin Fuchs, Mary D'Alton, and Dena Goffman. "Universal Screening for SARS-CoV-2 in Women Admitted for Delivery." *New England Journal of Medicine* 0, no. 0 (April 13, 2020): null. <https://doi.org/10.1056/NEJMc2009316>.

- Studies from a SNF in Washington state (US) and from the Diamond Princess cruise ship revealed a percentage of patients can have asymptomatic or have positive COVID-19 PCR results while "pre-symptomatic."
- In this study, 215 pregnant women were screened on admission for symptoms of Covid-19.
 - 4 had symptoms of Covid-19 on admission, and all 4 women tested positive for SARS-CoV-2.
- Among 210 tested asymptomatic women:
 - 29 (13.7%) were positive for SARS-CoV-2.
- Limitations: Limited follow-up to discern what percentage of asymptomatic patients would develop symptoms later on (i.e pre-symptomatic stage).
- Conclusions/Interpretations: The authors show further compelling evidence of asymptomatic COVID-19 infection. The rate of asymptomatic infection has significant implications on community spread, infection prevention efforts and potential herd immunity. Will centers start adopting universal screening in all patient populations?

Basic Science/Virology

Brought to you by: Sam Stampfer, MD, PhD

Gao, Yan et al. "Structure of the RNA-Dependent RNA Polymerase from COVID-19 Virus." *Science*, April 10, 2020. <https://doi.org/10.1126/science.abb7498>.

- The RNA-dependent RNA polymerase (RdRp) of RNA viruses is part of a multi-subunit complex responsible for viral replication and transcription. Nsp12 is the RdRp for coronaviruses.
- The authors determined the EM structure at 2.9 Angstrom resolution of SARS-CoV-2 nsp12 complexed with cofactors nsp7 and nsp8. The structure was analyzed both with reducing and nonreducing conditions, which yielded nearly identical results.
 - The cofactors were needed to visualize nsp12 effectively, as the monomer did not have as well-defined structure without them.
 - The structure is very similar to SARS-CoV-1 nsp12.
- Multiple divalent cation binding motifs are present in the active site, but no metal ions are present in this structure due to the absence of template RNA or NTPs. Similar motifs are found in many RdRp's, including in HCV ns5b, which has two manganese ions present in the active site.
- Through structural analysis, they find that remdesivir may bind SARS-CoV-2 nsp12 in a similar manner to sofosbuvir binding HCV ns5b, but that remdesivir's binding would be expected to be more stable due to presence of an intact ribose group.
- Conclusion: The structure of the RdRp of SARS-CoV-2 reveals a highly-conserved RNA polymerase with common structural motifs to distantly related viruses, including HCV. It is a drug target for broad-spectrum antivirals.

Shi, Jianzhong, Zhiyuan Wen, Gongxun Zhong, Huanliang Yang, Chong Wang, Baoying Huang, Renqiang Liu, et al. "Susceptibility of Ferrets, Cats, Dogs, and Other Domesticated Animals to SARS–Coronavirus 2." *Science*, April 8, 2020. <https://doi.org/10.1126/science.abb7015>.

- SARS-CoV-2 recently emerged as a pandemic virus and has zoonotic origins. COVID-19 eradication efforts may be hampered if it is able to establish long term infections in nonhuman reservoirs. In this paper, the authors investigate what other species with close contacts with humans could serve as viral reservoirs, as well as what species might make good clinical models for infection.
- Ferrets have been used as models for human respiratory infections. In this study, they were infected with a high inoculum of SARS-CoV-2 (10^5 PFU) either intranasally or intratracheally. Viral replication was mostly confined to the upper respiratory tract, with both infectious virus and RNA isolated from there. No viral RNA was found in the lower respiratory tract or other organs, although pathology in some ferrets revealed lung inflammation.
 - This is in contrast to SARS-CoV-1, which does infect the lower respiratory tract of ferrets.
 - 6/8 of the ferrets were asymptomatic at 12 days post-infection
- Cats infected in a similar manner were found to have both SARS-CoV-2 RNA and infectious virus in upper and lower respiratory tracts. RNA levels and viral titers were higher in juvenile cats (age 70-100 days) than subadult cats (age 6-9 months), and persisted longer. 1/6 cats died at day 13 (a juvenile). No adult cats were tested.
 - 2/6 uninoculated cats placed in adjacent cages ended up developing COVID-19. These cages were 4 cm from other cages, separated by 2 layers of netting, and with a constant 0.1 meter/second horizontal wind blowing from the inoculated to the uninoculated cats.
- SARS-CoV-2 RNA was isolated from the stool and GI tract of infected cats and ferrets, but none had infectious virus.
- Dogs, pigs, chickens, and ducks were all inoculated intranasally but none had any detectable viral RNA on oropharyngeal or rectal swabs at any timepoints, with the exception of 2/5 dogs on the rectal swab only. Those two dogs seroconverted. No other animals seroconverted.

- Conclusion: Cats and ferrets can be infected with SARS-CoV-2, though only cats were found to have viral RNA in their lower respiratory tracts. Cats can also transmit to other cats via droplet spread. Other animals tested (dogs, pigs, chickens, and ducks) did not have any viral RNA in their upper respiratory tracts in spite of high-dose inoculum. Cats may potentially serve as a reservoir for disease, while ferrets may function as an upper-respiratory-only animal model for SARS-CoV-2.

Wang, Xinling et al. "SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion." *Cellular & Molecular Immunology*, April 7, 2020, 1–3. <https://doi.org/10.1038/s41423-020-0424-9>.

- Lymphopenia is found in some patients with COVID-19. Lymphopenia is also a feature of MERS, which can infect T-lymphocytes and induce apoptosis (though cannot replicate within them). In this communication, the authors investigate whether SARS-CoV-2 is able to infect T-lymphocytes as well.
- They use a lentivirus pseudovirion system pseudotyped with spike proteins from SARS-CoV-1 or SARS-CoV-2. They validate it by showing these pseudovirions can infect cells expressing ACE2 but not HeLa cells, which lack it.
- They find that SARS-CoV-2 S protein allows infectivity into two T cell lines MT-2 and A3.01, in spite of extremely low levels of ACE2 RNA in these cells ($< 10^{-4}$ that of 293T/ACE2 cells). SARS-CoV-1-typed pseudovirions could not infect these cells.
- They investigate whether SARS-CoV-2 pseudovirions enter T-cells via receptor-mediated endocytosis (RME) versus entry at the cell surface. They found that EK1, an RME-inhibitor, reduced entry into T-cells but only when used at a high concentration. This implies that there is some entry by RME (blocked by EK1), and some entry by an alternative pathway.
- This was further investigated by a cell-cell fusion assay, where RME is not possible. Cells expressing spike protein on their surface were tested for cell-cell fusion with MT-2 cells. SARS-CoV-2 spike could mediate cell-cell fusion; SARS-CoV-1 spike could not.
- They finally validate their findings by using actual SARS-CoV-2 virus, which they show is able to directly infect MT-2 cells (though at a low level only). Post-infection, the amount of viral RNA in the supernatant never increased, indicating that—while SARS-CoV-2 could infect MT-2 cells—it could not replicate within them.
- Limitations: Based on these investigations, the authors propose that SARS-CoV-2 might use an alternate receptor to infect T-cells; evidence from another paper suggests that CD147 may play a role. However, the systems used here are artificial and may not correspond with what is happening *in vivo*. The spike protein from SARS-CoV-2 is more easily triggered for fusion than that of SARS-CoV-1, and that easy-triggering by the very low-levels of ACE2 on T-cells could be an alternate explanation for the results seen here. This discrepancy could be resolved by repeating these assays with different T-cell lines that are completely devoid of ACE2, and thus lack any trigger from the known SARS-CoV-2 receptor. Additionally, *in vivo* relevance could be assessed by isolating peripheral blood T-cells from COVID-19 patients and checking for the presence of SARS-CoV-2 RNA.
- Conclusion: The authors demonstrate that SARS-CoV-2 is able to infect T-lymphocytes in spite of only extremely low amounts of the receptor (ACE2) on these cells, and an inhibitor that would block this route of entry is only partly effective. They propose that there may be an alternate receptor besides ACE2 on human T-lymphocytes, and suggest that T-cell infection by SARS-CoV-2 may be responsible for the lymphopenia seen in COVID-19.

Pediatrics

Brought to you by: Maddie Goldstein, DO, MPH

Tagarro A, Epalza C, Santos M, et al. Screening and Severity of Coronavirus Disease 2019 (COVID-19) in Children in Madrid, Spain [published online ahead of print, 2020 Apr 8]. *JAMA Pediatr.* 2020;e201346. doi:10.1001/jamapediatrics.2020.1346

- What was known before: Only 21 of 731 children with confirmed COVID-19 (2.8%) in China had severe disease (hypoxia and oxygen saturation less than 92%) or critical disease.
- 365 children were screened from 3/2 to 3/16 by pediatricians in 30 secondary and tertiary hospitals in Madrid, Spain, during the first 2 weeks of the epidemic
- 41 of 365 patients (11.2%) had positive test results
 - By 3/16, 41 of the 4,695 confirmed cases (0.8%) in Madrid region were children younger than 18 years old
 - Median age of the tested patients was 3yo; median age of the patients with positive results was 1yo
 - Of the 41 positive cases: 25 (60%) were hospitalized; 4 (9.7%) required PICU; 4 (9.7%) required respiratory support other than nasal cannula
- Conclusion: Infections in children occur early in COVID-19 epidemics. Less than 1% of confirmed cases were children younger than 18yo, consistent with other epidemiological studies of COVID-19 in children, however they can have severe/critical illness.
- Limitations: Testing may have been biased to moderate to severe patients. Unknown sensitivity of the RT-PCR SARS-CoV-2 test.

Bioethics/Medical Humanities

Brought to you by: Jane Yoon, MD

Emanuel, Ezekiel J. et al. "Fair Allocation of Scarce Medical Resources in the Time of Covid-19." *New England Journal of Medicine*, March 23, 2020. <https://doi.org/10.1056/NEJMs2005114>.

- The COVID-19 pandemic is rapidly overwhelming health care systems and has created supply/demand imbalances in multiple countries – *how can we ration resources fairly?*
- General ethical principles for fair allocation of resources: (1) maximize benefits produced by scarce resources, (2) treat people equally, (3) promote and reward instrumental value, and (4) give priority to the worst off.
- **COVID-19 pandemic-specific recommendations:**
 1. Maximize benefits – aim to save the most lives or save the most life-years (maximize prognosis).
 2. Prioritize health care workers – essential supplies and equipment, diagnostics, therapeutics, and vaccines should go first to front-line HCWs because of their instrumental value in the pandemic response.
 3. Do not allocate on a first-come, first-served basis – for patients with similar prognoses, consider random selection (i.e., lottery).

4. Be responsive to evidence – allocation guidelines should differ by intervention based on scientific evidence (i.e., vaccine priority for elderly, higher-risk individuals; ventilator priority for younger, healthier patients with a better prognosis).
 5. Recognize research participation – those who participate in COVID-19 research should be rewarded by receiving priority for COVID-19 interventions.
 6. Apply the same principles to COVID-19 and non-COVID-19 patients – prioritize the value of maximizing benefits across all patients who need resources.
- **Conclusion:** Based on the above recommendations, consistent and transparent prioritization guidelines and allocation procedures should be developed in order to ensure the public’s trust and to decrease clinicians’ burden of decision-making.

Gostin, Lawrence O., Eric A. Friedman, and Sarah A. Wetter. “Responding to COVID-19: How to Navigate a Public Health Emergency Legally and Ethically.” *Hastings Center Report* n/a, no. n/a. Accessed April 15, 2020. <https://doi.org/10.1002/hast.1090>.

- Access to the Health System: Vulnerable populations include uninsured / underinsured persons, immigrants, refugees, and the homeless. Free testing and care, language services, enforcement-free zones for undocumented immigrants, and access to hygiene should be provided in health facilities.
- Ethical Physical Distancing: While people should adhere to mandates for social distancing, governments also need to ensure that their essential needs (food/water, housing, medicine) are met. Particularly in settings such as prisons, homeless shelters, and nursing homes, appropriate medical care, sanitary facilities, and hygiene should be available. For prisons, compassionate release programs, prisoner release with electronic monitoring, and reduction of arrests should be considered. For the homeless population, hotels and emergency shelters should be provided by the government.
- Isolation, Quarantine, Cordon Sanitaire, and Physical Distancing: In order to balance public health and civil liberties, governments should employ the least restrictive means necessary to protect public health. People under isolation, quarantine, or cordon sanitaire orders must be provided a safe environment with provision of essential needs. Voluntary compliance through self-isolation and self-quarantine are preferable to government containment orders.
- **Conclusion:** “We are only as safe as the most vulnerable among us – both in the United States and globally. Equity and public health go hand in hand... If we want to safeguard the public’s health while being faithful to our most fundamental values, then we must ensure that our response is effective, ethical, and equitable.”

Note: Only specific sections from this article were covered for brevity.

Lai, Jianbo et al. “Factors Associated With Mental Health Outcomes Among Health Care Workers Exposed to Coronavirus Disease 2019.” *JAMA Network Open* 3, no. 3 (March 2, 2020): e203976–e203976. <https://doi.org/10.1001/jamanetworkopen.2020.3976>.

- Region-stratified, cross-sectional survey of 1257 HCWs in 34 hospitals in China from Jan 29, 2020 - Feb 3, 2020 to evaluate mental health outcomes in the COVID-19 pandemic.
 - 39.2% physicians, 60.8% nurses, 76.7% women, 64.7% aged 26-40 years, 41.5% front-line health care workers, 60.5% worked in Wuhan.
- Degree of symptoms (including depression, anxiety, insomnia, and distress) was assessed using questionnaires and measurement tools; factors associated with mental health outcomes were identified using multivariable logistic regression analysis.
 - 50.4% reported depression, 44.6% anxiety, 34% insomnia, and 71.5% distress.

- **Conclusion:** Front-line HCWs, nurses, women, and those working in Wuhan reported more severe degrees of symptoms (all with statistical significance). Long-term follow-up of psychological effects in this population would be worth investigating. Immediate implementation of interventions that promote and address mental health of HCWs during the COVID-19 pandemic is necessary.

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!