2020-04-13

It's chamber music for Monday! Here is the Beaux Arts Trio playing Schubert's sublime trio in e flat: https://www.youtube.com/watch?v=6v8omgNS4Iw I have a great fondness for this group as they premiered their tour recital for free at Indiana University every year when I was in grad school. The pianist, Menachem Pressler, is still on the faculty at the school of music at the young age of 97! I remember when the IU opera house opened in 1973. The hall was consecrated with a performance of Beethoven's 9th symphony. It was open seating and I ended up sitting right next to Professor Pressler who enjoyed the performance just as much as I did. Trivia moment for you filmophiles: the slow movement was prominently featured in Stanley Kubrick's mediocre (IMO) film 'Barry Lyndon.' Kubrick made another mistake in picking a piece of music written almost 100 years after the time period of the film. [**note: see what kind of good stuff you get to read and listen to from this newsletter!**]

Still skeptical about the need to mask up? Here is a nice evidence-based review as to why you should: https://www.preprints.org/manuscript/202004.0203/v1 "Reducing disease spread requires two things: first, limit contacts of infected individuals via physical distancing and contact tracing with appropriate quarantine, and second, reduce the transmission probability per contact by wearing masks in public, among other measures. The preponderance of evidence indicates that mask wearing reduces the transmissibility per contact by reducing transmission of infected droplets in both laboratory and clinical contexts. Public mask wearing is most effective at stopping spread of the virus when compliance is high. The decreased transmissibility could substantially reduce the death toll and economic impact while the cost of the intervention is low. Thus we recommend the adoption of public cloth mask wearing, as an effective form of source control, in conjunction with existing hygiene, distancing, and contact tracing strategies. We recommend that public officials and governments strongly encourage the use of widespread face masks in public, including the use of appropriate regulation." [**I've been supporting the mask making industry, purchasing a variety of designer masks from all over. Let's help small businesses who are creatively re-purposing.**]

MODELING

- Here is an interesting case study of a small town in Germany that had a large cluster of SARS-CoV-2 infections: https://www.land.nrw/sites/default/files/asset/document/zwischenergebnis_covid19_case_study_gangelt_en.pdf A current immunity of approx.14% (anti SARS-CoV2 IgG positive, specificity of the method >.99%) was determined. Around 2% of individuals exhibited a current SARS-CoV2 infection identified via PCR method. The infection rate (current or past infection) was approx. 15%. The lethality (case fatality rate) based on the total number of infected individuals in the municipality of Gangelt is, with the preliminary data from this study, approx. 0.37%. The current lethality in Germany calculated by Johns Hopkins University is 1.98%, and is thus five times higher. The mortality based on the total population in Gangelt currently amounts to 0.06%. [**note: Hey US policy people, when are we going to do serology testing at scale to figure out stuff like this?**]

NEWLY REGISTERED CLINICAL TRIALS

- Here's a new approach, potato starch!!! I use it for baking during Passover so maybe I'll continue to keep using it. This study is a multicenter randomized trial to evaluate the efficacy of resistant potato starch in reducing rates of hospitalization and improving time to clinical recovery in currently unhospitalized COVID-19 positive patients. Resistant potato starch (RPS) has been shown to decrease IL-6 in humans, partly through its ability to increase butyrate levels. Butyrate not only reduces IL-6 production and overall inflammation, but also has been shown to specifically decrease lung inflammation in animal models through cytokine suppression. Further, it may reduce ACE2 receptor expression, which is the main entry mechanism for COVID-19 into epithelial lung cells. Increased butyrate in the intestinal microbiome is also associated with less viral lower respiratory tract infections in allo- HCT recipients. Our preliminary data shows an increase in butyrate levels in participants' stool within one week of RPS therapy (20 grams twice daily) with no noticeable side effect. To this end, we have designed a multicenter randomized clinical trial to determine the efficacy of resistant potato starch in reducing the need for hospitalization for COVID-19 positive patients. We will enroll 1300 unhospitalized COVID-19 positive individuals who are being monitored in the outpatient setting. Patients will be randomized to either receive RPS therapy (2 tablespoons (~ 20 grams) of RPS twice daily) or a placebo (2 tablespoons of non-resistant, digestible starch twice daily) , each for 14 days. Our primary outcome is the rate of hospitalization for COVID-19 related complications. Secondary outcomes will look at time to recovery and symptom severity scores. [**note: I just checked and Bob's Red Mill still has this in stock so place your orders right now!!! Unfortunately, they are still out of dark rye flour and I need some for bread baking!!! When will we see a psyllium fiber trial?**] NCT04342689

- A Paris group is going to look at the safety and efficacy of nivolumap, an anti-cancer treatment. It appears interesting to use nivolumab in severe patients infected with SARS-CoV-2 requiring hospitalization in conventional unit or in ICU. [**note: this is from the CT brief summary and I'm unsure of what scientific foundation there is. Can Merck be far behind in setting up a Keytruda study?**] NCT04343144

- *Channeling Linus Pauling, we want to see your Vitamin C work ASAP.* The esteemed Cleveland Clinic is setting up a Vitamin C & zinc trial. We aim to see whether ascorbic acid and zinc gluconate which has limited side effect profile and is readily available over the counter can decrease the duration of symptoms seen in patients with new diagnosis of COVID-2019. A secondary purpose is to see whether Zinc and/or Ascorbic acid supplementation can prevent progression of the severe manifestations of the disease including development of dyspnea and acute respiratory distress syndrome which may require hospitalization, mechanical ventilation, and or lead to death. This is a single-center, prospective, randomized study which plans to enroll 520 patients with a principal diagnosis of COVID-2019, managed in an outpatient setting, who presented after being sent by a healthcare provider to get tested and receive a PCR (Polymerase Chain Reaction) -assay based confirmed diagnosis of the disease. All patients who agree to participate in the study will answer a baseline questionnaire about their symptoms at the time of inclusion. Patients will then be randomized to one of 4 study arms. Patients in Arm A (n=130) will receive vitamin C (to be taken divided over 2-3 times a day with meals), patients in Arm B (n=130) will receive zinc gluconate to be taken at bedtime, patients in Arm C (n=130) will receive both vitamin C (to be taken divided over 2-3 times a day with meals) and zinc gluconate (taken at bedtime). Patients in arms A, B and C will take study supplements daily for 10 days. Patients in Arm D (n=130) will not receive any of the study medications and continue on standard of care. Patients will then track their symptoms daily from day 0 to day 28 answering 4 basic

questions on illness severity. They will stop filling out their daily questions once they reach 0 for all categories or they reach the end of the 28 day study period. Study team members will call patients at days 7, 14, 21, and 28 of the study period to assess need for hospitalization, ER visit, or additional medications prescribed by a healthcare provider, and any side effects from the supplements that the patient could have experienced. [**note: There are a smattering of Vitamin C trials going on. I'm already doing a extremely small clinical trial exploring this. I take a proprietary mixture of Vitamin C, Zn, Cu and a couple of plant compounds for eye health. I'm not telling you the brand name as I need to make sure I have enough to finish the trial!!**] NCT04342728

CLINICAL TRIAL RESULTS

- Nothing new, probably because of the holiday weekend. Let's hope we begin to see the hydroxychloroquine and remdesivir trial data soon.

DRUG DEVELOPMENT

- Using DNA/RNA snippets as drug therapies have been tried on and off for some years. I think there has only been on such approach approved in the US. Here is an interesting paper from Bangladesh [**note: first paper from that country that I've read!**] Surface glycoprotein and nucleocapsid phosphoprotein are two important proteins of this virus facilitating its entry into host cell and genome replication. Small interfering RNA (siRNA) is a prospective tool of the RNA interference (RNAi) pathway for the control of human viral infections by suppressing viral gene expression through hybridization and neutralization of target complementary mRNA. So, in this study, the power of RNA interference technology was harnessed to develop siRNA molecules against specific target genes namely, nucleocapsid phosphoprotein gene and surface glycoprotein gene. Conserved sequence from 139 SARS-CoV-2 strains from around the globe was collected to construct 78 siRNA that can inactivate nucleocapsid phosphoprotein and surface glycoprotein genes. Finally, through a rigorous filtering process 8 siRNA molecules were selected with exerts the best action. These predicted siRNAs should effectively silence the genes of SARS-CoV-2 during siRNA mediated treatment assisting in the response against SARS-CoV-2. [**note: there is an obvious drug delivery issue here but congrats for thinking of this**] https://www.biorxiv.org/content/10.1101/2020.04.10.036335v1

DIAGNOSTIC DEVELOPMENT

- Here is a nice news clip from NBC news on how some states are beginning to use serology testing: https://www.nbcnews.com/health/health-news/los-angeles-county-launches-large-scale-covid-19-antibody-study-n1182031 looking at the video clip it appears they are all using finger prick tests that have not received an FDA-EUA. For me this is OK as the States are being proactive and will come up with their own approaches to figuring out the base rate of infection.
- Here is a cautionary tale about one widely publicized effort that ran into problems: https://www.fiercebiotech.com/medtech/colorado-ski-community-planned-to-test-everyone-

for-covid-19 [**note: any company claiming their test has 100% sensitivity & specificity must be viewed with a dash of skepticism.**]

- Great thinking outside the box from a Berkeley CA group who established a pop-up SARS-CoV-2 testing lab. Effective public health measures require extensive, accurate, and rapid testing to determine infection rates. Here we describe the strategy we used to establish a CLIA-licensed clinical laboratory to perform a validated Laboratory-Developed Test (LDT) for SARS-CoV-2 in Berkeley, California and the surrounding Bay Area community. Our procedures for implementing the technical, regulatory, and data management workstreams necessary for clinical sample processing provide a roadmap to aid others in setting up similar testing centers. [**note: more creative thinking is needed to get lots of people tested**]
  https://www.medrxiv.org/content/10.1101/2020.04.11.20061424v1

>>

2020-04-14

There are some pieces of music that upon first hearing, remain indelibly in one's mind. So it was when Stan Getz and Joao Gilberto released their album of Bossa Nova music in 1964. The main track, 'The Girl from Ipanema,' was a major hit on the radio but it was the 'B' side of the 45 release, 'Corcovado,' that I liked and continue to enjoy today. The album made a star of Astrud Gilberto, then Joao's wife, who was and remained a singer with a whispery naïve voice. I learned the Portuguese words and it was my favorite lullaby that helped get both my daughters to sleep. Here is a nice version from the Brazilian singer, Gal Costa: https://www.youtube.com/watch?v=ReE4jDvJVLw

On my morning walk yesterday, I listened to a very good interview with former FDA Commissioner, Scott Gotlieb, on the Ezra Klein show: https://www.vox.com/ezra-klein-show-podcast It's maybe 40 minutes long and Scott gives a very cogent explanation of what is needed, largely based on the AEI papers:

https://www.aei.org/research-products/report/a-national-covid-19-surveillance-system-achieving-containment/

https://www.aei.org/research-products/report/national-coronavirus-response-a-road-map-to-reopening/

There are a number of papers describing mutations in SARS-CoV-2 but this is expected. I have not seen one that talks of a mutation that might alter immunogenicity of the coat structure. Gottlieb discusses drug therapy in the talk and it pretty much is in accord with my thinking. We will certainly know if remdesivir works but that is an IV drug and maybe only useful in people who are at risk of disease progression. Ideally, an oral drug that can be given right after infection such as oseltamivir would be most useful but with all the chloroquine trials drowning things out, that might not be possible. I also think we will have some monoclonal antibody therapy(s) but the summer. What cohort of patients they help needs to be defined. Also, can they be formulated as an auto-injectable (monthly or every two months dosing) that could protect healthcare workers, first responders, etc.? that would be good progress.

Will omeprazole start flying off the shelves? - https://blogs.sciencemag.org/pipeline/archives/2020/04/13/omeprazole-as-an-additive-for-coronavirus-therapy

Good news on the vaccine front as GSK and Sanofi are joining forces: https://www.fiercepharma.com/vaccines/sanofi-gsk-tie-up-for-covid-19-vaccine-work-eyes-possible-2021-rollout Like J&J they have the capability of producing vaccine at scale.

MODELING

- Here is 'The 538' on pandemic modeling: https://fivethirtyeight.com/features/a-comic-strip-tour-of-the-wild-world-of-pandemic-modeling/ and to sum this up here is a bonus music track: https://www.youtube.com/watch?v=SaV-6qerkqI
- The Diamond Princess cruise ship has been identified as an epidemiological model for wider spread dissemination of SARS-CoV-2. Here is an interesting model of transmission routes of the virus on the ship. We collected the daily number of 197 symptomatic cases, and that of the 146 passenger cases in two categories, i.e. those who stayed and did not stay in the same stateroom. We retrieved the quarantine details and the ship's 14-day itinerary. We searched the websites of national/local health authority along the cruise routes and local news using Google for locally confirmed cases associated with the ship. We obtained the design of air conditioning and sewage treatment of the ship from literature. We back-calculated the dates of infection from the epidemic curve and compared with the start of on-board quarantine. Results: Major infections started on Jan 28 and completed by Feb 6 for passengers except those who stayed in the same stateroom with infected individual(s). No other confirmed cases were identified among the disembarked people in Hong Kong except an 80 years old passenger. No confirmed cases were reported in three other stopovers between Jan 27-31 associated with disembarked passengers or visitors from the ship, however two Okinawa taxi drivers became confirmed cases in association with driving the ship passengers. Infection among passengers after Feb 6 was limited to those who stayed in the same stateroom with an infected passenger. Infections in crew members peaked on Feb 7, suggesting significant transmission among crew members after quarantine on Feb 5. Conclusions: *We infer that the ship central air conditioning system did not play a role, i.e. the long-range airborne route was absent in the outbreak*. Most transmission appears to have occurred through close contact and fomites. [**note: I am a firm believer in 'mask up' but when I make by weekly trip to the grocery store and feel the wafting breeze of the HVAC system, I wonder about transmission of the virus via that route. I suspect it is minimal and this paper makes me feel a little better.**]
  https://www.medrxiv.org/content/10.1101/2020.04.09.20059113v1

NEWLY REGISTERED CLINICAL TRIALS

- Australia is launching a trial to see if BCG vaccination of health care workers offers some protection. 4000 to be enrolled. https://www.clinicaltrialsarena.com/news/australia-bcg-vaccine-trial-covid-19/
- Not a trial per se, but a protocol for systematic review and meta-analysis of randomized controlled trials of remdesivir from Ethiopian researchers. I'm not sure that his is worthwhile as we will likely get the results of controlled trials in before this study can be completed. https://www.medrxiv.org/content/10.1101/2020.04.09.20059196v1

- In addition to about a 1000 more hydroxychloroquine trials [**note: just joking but there are a bunch more that were just registered.**], here is a small trial from Columbia that is looking at the effectiveness of oral chlorine dioxide in the treatment of SARS-CoV-2. The objective of this study is to review, through prospective case research, the efficacy of oral chlorine dioxide in the treatment of patients with COVID infection 19. The research will be carried out between April and June 2020 with a quasi-experimental design in two health care centers on a sample of twenty (20) patients, through direct intervention, who will measure the changes in the manifest symptoms of infection and negativity. a COVID 19 after administration of the study preparation, to determine the effectiveness of chlorine dioxide in the treated group. Based on the results that are found and on the evaluation of efficacy on the basis of clinical improvement on a scale of 1 to 5, and of the negativization of COVID 19, we can conclude whether the therapeutic efficacy in this investigation is considered good by verifying whether or not there is efficacy of treatment with chlorine dioxide in COVID 19. [**note: do NOT rush to your handy bottle of Clorox bleach and try this at home!!! I'm a Clorox shareholder and do not want to see the company sued.**] NCT04343742
- We desperately need something for the prophylaxis of SARS-CoV-2, particularly in long term care facilities where much of the mortality is observed. Will nitazoxanide solve this? This trial will find out. 600mg BID for six weeks. NCT04343248

- Eli Lilly jumps into the fray! Here is a study of LY3127804, LY3127804, an investigational selective monoclonal antibody against Angiopoietin 2 (Ang2), to Phase II testing in pneumonia patients hospitalised with COVID-19 who are at a higher risk of progressing to acute respiratory distress syndrome (ARDS). Ang2 is known to be elevated in ARDS patients and Lilly will test whether inhibiting the effects of Ang2 with a monoclonal antibody can reduce the progression to ARDS or the need for mechanical ventilation in COVID-19 patients. NCT04342897
- A small Egyptian trial looking at enalapril and captopril against chloroquine has been registered. NCT04345406

CLINICAL TRIAL RESULTS

- More research from Wuhan on the early diagnosis of SARS-CoV-2. Although the real-time RT-PCR detection of the virus nucleic acid is the current golden diagnostic standard, it has high false negative rate when only apply single test. Objective Summarize the baseline characteristics and laboratory examination results of hospitalized COVID-19 patients. Analyze the factors that could interfere with the early diagnosis quantitatively to support the timely confirmation of the disease. Methods All suspected patients with COVID-19 were included in our study until Feb 9th, 2020. The last day of follow-up was Mar 20th, 2020. Throat swab real-time RT-PCR test was used

to confirm SARS-CoV-2 infection. The difference between the epidemiological profile and first laboratory examination results of COVID-19 patients and non-COVID-19 patients were compared and analyzed by multiple logistic regression. Receiver operating characteristic (ROC) curve and area under curve (AUC) were used to assess the potential diagnostic value in factors, which had statistical differences in regression analysis. Results In total, 315 hospitalized patients were included. Among them, 108 were confirmed as COVID-19 patients and 207 were non-COVID-19 patients. Two groups of patients have significance in comparing age, contact history, leukocyte count, lymphocyte count, C-reactive protein, erythrocyte sedimentation rate ($p<0.10$). Multiple logistic regression analysis showed age, contact history and decreasing lymphocyte count could be used as individual factor that has diagnostic value ($p<0.05$). The AUC of first RT-PCR test was 0.84 (95% CI 0.73-0.89), AUC of cumulative two times of RT-PCR tests was 0.92 (95% CI 0.88-0.96) and 0.96 (95% CI 0.93-0.99) for cumulative three times of RT-PCR tests. Ninety-six patients showed typical pneumonia radiological features in first CT scan, AUC was 0.74 (95% CI 0.60-0.73). The AUC of patients age, contact history with confirmed people and the decreased lymphocytes were 0.66 (95% CI 0.60-0.73), 0.67 (95% CI 0.61-0.73), 0.62 (95% CI 0.56-0.69), respectively. Taking chest CT scan diagnosis together with patients age and decreasing lymphocytes, AUC would be 0.86 (95% CI 0.82-0.90). The age threshold to predict COVID-19 was 41.5 years, with a diagnostic sensitivity of 0.70 (95% CI 0.61-0.79) and a specificity of 0.59 (95% CI 0.52-0.66). Positive and negative likelihood ratios were 1.71 and 0.50, respectively. Threshold of lymphocyte count to diagnose COVID-19 was 1.53x109/L, with a diagnostic sensitivity of 0.82 (95% CI 0.73-0.88) and a specificity of 0.50 (95% CI 0.43-0.57). Positive and negative likelihood ratios were 1.64 and 0.37, respectively. Conclusion Single RT-PCR test has relatively high false negative rate. When first RT-PCR test show negative result in suspected patients, the chest CT scan, contact history, age and lymphocyte count should be used combinedly to assess the possibility of SARS-CoV-2 infection. (**note: I wonder if the RT-PCR test protocol has improved since these patients were initially diagnosed. It is difficult to get data on the % false negatives.**] https://www.medrxiv.org/content/10.1101/2020.04.09.20059352v1

- It looks like we better add calcium channel blockers to the hydroxychloroquine cocktail!!! Chinese researchers show report that calcium channel blockers (CCBs), a type of anti-hypertension drugs that are widely used in the clinics, can significantly inhibit the post-entry replication events of SARS-CoV-2 in vitro. Comparison with two other major types of anti-hypertension drugs, the angiotensin converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB), showed that only CCBs display significant anti-SARS-CoV-2 efficacy. Combined treatment with chloroquine and CCBs significantly enhanced the anti-SARS-CoV-2 efficacy. Retrospective clinical investigation of COVID-19 patients revealed that the CCB amlodipine besylate administration distinctly reduced the case fatality rate of patients with hypertension. Results from this study suggest that CCB administration for COVID-19 patients with hypertension as the comorbidity might improve the disease outcome. https://www.medrxiv.org/content/10.1101/2020.04.08.20047134v1
- Maybe the Governor of South Dakota should call for social distancing rather than ask for hydroxychloroquine to address the big outbreak in Sioux City. Hydroxychloroquine (HCQ) has received worldwide attention because of positive results from small studies. Methods We used data collected from routine care of all adults in 4 French hospitals with documented SARS-CoV-2 pneumonia and requiring oxygen ≥ 2 L/min to emulate a target trial aimed at assessing the

effectiveness of HCQ at 600 mg/day. The composite primary endpoint was transfer to intensive care unit (ICU) within 7 days from inclusion and/or death from any cause. Analyses were adjusted for confounding factors by inverse probability of treatment weighting. Results This study included 181 patients with SARS-CoV-2 pneumonia; 84 received HCQ within 48 hours of admission (HCQ group) and 97 did not (no-HCQ group). Initial severity was well balanced between the groups. In the weighted analysis, 20.2% patients in the HCQ group were transferred to the ICU or died within 7 days vs 22.1% in the no-HCQ group (16 vs 21 events, relative risk [RR] 0.91, 95% CI 0.47-1.80). In the HCQ group, 2.8% of the patients died within 7 days vs 4.6% in the no-HCQ group (3 vs 4 events, RR 0.61, 95% CI 0.13-2.89), and 27.4% and 24.1%, respectively, developed acute respiratory distress syndrome within 7 days (24 vs 23 events, RR 1.14, 95% CI 0.65-2.00). Eight patients receiving HCQ (9.5%) experienced electrocardiogram modifications requiring HCQ discontinuation. Interpretation *These results do not support the use of HCQ in patients hospitalised for documented SARS-CoV-2-positive hypoxic pneumonia.* [**Looks like this is a continuation of the fight between French researchers in Paris vs. those in Marseilles. I am sure this is not the last word in this fight.**] https://www.medrxiv.org/content/10.1101/2020.04.10.20060699v1

- Note a clinical result but an interesting conjecture nonetheless. We used a number of bioinformatics tools to computationally characterize ACE2 by determining its cell-specific expression, putative functions, and transcriptional regulation. The small intestine expressed higher levels of ACE2 than any other organ. The large intestine, kidney and testis showed moderate signals, whereas the signal was weak in the lung specimens. Single cell RNA-Seq data indicated positive signals along the respiratory tract in the key protective cell types including the goblet and ciliary epithelial cells, as well as in the endothelial cells and type I pneumocytes. Gene ontology analysis suggested that, besides its classical role in renin-angiotensin system, ACE2 may be functionally associated with angiogenesis/blood vessel morphogenesis. A novel tool for the prediction of transcription factor binding sites identified several putative sites for determined transcription factors within the ACE2 gene promoter. Our results also confirmed that age and gender play no significant role in the regulation of ACE2 mRNA expression in the lung. https://www.biorxiv.org/content/10.1101/2020.04.13.038752v1

DRUG DEVELOPMENT

- This nice paper from the Fred Hutchinson Research Center in Seattle addresses peak virus population and optimal dosing of an antiviral (**whenever we get one!!**). We therefore developed a mathematical model which allows projection of all possible therapeutic approaches. Our model recapitulates off-treatment viral dynamics and predicts a three-phase immune response. Addition of treatment with remdesivir, hydroxychloroquine, neutralizing antibodies or cellular immunotherapy demonstrates that if in vivo drug potency is high, then rapid elimination of virus is possible. Potent therapies dosed soon after peak viral load when infected people typically develop symptoms, are predicted to decrease shedding duration and intensity of the effector immune response, but to have little effect on viral area under the curve, which is driven by high levels of early SARS CoV-2 replication. Potent therapy dosed prior to peak viral load, when infection is usually pre-symptomatic, is predicted to be the only option to lower viral area under the curve. We also identify that clinically meaningful drug resistance is

less likely to emerge with a highly potent agent that is dosed after peak viral load. Our results support an early test and treat approach for COVID-19, but also demonstrate the need to identify early viral shedding kinetic features that are the most predictive surrogates of clinical severity and transmission risk. [**trivia question and prize offering just to see if you are reading my comments. First person to correctly identify Fred Hutchinson without using Google (we are on the honor system here!) will get a nice prize from me. Put on your thinking caps.**] https://www.medrxiv.org/content/10.1101/2020.04.10.20061325v1

DIAGNOSTIC DEVELOPMENT

- Here is an interesting paper looking at using simple blood exams and artificial intelligence to screen for SARS-CoV-2. The authors note that this is applicable to countries who may lack access to current diagnostic test kits. In this Case-control quantitative study, we developed a strategy backed by artificial intelligence to perform an initial screening of suspect COVID-19 cases. We developed a machine learning classifier that takes widely available simple blood exams as input and predicts if that suspect case is likely to be positive (having SARS-CoV-2) or negative(not having SARS-CoV-2). Based on this initial classification, positive cases can be referred for further highly sensitive testing (e.g. CT scan, or specific antibodies). We used publicly available data from the Albert Einstein Hospital in Brazil from 5,644 patients. Focussing on using simple blood exams, a sample of 599 subjects that had the fewest missing values for 16 common exams were selected. From these 599 patients, only 81 were positive for SARS-CoV-2 (determined by RT-PCR). Based on this data, we built an artificial intelligence classification framework, ER-CoV, aiming at determining which patients were more likely to be negative for SARS-CoV-2 when visiting an ER and that were categorized as a suspect case by medical professionals. The primary goal of this investigation is to develop a classifier with high specificity and high negative predictive values, with reasonable sensitivity. Findings: We identified that our framework achieved an average specificity of 92.16% [95% CI 91.73 - 92.59] and negative predictive value (NPV) of 95.29% [95% CI 94.65% - 95.90%]. Those values are completely aligned with our goal of providing an effective low-cost system to triage suspected patients at ERs. As for sensitivity, our model achieved an average of 63.98% [95% CI 59.82% - 67.50%] and positive predictive value (PPV) of 48.00% [95% CI 44.88% - 51.56%]. An error analysis identified that, on average, 45% of the false negative results would have been hospitalized anyway, thus the model is making mistakes for severe cases that would not be overlooked, partially mitigating the fact that the test is not high-sensitive. All code for our AI model, called ER-CoV is publicly available at https://github.com/soares-f/ER-CoV. Interpretation: Based on the capacity of our model to accurately predict which cases are negative from suspected patients arriving at emergency rooms, we envision that this framework can play an important role in patient triage. Probably the most important outcome is related to testing availability, which at this point is extremely low in many countries. Considering the achieved specificity, we would reduce by at least 90% the number of SARS-CoV-2 tests performed at emergency rooms, with the chance of getting a false negative at around 5%. The second important outcome is related to patient management in hospitals. Patients predicted as positive by our framework could be immediately separated from the other patients while waiting for the results of confirmatory tests. This could reduce the spread rate inside hospitals since in many hospitals all suspected cases are kept in the same

ward. In Brazil, where the data was collected, rate infection is starting to quickly spread, the lead time of a SARS-CoV-2 can be up to 2 weeks [**note: good outside the box thinking**] https://www.medrxiv.org/content/10.1101/2020.04.10.20061036v1

- Here is an approach to large scale testing. Pooling of samples can increase lab capacity when using Polymerase chain reaction (PCR) to detect infections such as COVID-19. However, pool testing is typically performed via an adaptive testing strategy which requires a feedback loop in the lab and at least two PCR runs to confirm positive results. This can cost precious time. We discuss a non-adaptive testing method where each sample is distributed in a prescribed manner over several pools, and which yields reliable results after one round of testing. More precisely, assuming knowledge about the overall infection incidence rate, we calculate explicit error bounds on the number of false positives which scale very favourably with pool size and sample multiplicity. This allows for hugely streamlined PCR testing and cuts in detection times for a large-scale testing scenario. A viable consequence of this method could be real-time screening of entire communities, frontline healthcare workers and *international flight passengers*, for example, using the PCR machines currently in operation. [**note: we obviously cancelled our trip to Milan that was set for next month but hope to go next spring; figure this testing protocol out!!**] https://www.biorxiv.org/content/10.1101/2020.04.06.028431v1
- I didn't see a post on the FDA website but here is a protocol for saliva collection and RT-PCR testing. It's certainly more convenient than swabs: https://www.fiercebiotech.com/medtech/rutgers-saliva-based-test-nets-fda-greenlight-for-covid-19

>>

2020-04-15

It's always fun when you find a piece of music that is new and doubly fun when it's a chamber music piece with stings and wind instruments. Here is Dutch violinist Janine Janssen and friends with the Beethoven Septet in E major: https://www.youtube.com/watch?v=LQ5vciYlfk8 I sent the link on to my bassoonist daughter who is a music therapist at UCSF's Children's Hospital. Here response back, "OMG, I played this piece in a small chamber group several years ago and it was a wonderful experience." Unfortunately, no recording of that performance is available.

Of course I follow celebrities! My news feed yesterday sent me a story of Rita Wilson's unfortunate experience with chloroquine after she and hubby Tom Hanks contracted SARS-CoV-2 in Australia. Yes, the drug is not for everybody and we still don't know if it works: https://www.yahoo.com/entertainment/rita-wilson-says-she-had-extreme-side-effects-from-controversial-drug-chloroquine-during-covid-19-treatment-155151909.html

MODELING

- I've not been posting much modeling lately but this one warrants a highlight. Sweden has taken a different approach from neighboring countries, keeping lots of things open. Here is a paper from Swedish researchers on the impact of different scenarios on the health care system. In recent days there has been an increase in case load and mortality compared to Denmark and

Norway. One wonders whether the Swedes will change things. Setting: Sweden Participants: A model to simulate all 10.09 million Swedish residents. Interventions: 5 different non-pharmaceutical public-health interventions including the mitigation strategy of the Swedish government as of 10 April; isolation of the entire household of confirmed cases; closure of schools and non-essential businesses with or without strict social distancing; and strict social distancing with closure of schools and non-essential businesses. Main outcome measures: Estimated acute care and intensive care hospitalisations, COVID-19 attributable deaths, and infections among healthcare workers from 10 April until 29 June. Findings: Our model for Sweden shows that, under conservative epidemiological parameter estimates, the current Swedish public-health strategy will result in a peak intensive-care load in May that exceeds pre-pandemic capacity by over 40-fold, with a median mortality of 96,000 (95% CI 52,000 to 183,000). The most stringent public-health measures examined are predicted to reduce mortality by approximately three-fold. Intensive-care load at the peak could be reduced by over two-fold with a shorter period at peak pandemic capacity. Conclusions: Our results predict that, under conservative epidemiological parameter estimates, current measures in Sweden will result in at least 40-fold over-subscription of pre-pandemic Swedish intensive care capacity, with 15.8 percent of Swedish healthcare workers unable to work at the pandemic peak. Modifications to ICU admission criteria from international norms would further increase mortality. https://www.medrxiv.org/content/10.1101/2020.04.11.20062133v1

- Here is a nice time-varying mode of viral reproduction in the US. The basic reproduction number is the average number of people to whom an infected person transmits the infection when virtually all individuals in a population are susceptible. We sought to calculate the current reproduction number for COVID-19 for each state in the United States. For the entire United States, the reproduction number declined from 4.02 to 1.51 between March 17 and April 1, 2020. We also found that the reproduction number for COVID-19 has declined in most states over the past two weeks which suggests that social isolation measures may be having a beneficial effect. https://www.medrxiv.org/content/10.1101/2020.04.10.20060863v1

NEWLY REGISTERED CLINICAL TRIALS

- I don't know what to make of this one. A South Korean pharma company is going to try a Hep B antiviral clevudine to see if it works against SARS-CoV-2. HOWEVER, it appears that this is a non-controlled trial with a parallel assignment of patients to hydroxychloroquine therapy (it's really not clear from the description). [**note: I guess hydroxychloroquine might be considered placebo therapy based on information to date.**] NCT04347915
- AstraZeneca are launching a trial of acalabrutinib to test efficacy against SARS-CoV-2. Control is best supportive care. NCT04346199

- NYU med school is launching a trial of the MAb, clazakizumab. The limited understanding of the clinical behavior of patients infected with SARS-CoV-2 (the viral organism responsible for COVID-19 disease) is evolving on a daily basis. Reports from China indicate that a subset of patients with the worst clinical outcomes may manifest cytokine storm syndrome. Hypotheses that excess cytokines may trigger a secondary hemophagocytic lymphhistiocytosis (sHLH) have been proposed. Indeed, cytokine profiles consistent with this picture were observed in Chinese

patients with severe pulmonary involvement. Specifically, elevated ferritin and interleukin-6 (IL-6) were associated with fatalities among the infected patients. A role for targeted anti-inflammatory and anti-cytokine therapies in the treatment of pulmonary hyperinflammation has been proposed. Clazakizumab is a genetically engineered humanized IgG1 monoclonal antibody (mAb) that binds with high affinity to human IL-6. This investigational agent is currently being studied as a treatment for chronic active antibody mediated rejection of renal allografts. In this study we propose to administer clazakizumab to patients with life-threatening pulmonary failure secondary to COVID-19 disease. NCT04343989

- Maybe nasal sprays are the way to go!! Here is a Stanford study looking at povidone-iodine nasal spray. The study aims to determine the safety and efficacy of povidone-iodine (PVP-I) containing nasal sprays as compared to isotonic saline nasal sprays in COVID-19 positive patients. The primary outcome measure is SARS-CoV-2 viral titers in the nasal cavity and nasopharynx. In vitro studies have shown PVP-I to be highly virucidal against the viruses which cause SARS and MERS. Additionally, clinical studies have shown PVP-I saline sprays to be well tolerated in human subjects. PVP-I oral rinses and sprays have been trialed as methods to reduce the incidence and symptoms of viruses which cause the "common cold." NCT04347954
- Here is a small molecule drug that has been in clinical trials for migraines via intra-nasal delivery. Vazegepant, is a small molecule calcitonin gene-related peptide receptor antagonist. The purpose of this study is to determine if a CGRP receptor antagonist may potentially blunt the severe inflammatory response at the alveolar level, delaying or reversing the path towards oxygen desaturation, ARDS, requirement for supplemental oxygenation, artificial ventilation or death in patients with COVID-19 on supplemental oxygen. NCT04346615
- I'm not sure about the scientific rationale for this trial in India. The trial is randomized, blinded, two arms, active comparator controlled, clinical trial to evaluate the safety and efficacy of Mycobacterium w in combination with standard care as per hospital practice versus standard care alone in critically ill adult patients suffering from COVID-19 infection. NCT04347174
- Another experimental monoclonal antibody trial against cytokines. This is a randomized, double-blind, placebo-controlled, multi-center trial to evaluate the safety and efficacy of TJ003234 administered as an intravenous (IV) infusion in subjects with severe COVID-19 under supportive care, and to assess the effect of TJ003234 on the levels of cytokines. NCT04341116
- STOCK UP ON BABY SHAMPOO!!! I ALREADY HAVE A BIG BOTTLE!!!! Nasal saline irrigations are a safe and commonly used mechanism to treat a variety of sinonasal diseases including sinusitis, rhinitis, and upper respiratory tract infections. When used properly, these irrigations are a safe and easy intervention available over the counter without a prescription. Additionally, baby shampoo has been found to be a safe additive functioning as a surfactant when a small amount is added to the saline rinses which may help augment clearance of the sinonasal cavity. While many systemic medications and treatments have been proposed for COVID-19, there has not yet been a study looking at targeted local intervention to the nasal cavity and nasopharynx where the viral load is the highest. Studies have shown that the use of simple over the counter nasal saline irrigations can decrease viral shedding in the setting of viral URIs, including the common coronavirus (not SARS-CoV-2). Further, as SARS-CoV-2 is an enveloped virus, mild-detergent application with nasal saline would neutralize the virus further. It is our hypothesis that nasal saline or nasal saline with baby shampoo irrigations may decrease viral shedding/viral load and viral transmission, secondary bacterial load, nasopharyngeal inflammation in patients infected

with the novel SARS-CoV-2. [**note: I wonder if J&J will seek a health claim for their baby shampoo. I'm staying long on J&J stock!**] NCT04347538

- BLD-2660 is a novel, synthetic, orally active, small molecule inhibitor of calpain (CAPN) 1, 2, and 9 that is selective over the cathepsins as well as other protease families, displays good metabolic stability and permeability, oral bioavailability and low cytochrome P450 (CYP) inhibition. It is under development for the treatment of coronavirus disease-19 (COVID-19) resulting from infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV2), where there is significant unmet medical need. [**note: This is from a small drug discovery company, Blade Therapeutics.**] NCT04334460
- Here is a Bristol-Myers Squibb trial on cancer patients. The purpose of this study is to see whether neutralizing interleukin-8 (IL-8) with BMS-986253 can help improve the health condition of cancer participants infected with COVID-19. This is the first in-human study of this investigational product specifically in cancer patients with severe COVID-19. Currently there are no FDA approved medications that improve the chance of survival in patients diagnosed with COVID-19. However there are usual treatments currently being used to help treat COVID-19 patients and BMS-986253 will be compared to these standard of care treatments in this study. NCT04347226
- Here is a Turkish study intended to evaluate the effects of commonly used diuretic, spironolactone, on oxygenation in covid-19 ARDS patients. NCT04345887

CLINICAL TRIAL RESULTS

- More interesting findings from Wuhan. Thrombocytopenia at admission was prevalent, while late phase or delayed phase thrombocytopenia is obscure. This retrospective case series analyzed patients with COVID19 at the Union Hospital, Wuhan, China, from January 25th to March 9th, 2020. Analysis began on March 11th, 2020. COVID19 associated delayed phase thrombocytopenia was occurred in 11.8% percent of enrolled patients. The delayed phase thrombocytopenia in COVID19 is prone to develop in elderly patients or patients with low lymphocyte count on admission. The delayed-phase thrombocytopenia is significantly associated with increased length of hospital stay and higher ICU admission rate. Delayed phase nadir platelet counts demonstrated a high and significantly negative linear correlation with B cell percentages and serum IL 6 levels. We also presented bone marrow aspiration pathology of three patients with delayed phase thrombocytopenia, showing impaired maturation of megakaryocytes. We speculated that the delayed phase platelet destruction might be mediated by antibodies, and suggest immunoregulatory treatment in severe patients to improve outcomes. Besides, clinicians need to pay attention to the delayed phase thrombocytopenia especially at 3 to 4 weeks after symptom onset.
  https://www.medrxiv.org/content/10.1101/2020.04.11.20059170v1
- Intravenous immunoglobulin therapy may only help the most critically ill patients. The purpose of this study is to determine the clinical efficacy of intravenous immunoglobulin (IVIG) therapy on COVID-19. Methods In this multicenter retrospective cohort study, adult critical COVID-19 patients (including severe type and critical type, according to the clinical classification defined by National Health Commission of China) in 8 government designated treatment center in China

from Dec 23, 2019 to Mar 31, 2020 were enrolled. Demographic, clinical, treatment, and laboratory data, prognosis were extracted from electronic medical records, and IVIG was exposure factor. Primary outcomes were the 28 days and 60 days mortality, and secondary outcomes were the total length of in-hospital and the total duration of the disease. Meanwhile, the parameters of inflammation response and organ function were detected. The risk factors were determined by COX proportional hazards model. The subgroup analysis was carried out according to clinical classification of COVID-19, IVIG dosage and timing. Findings 325patients were included in this study, of whom 222 (68%) were severe type, 103 (32%) were critical type. 42 (13%) died in 28 days within hospitalization, total 54 (17%) died in 60 days, and 6 (3%) died in severe type, 48 (47%) died in critical type. 174 cases were used IVIG, and 151 cases were not. Compared with the baseline characteristics between two groups, the results showed that the patients in IVIG group had higher Acute Physiology and Chronic Health Evaluation (APACHII) score, Sequential Organ Failure Assessment (SOFA) score, IL-6 and lactate level, lower lymphocyte count and oxygenation index (all P<0.05). The 28 day and 60 day mortality did not improve with IVIG in overall patients. The in-hospital stay and the total duration of disease were longer in IVIG group (p<0.001). Risk factors were clinical classification (hazards ratio 0.126, 95% confidence interval 0.039-0.413, P=0.001), and using IVIG (hazards ratio 0.252, 95% confidence interval 0.107-0.591, P=0.002) with COX regression. Subgroup analysis showed that only in patients with critical type, IVIG could significantly reduce the 28 day mortality, decrease the inflammatory response and improve some organ functions (all p<0.05), and 60-day mortality reduced significantly by using IVIG in the early stage (admission≤7 days) and with high dose (>15 g/d). Interpretation Early and high dose of IVIG therapy may improve the prognosis of COVID-19 patients only in critical type, which provides the clinical basis for the choice of treatment population and method of IVIG therapy for the SARS-CoV-2 infection.
https://www.medrxiv.org/content/10.1101/2020.04.11.20061739v1

- Here is a large observation study on the hospitalization time and outcome in patients with SARS-CoV-2 from Chinese hospital data. The data of COVID-19 patients in china were collected from the websites of provincial and municipal health commissions. The mean hospitalization time and mortality in the mild or severe patients and the mean time from severe to mild illness were calculated by Gaussian mixture modeling. Results: The mean hospitalization time among mild patients in Hubei province, other areas except Hubei province, and the national areas was 20.71 ± 9.30, 16.86 ± 8.24, and 19.34 ± 9.29 days, respectively. The mean transition time from severe to mild illness in the above three areas were 15.00, 17.00, and 14.99 days, respectively. The death rate of mild and severe patients in Hubei province and the national areas were 1.10% and 18.14%, and 1.10% and 17.70%, respectively. Among those patients who died of COVID-19, the mean time from severe transition to death in Hubei province and the national areas was 6.22 ± 5.12 and 6.35 ± 5.27 days, respectively. Conclusion: There were regional differences in the average length of stay between Hubei province and other regions, which may be related to different medical configurations. For those severe patients who died of COVID-19, the average time from hospitalization to death was about one week, and proper and effective treatments in the first week were critical.
https://www.medrxiv.org/content/10.1101/2020.04.11.20061465v1

DRUG DEVELOPMENT

- The OHDSI group whom I have often cited had a good teleconference yesterday on drug repurposing for SARS-CoV-2. Professor Tudor Oprea from University of New Mexico presented and you can see his slides here: https://www.ohdsi.org/resources/presentations/community-meeting-presentations/ They are available in Power Point or PDF format. It was a very good presentation. [**note: I was notified by email last evening that OHDSI gave me a badge as making important contributions as a "new user." I am humbled by this award and thank OHDSI for the continuing good work!!!**]
- OK, it's time to take that unused gold you have been hoarding and make a difference!!!! The FDA-approved gold salt, auranofin, inhibits SARS-CoV-2 replication and attenuates inflammation in human cells!! the FDA-approved gold drug, auranofin, inhibits SARS-COV-2 replication in human cells at low micro molar concentration. Treatment of cells with auranofin resulted in a 95% reduction in the viral RNA at 48 hours after infection. Auranofin treatment dramatically reduced the expression of SARS-COV-2-induced cytokines in human cells. These data indicate that auranofin could be a useful drug to limit SARS-CoV-2 infection and associated lung injury due to its anti-viral, anti-inflammatory and anti-ROS properties. Auranofin has a well-known toxicity profile and is considered safe for human use. [**note: this raises the issue regarding the weight of evidence needed to put a compound into clinical trials. Compounds such as this one don't have a particular mode of action and their clinical usefulness is questionable. Of course, one can say the same thing about hydroxychloroquine and look at the widespread use.**] https://www.biorxiv.org/content/10.1101/2020.04.14.041228v1

DIAGNOSTIC DEVELOPMENT

- WOW! Validation study of a serology test from Spain. We evaluated an immunochromatographic test (AllTest COV-19 IgG / IgM kit) which detects IgG and IgM antibodies. First, we performed a validation of the serologic test using serum samples from 45 healthy control patients (group 1) and 55 confirmed by PCR cases of COVID-19 (group 2) in order to establish the specificity and sensitivity, respectively. Then we prospectively employed the test in 63 patients diagnosed with pneumonia of unknown etiology that were SARS-CoV-2 negative by PCR (group 3), to establish the diagnostic performance in these patients. Results: All patients from group 1 (healthy controls) resulted negative for the serologic test (specificity = 100%). Regarding group 2 (PCR positive) patients, the median time from the onset of symptoms was 11 days and the test was positive for either IgM or IgG in 26 out of 55 patients (overall sensitivity = 47.3%). However, in those patients with 14 days or more from onset of symptoms, the sensitivity was 73.9%. Regarding group 3 patients, the median days from onset of symptoms was 17 and the test was positive in 56 out of 63 patients (88.9% positivity rate). In these group 3 patients with 14 days or more from onset of symptoms, the positivity rate was 91.1%. Conclusions: Our study shows that serologic rapid tests can be used as a complement of PCR to diagnose SARS-CoV-2 infection after 14 days from the onset of symptoms. These immunochromatographic devices could be especially useful in hospitalized patients with pneumonia of unknown etiology with 14 or more days from the onset of symptoms and in whom the PCR has been negative. [**note: there is still work to be done in understanding the**

rise in the immune response and presence of antibodies. There have been papers showing that recovered asymptomatic individuals can still present with virus and negligible antibody titer. Still this will be a useful tool to look across populations.]
https://www.medrxiv.org/content/10.1101/2020.04.11.20062158v1

- More good outside the box thinking to expand testing. A UCLA group shows that self-collected oral fluid and nasal swabs demonstrate comparable sensitivity to clinician collected nasal swabs. We recruited individuals recently tested for SARS-CoV-2 infection through a testing program (drive-through). In homes of participants, we assessed the performance of self-collected oral fluid swab specimens with and without clinician supervision, clinician-supervised self-collected mid-turbinate (nasal) swab specimens, and clinician-collected nasopharyngeal swab specimens. We tested specimens with a validated reverse transcription-quantitative polymerase chain reaction assay for the detection of SARS-CoV-2 and measured cycle threshold values. Symptom status and date of onset of symptoms was also recorded for each participant. Results: We recruited 45 participants. The median age of study participant was 42 years old (Interquartile range, 31 to 52 years). Of the participants, 29 had at least one specimen test positive for SARS-CoV-2. Of those, 21 (73%) of 29 reported active symptoms. By specimen type and home-based collection method, clinician-supervised self-collected oral fluid swab specimens detected 26 (90%) of 29 infected individuals, clinician-supervised self-collected nasal swab specimens detected 23 (85%) of 27, clinician-collected posterior nasopharyngeal swab specimens detected 23 (79%) of 29, and unmonitored self-collected oral fluid swab specimens detected 19 (66%) of 29. Despite nasopharyngeal swabs being considered the gold standard, 4 participants tested negative by clinician-collected nasopharyngeal swab and positive by the 3 other specimen types. Additionally, false negative results by each sample type were seen to generally not overlap. Conclusions: Supervised self-collected oral fluid and nasal swab specimens performed similarly to, if not better than clinician-collected nasopharyngeal swab specimens for the detection of SARS-CoV-2 infection. No sample type captured all SARS-CoV-2 infections, suggesting potential heterogeneity in the distribution of viral load in different parts of the respiratory tract between individuals. Supervised self-collection performed comparably to clinician collection and would allow for rapid expansion of testing capacity in the United States by reducing the need for trained healthcare workers, reducing exposure of healthcare workers, and reducing the amount of PPE (personal protective equipment) being used for testing during a critical shortage. [**note: I hope someone besides me is collecting all this stuff. If we really want to ramp up testing, creative ways of collecting samples and getting them tested need to be employed.**]
https://www.medrxiv.org/content/10.1101/2020.04.11.20062372v1

>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>

2020-04-16

It difficult to grasp how international air travel has all but collapsed. A couple of years ago my wife and I visited the Basque region of Spain. We flew to Barcelona where we had vacationed some years before and took a short flight on to Bilbao. On the plane were members of the Joan Chamorro Quintet and their lead singer and trumpeter Andrea Motis. I ended up sitting next to guitarist, Josep Traver, and we spent the hour talking about jazz music. I had not heard of the group. He said they had a lot of stuff up on YouTube and that they would be performing in Bilbao over the weekend. Unfortunately, we were spending that time in San Sebastian so I wasn't able to see them live. Here is a nice cover of 'Someday

my Prince will Come' featuring Ms. Motis (she was 18 at the time): https://www.youtube.com/watch?v=3qu52nXuEZ0 [**contest warning!!! This one is easy and I want to give away a prize. First person to tell me the origin of the song *without using Google* wins a prize related to the Quintet**l] Since it's Friday and everyone is worn out from a hard week of sheltering in place, here is a special COVID-19 performance from Anne-Sophie Mutter (I'm still looking for the pianist): https://www.youtube.com/watch?v=DCY7XaBqWMI

I am now archiving weekly compilations of the emails you have been receiving on my website. I will be adding other material as it is developed. Here is the link: https://agoldhammer.com/covid_19

Before I get into my **RANT**, here is a great post from Derek Lowe on the present state of vaccine research: https://blogs.sciencemag.org/pipeline/archives/2020/04/15/coronavirus-vaccine-prospects there are some very good hyperlinks to broad overviews in this product area.

[**Beginning of RANT; feel free to skip ahead. There are some interesting new Clinical Trials.**]

WOW! I can only say the research infrastructure in the US is more incompetent than I thought. Carolyn Johnson has a fine article in the Washington Post on the chaotic search for coronavirus treatments: https://www.washingtonpost.com/health/2020/04/15/coronavirus-treatment-cure-research-problems/ So Cliff Lane who worked closely with Tony Fauci for a lot of years goes to China in February, "He was troubled by the lack of a strategic plan to prioritize and fast-track the most promising treatments, leading to a mosaic of inconclusive findings." Of course there is this wonderful quote from Frances Collins, Collins said the month-long discussions have been kept under wraps to ensure buy-in for an approach likely to require sacrifices of personal recognition, scientific credit and profit — a centralized decision, for example, not to proceed with tests of one one company's drug to move faster on a competitor's. "I think we have the necessary clout to steer this whole complicated ecosystem," he said. "When you look at some of the things that are happening sporadically, we may be unlikely to learn what we need to from such disconnected, small trials. The whole point is to replace that with a coherent, evidence-based approach. … I want to know what works, and I want to have it answered by June or July."

And there is this, "A $50 million effort at the Duke Clinical Research Institute will test hydroxychloroquine in 15,000 health care workers and create a registry that can be tapped to speed up future trials, such as for a vaccine." Can someone enlighten me about how this will accelerate vaccine development?

JUNE OR JULY????????????? These are questions that could have been answered within the next four weeks had a centralized multi-center trial system been in place. In my lessons learned paper (in progress), here is what I have to say:

The following schema is but one approach to accelerating the development of SARS-CoV-2 therapies:

1. Multi-center clinical trials are essential. Such an approach has been used by the National Cancer Institute as well as the National Institute for Allergy and Infectious Diseases. The United States has many clinical research institutions that can be organized into a massive trial infrastructure. This increases the total pool of patients affected by SARS-CoV-2 allowing statistically relevant trials to be designed, promptly carried out and analyzed.

2. Protection of research subjects cannot be compromised, but rather than increase bureaucratic complexity, a Central IRB should be constituted for this purpose. Meetings via teleconference can substitute for in person and each drug trial might warrant its own 'sub-central IRB' depending on whether special issues are posed. It goes without saying that IRB decisions must be made quickly.
3. A central Data Safety Monitoring Board(s) shall be established for the trial of a respective drug or combination drug. Looking at the data across multiple trials sites for emerging safety and efficacy signals can be facilitated this way.
4. Data collection must be collected electronically and uploaded promptly so that it can be aggregated and analyzed. The pharmaceutical industry routinely sets up automated systems to accomplish this. [Aside: Back in 2002, one of our PhRMA committees had a presentation from Pfizer clinical IT folks that showed how their model worked. Everything from case report forms on was automated and electronically filed. They had research groups in England, the US and Australia so that critical drug development analyses could be done in 24-hour cycles rather than just during US work hours. I have not talked to PhRMA about this but suspect they would be happy to share experiences. This type of infrastructure is scalable.]
5. A policy needs to be in place to inform trial sites about discontinuation or expansion of specific trials. Well defined criteria for decision making should be established.

I'm reminded of the classic story of the investigation of the Space Shuttle Challenger and how Ricard Feynman figured it out. It turned out to be fairly simple: http://www.feynman.com/science/the-challenger-disaster/

I am saddened by this state of affairs! [**End of Rant; I guess this will disqualify me from being appointed to any Blue Ribbon Panel**]

Here is some news from the Reagan-Udall Foundation for the FDA. To help patients, caregivers, physicians, and other healthcare providers find COVID-19 treatment resources as quickly and easily as possible, the Reagan-Udall Foundation for the FDA today launched the online COVID-19 Treatment Hub.

The Hub is a critical enhancement to the existing Expanded Access Navigator, which was developed at the request of the U.S. Food and Drug Administration to help facilitate pre-approval access to drugs. The Hub helps users sift through the new clinical trials being announced every day as government, academia, and the global biopharmaceutical industry rally to find solutions to the pandemic.

"We are facing a health challenge unlike any of us have experienced in our lifetimes," said Ellen Sigal, PhD, Chair of the Reagan-Udall Foundation. "We are grateful to work with FDA to make it easier for the public and for healthcare providers to navigate through the information and to find credible resources in one place."

The COVID-19 Treatment Hub includes a directory of companies developing COVID-19 therapies, a searchable listing of relevant clinical trials and expanded access opportunities culled from ClinicalTrials.gov, and links to the latest FDA, CDC, and NIH updates. In addition to medical interventions, the COVID-19 Treatment Hub also links to key FDA resources for consumers and industry focused on food and veterinary safety.

Alan

SARS-CoV-2 (AKA, COVID-19): It's here; we know what to do; and we are doing it!

Stay Safe, Mask Up, & Wash Hands

MODELING

- I always enjoy models that support the wearing of masks. Speaking of masks, on the purveyors of bow ties who I have patronized is making some really nice ones: https://www.bowtie.com/shop.php#!/Cotton-Face-Masks/c/48089187 (I have no financial interest in Ms. Eaton's company). One widely-discussed strategy to limit transmission of SARS-CoV2, particularly from presymptomatic individuals, has been population-level wearing of masks. Modelling for pandemic influenza suggests some benefit in reducing total numbers infected with even 50% mask-use. COVID-19 has a higher hospitalization and mortality rate than influenza, and the impacts on these parameters, and critically, at what point in the pandemic trajectory mask-use might exert maximal benefit are completely unknown. We derived a simplified SIR model to investigate the effects of near-universal mask-use on COVID-19 assuming 8 or 16% mask efficacy. We decided to model, in particular, the impact of masks on numbers of critically-ill patients and cumulative mortality, since these are parameters that are likely to have the most severe consequences in the COVID-19 pandemic. Whereas mask use had a relatively minor benefit on critical-care and mortality rates when transmissibility (Reff) was high, the reduction on deaths was dramatic as the effective R approached 1, as might be expected after aggressive social-distancing measures such as wide-spread lockdowns. One major concern with COVID-19 is its potential to overwhelm healthcare infrastructures, even in resource-rich settings, with one third of hospitalized patients requiring critical-care. We incorporated this into our model, increasing death rates for when critical-care resources have been exhausted. Our simple model shows that modest efficacy of masks could avert substantial mortality in this scenario. Importantly, the effects on mortality became hyper-sensitive to mask-wearing as the effective R approaches 1, i.e. near the tipping point of when the infection trajectory is expected to revert to exponential growth, as would be expected after effective lockdown. Our model suggests that mask-wearing might exert maximal benefit as nations plan their post-lockdown strategies and suggests that mask-wearing should be included in further more sophisticated models of the current pandemic. [**note: at the risk of being repetitious – mask up when you go out!**] https://www.medrxiv.org/content/10.1101/2020.04.13.20063529v1

NEWLY REGISTERED CLINICAL TRIALS

- Here is a trial to look at the effect of the IL-1 inhibitor canakinumab. The study is configured as a retrospective and prospective observational study. The study will be multi-center and will involve all COVID-19 pneumonia patients treated with canakinumab administered subcutaneously. NCT04348448
- Two diseases for the price of one!! Here is a Phase 1 trial on galidesivir for both Yellow Fever or SARS-CoV-2. NCT03891420
- A new approach to a pandemic clinical trial – remote contact with the patient. This is an "at home" placebo-controlled trial of those who have mild SARS-CoV-2 symptoms with fluvoxamine.

This is an SSRI drug usually prescribed for OCD symptoms. Investigators want to see if it will prevent more serious complications such as shortness of breath. NCT04342663

- Iraq joins the list of countries running SARS-CoV-2 trials!! Picking up from the Australian *in vitro* study, they plan to look at ivermectin as an adjuvant to hydroxychloroquine. [**note: my reading of the Australian paper is ivermectin is potent by itself; I guess it is getting very difficult not to treat with hydroxychloroquine these days.**] NCT04343092

- Here is an approach I've not seen before. Mexican research want to study pyridostigmine, a peripheral acetylcholinesterase inhibitor. Here is the full study descriptions for the clinicians in the audience: Our hypothesis is that, in comparison to the placebo, pyridostigmine will reduce in at least 10% a composite outcome [death; mechanical ventilation; >2 point-increase in the SOFA score) by day 28. We will also evaluate interleukin (IL)-6 kinetics during the first 14 days of in-hospital stay. It is estimated that 25-33% of patients hospitalized for COVID-19 are admitted to intensive care units (ICU) for severe hypoxemia. The reported mortality in those with severe disease ranges between 38% and 49%. So far, there is no pharmacological therapeutic (or else) strategy known to reduce morbidity and mortality in these patients. Mortality in COVID-19 appears to be mediated not necessarily by the direct effect of the infection, but by the disproportionate inflammatory response of the host. Pyridostigmine is an old drug that, by inhibiting acetylcholine-esterase, the enzymatic machinery that degrades acetylcholine (ACh), results in increased ACh bioavailability. ACh, in turn, ligates to nicotinic-alpha7 receptors in macrophages and T cells, resulting in reduced overactivation of these immune cells. In experimental murine sepsis, this family of drugs has resulted in reduced inflammation and mortality. Human evidence is scarce for severe inflammatory conditions. However, recent evidence from our group and others indicates that pyridostigmine has an immunomodulatory effect in people living with HIV, resulting in elevation of CD4+ T cell counts, decreased immune activation, and reduction in inflammatory mediators. Altogether, this suggests that ACh-esterase inhibitors may act as immunomodulators during viral infections, potentially reducing the inflammatory cascade (the so-called "cytokine storm") observed in critically ill COVID-19 patients. At the proposed dose (60mg/d), the rate of minor adverse events is less than 5% with no reported serious adverse effects. From that perspective, we consider that pyridostigmine can function as an immuno-modulator and reduce morbidity and mortality in COVID-19-stricken patients, with the added value of a safe pharmacological profile. Moreover, as an old drug, re-purposing it for a novel indication may be a simpler, more efficient approach than developing a novel one from the ground up. NCT04343963

- Since it is Friday and the weekend is coming up as we all take some time off…..wait….we are taking time off constantly during the pandemic with shelter in place and social distancing. This Cypriot trial is RIGHT ON TARGET!!! The aim of this study is to assess the changes in the dietary habits of adults spending most of their time in their homes due to the Coronavirus (COVID-19) outbreak. Eating habits of individuals may vary greatly depending on several factors such as geographic location, socioeconomic conditions, education level, knowledge about nutrition and psychological factors. Since this period of quarantine is economically and psychologically stressful, we hypothesise that individuals may alter their usual eating habits. [**note: ABSOLUTELY!! I am baking and eating way too many chocolate chip cookies. I better enroll in this trial.**] NCT04339842

CLINICAL TRIAL RESULTS

- Here is a cohort study from Reggia, Italy. No surprising findings. All 2653 symptomatic patients who tested positive for SARS-CoV-2 from February 27 to April 2, 2020 in the province of Reggio Emilia. Main outcome measures. Hospitalization and death up to April 2, 2020. Results. Females had higher prevalence of infection than males below age 50 (2.61 vs. 1.84 per 1000), but lower in older ages (16.49 vs. 20.86 per 1000 over age 80). Case fatality rate reached 20.7% (22/106) in cases with more than 4 weeks follow up. After adjusting for age and comorbidities, men had a higher risk of hospitalization (hazard ratio (HR) 1.4 95% confidence interval (95% CI) 1.2 to 1.6) and of death (HR 1.6, 95% CI 1.2 to 2.1). Patients over age 80 compared to < age 50 had HR 7.1 (95% CI 5.4 to 9.3) and HR 27.8 (95% CI 12.5 to 61.7) for hospitalization and death, respectively. Immigrants had a higher risk of hospitalization (HR 1.3, 95% CI 0.99 to 1.81) than Italians and a similar risk of death. Risk of hospitalization and of death were higher in patients with heart failure (HR 1.6, 95% CI 1.2 to 2.1and HR 2.3, 95% CI 1.6 to 3.2, respectively), arrhythmia (HR 1.5, 95% CI 1.2 to 1.9 and HR 1.8, 95% CI 1.3 to 2.5, respectively), dementia (HR 1.2, 95% CI 0.9 to 1.8 and HR 1.8, 95% CI 1.1 to 2.8, respectively), ischemic heart disease (HR 1.3, 95% CI 1.0 to 1.7 and HR 1.7, 95% CI 1.2 to 2.5, respectively), diabetes (HR 1.5, 95% CI 1.3 to 1.9 and HR 1.6, 95% CI 1.1 to 2.2, respectively), and hypertensions(HR 1.4, 95% CI 1.2 to 2.6 and HR 1.6, 95% CI 1.2 to 2.1, respectively), while COPD increased the risk of hospitalization (HR 1.9, 95% CI 1.4 to 2.5) but not of death (HR 1.1, 95% CI 0.7 to 1.7). Previous use of ACE inhibitors has no effect on risk of death (HR 0.97, 95% CI 0.69 to 1.34) Conclusions. The mechanisms underlying these associations are mostly unknown. A deeper understanding of the causal chain from infection, disease onset, and immune response to outcomes may explain how these prognostic factors act. https://www.medrxiv.org/content/10.1101/2020.04.13.20063545v1
- This is what observational research can do!!! It's a small study of EHRs in Massachusetts and the results are confounding but indicative of utility. To identify commonly-prescribed medications that may be associated with lesser risk of morbidity with COVID-19 across 5 Eastern Massachusetts hospitals. Design: In silico cohort using electronic health records between 7/1/2019 and 4/07/2020. Setting: Outpatient, emergency department and inpatient settings from 2 academic medical centers and 3 community hospitals. Participants: All individuals presenting to a clinical site and undergoing COVID-19 testing. Main Outcome or Measure: Inpatient hospitalization; documented requirement for mechanical ventilation. Results: Among 12,818 individuals with COVID-19 testing results available, 2271 (17.7%) were test-positive, and 707/2271 (31.1%) were hospitalized in one of 5 hospitals. Based on a comparison of ranked electronic prescribing frequencies, medications enriched among test-positive individuals not requiring hospitalization included ibuprofen, valacyclovir, and naproxen. Among individuals who were hospitalized, mechanical ventilation was documented in 213 (30.1%); ibuprofen and naproxen were also more commonly prescribed among individuals not requiring ventilation. Conclusions and Relevance: These preliminary findings suggest that electronic health records may be applied to identify medications associated with lower risk of morbidity with COVID-19, but larger cohorts will be required to address confounding by indication. Larger scale efforts at repositioning may help to identify FDA-approved medications meriting study for prevention of COVID-19 morbidity and mortality.
  https://www.medrxiv.org/content/10.1101/2020.04.11.20061994v1

- Here is a large cohort study of age related mortality in Europe. We evaluated the distribution of COVID-19-related fatalities by age groups in Europe. On April 6, 2020, we systematically reviewed COVID-19-related mortality data from 32 European countries (European Union/European Economic Area and the United Kingdom). We collated official reports provided by local Public Health or Ministry of Health websites. We included countries if they provided data regarding more than 10 COVID-19-related deaths stratified by age according to pre-specified groups (i.e., < 40, 40-69, ≥ 70 years). We used random-effects meta-analysis to estimate the proportion of age groups among all COVID-19-related fatalities. Results: Thirteen European countries were included in the review, for a total of 31,864 COVID-19-related deaths (range: 27-14,381 per country). In the main meta-analysis (including data from Germany, Hungary, Italy, Netherlands, Portugal, Spain, Switzerland; 21,522 COVID-19-related fatalities), the summary proportions of persons < 40, 40-69, and ≥ 70 years of age among all COVID-19-related deaths were 0.1% (0.0-0.2%; I2 24%), 12.8% (10.3-15.6%; I2 94%), and 84.8% (81.3-88.1%; I2 96%), respectively. Conclusions: People under 40 years of age represent a small fraction of the total number of COVID-19-related deaths in Europe. [**note: get me to the nearest time machine so I can drop 40 years off my age!!!**]
  https://www.medrxiv.org/content/10.1101/2020.04.11.20061721v1
- Cohort studies are very popular today! Here is a nice one looking across the Kaiser Permanente system on the West Coast. Methods: We assessed incidence, duration of hospitalization, and clinical outcomes of acute COVID-19 inpatient admissions in a prospectively-followed cohort of 9,596,321 individuals enrolled in comprehensive, integrated healthcare delivery plans from Kaiser Permanente in California and Washington state. We also estimated the effective reproductive number (RE) describing transmission in the study populations. Results: Data covered 1277 hospitalized patients with laboratory- or clinically-confirmed COVID-19 diagnosis by April 9, 2020. Cumulative incidence of first COVID-19 acute inpatient admission was 10.6-12.4 per 100,000 cohort members across the study regions. Mean censoring-adjusted duration of hospitalization was 10.7 days (2.5-97.5%iles: 0.8-30.1) among survivors and 13.7 days (2.5-97.5%iles: 1.7-34.6) among non-survivors. Among all hospitalized confirmed cases, censoring-adjusted probabilities of ICU admission and mortality were 41.9% (95% confidence interval: 34.1-51.4%) and 17.8% (14.3-22.2%), respectively, and higher among men than women. We estimated RE was 1.43 (1.17-1.73), 2.09 (1.63-2.69), and 1.47 (0.07-2.59) in Northern California, Southern California, and Washington, respectively, for infections acquired March 1, 2020. RE declined to 0.98 (0.76-1.27), 0.89 (0.74-1.06), and 0.92 (0.05-1.55) respectively, for infections acquired March 20, 2020. Conclusions: We identify high probability of ICU admission, long durations of stay, and considerable mortality risk among hospitalized COVID-19 cases in the western United States. Reductions in RE have occurred in conjunction with implementation of non-pharmaceutical interventions.
  https://www.medrxiv.org/content/10.1101/2020.04.12.20062943v1
- I guess I need to post this one for the obviousness of it. We identified 12 papers with a total of 9,025 COVID-19 patients, 878 (9.7%) with severe disease and 495 with a history of smoking (5.5%). The meta-analysis showed a significant association between smoking and progression of COVID-19 (OR 2.25, 95% CI 1.49-3.39, p=0.001). Limitations in the 12 papers suggest that the actual risk of smoking may be higher. Conclusions: Smoking is a risk factor for progression of COVID-19, with smokers having higher odds of COVID-19 progression than never smokers.

Physicians and public health professionals should collect data on smoking as part of clinical management and add smoking cessation to the list of practices to blunt the COVID-19 pandemic. https://www.medrxiv.org/content/10.1101/2020.04.13.20063669v1

DRUG DEVELOPMENT

- I don't see any NMEs at this point. I don't think I need to regularly cover all the repurposed drug studies. If something striking does come out you all will be the first to know about it.

DIAGNOSTIC DEVELOPMENT

- Here is a bit of good news from Abbott: https://www.fiercebiotech.com/medtech/abbott-launches-coronavirus-antibody-lab-test-plans-to-ship-20m-per-month-summer Interesting that they are shipping right now before getting an FDA Emergency Use Authorization.
- Dubai-based Emirates Airline (sponsors of a number of Euro soccer clubs; how I wish the seasons could resume, especial for my fave Ajax of Amsterdam) is conducting blood tests on passengers at the airport prior to the flight: https://www.cnn.com/travel/article/emirates-passengers-blood-test-covid-19/index.html A sign of things to come???
- Two EUAs from FDA for serology tests!!!! YES!!!!!!!!!!!!! Here are the letters. Chembio Diagnostic Systems: https://www.fda.gov/media/136965/download Mt. Sinai School of Medicine: https://www.fda.gov/media/137032/download (**note: this one is limited to being performed at the Mt. Sinai lab.**)

>>>

2020-04-17

A couple of things before we get started this Friday. As one perceptive reader noted, I got the days mixed up in yesterday's newsletter. Yes, it was Thursday!! In the absence of sports scores, I am having difficulty staying oriented (or maybe it's just 'Groundhog Day' syndrome; we need an ICD code for this). Second, and more importantly, we had a winner in yesterday's contest. The song, 'Someday my Prince Will Come,' is from Walt Disney's 'Snow White,' the first of Disney's full-length animated films. Music was by Frank Churchill, lyrics by Larry Morey, and Adriana Caselotti sang it in the film. The prize will be going out in today's mail to the lucky winner. Don't lose your thinking caps as quizzes will pop up periodically.

Before we get into the musical selection today (these are programmed way in advance!), let's take a moment and remember saxophone great Lee Konitz who passed away from SARS-CoV-2 complications. Konitz was 92 and had a storied career playing with almost every jazz great since starting in the 1940s. Here is a live version of All the Things You Are: https://www.youtube.com/watch?v=0AnM3bTEXGk from 2012 (Mr. Konitz was 85).

On to the main selection. Those of us old enough to remember what 'camp' really meant will derive some pleasure from this piece. Those of you wanting an explanation are referred to the greatest reference 'book' of our time: https://en.wikipedia.org/wiki/Camp_(style) We have not featured Broadway, so it's time to dim the lights and strike up the band. Here is 'Tonight' from 'West Side Story.' The audience was enthralled with the performance, me not so much: https://www.youtube.com/watch?v=QC10LrVWtu4 Trivia question (no prizes for this one): who sang Tony, incurring the great wrath of Leonard Bernstein?

I've kept this newsletter pretty much apolitical and don't intent to change this. To quote MSNBC's Ari Melber, 'we need to let the science lead us.' That's just what we will do. Courtesy of NPR, here are the guidelines for the Reopening of America: https://www.npr.org/2020/04/16/836489480/read-white-house-guidelines-to-states-for-reopening Several days ago, I linked to a plan that Scott Gottlieb and collaborators had developed. I strongly believe that we need to get the country back to work in a safe and timely manner. The economy is in bad shape (of course you all received your checks from the government yesterday, correct?) and there will be continued suffering in almost all quarters with a prolonged shelter in place policy.

Now you might ask, do we have any good model for how, when facing an infectious disease, this can be accomplished? I'm glad you asked because actually there is one (don't even bother asking me how I know things like this.)!!! To help minimize sexually transmitted infections, the adult movie/video industry requires a blood panel for HIV, chlamydia, gonorrhea, etc. every 14 days and performers have to show proof of testing before being allowed on set. OK, this is an extreme case and applies to a very small number of people but the principles are the same – testing at scale, something the US is not currently prepared to do. Flattening the curve is great, but as you all well know, it does not mean elimination of SARS-CoV-2. The virus is here; in the absence of a vaccine, infections will continue. At last night's White House briefing, Drs. Birx and Fauci noted that there are regions of the country that have been only mildly impacted by SARS-CoV-2. Yes, this is true from looking at case numbers but when one factors in working conditions, even a small infection can spiral out of control. Here is a cautionary tale for today's Washington Post: https://www.washingtonpost.com/business/2020/04/16/meat-processing-plants-are-closing-due-covid-19-outbreaks-beef-shortfalls-may-follow/ the US may see 25% of the beef processing industry incapacitated because of worker infection!!

My old friend Zeke Emanuel made a good point last night; talking with Ari Melber he noted that at a minimum we should be testing healthcare workers, first responders, and those involved in the food distribution industry at regular intervals. He posited that this amounts to 6 million workers who probably should be tested every 14 days by RT-PCR. Grade school math tells us that we need a lot more testing capacity than we have right now. Money needs to be rapidly allocated to build this kind of capacity. Look at the third slide in the presentation. Testing and contact tracing are LEFT TO THE STATES (though head of CDC, Dr. Redfield, said they are ready to help; that instills confidence). I'll leave it to you to read the slide. If the testing capacity is not there, how can states possibly do their job? Right now, many states are facing catastrophic budget deficits and the availability of testing supplies should done with Federal funding (Paging Jared Kushner, you have an emergency call on line one).

OK, enough already, I'm preaching to the choir here. On with new developments. Some positive clinical trial data from Wuhan. There looks to be a big jump in Gilead stock price based on a talk earlier in the week from some University of Chicago researchers on the effectiveness of remdesivir.

Alan

SARS-CoV-2 (AKA, COVID-19): It's here; we know what to do; and we are doing it!

Stay Safe, Mask Up, & Wash Hands

MODELING

- I only include this model as it covers Lombardy, the site of our cancelled vacation (Milan & Lake Como). You can disregard this if your eyes begin to glaze over. BACKGROUND We described the epidemiological features of the codiv-19 outbreak, and evaluated the impact of interventions measures on the epidemic in the Lombardy region, Italy. METHODS Laboratory-confirmed covid-19 cases reported through the beginning of April were extracted from the Italian Civil Protection database. Based on key events and interventions, we divided the epidemic into three periods: before February 21, from February 22 to early March, after early March. We compared epidemiological characteristics across periods and developed a modified susceptible-exposed-infectious-recovered model to study the epidemic and evaluate the impact of interventions. We explicitly took into account for unascertained cases (positive cases with no symptoms or mild symptoms that have not been accounted for in official statistics). RESULTS Currently, the number of positive active cases has increased to around 30,000 in the Lombardy region. Due to restriction measures, the effective reproduction number dropped from 3.33 (95% CI: 2.03-3.69) during the first period, to 2.36 (95% CI: 2.21-2.70) during the second period. In the third period, the effective reproduction number is estimated to have dropped to 1.49 (95% CI: 1.35-1.62). The model estimates a great proportion of unascertained cases, about 90% of infected people has not been accounted for in official statistics. CONCLUSIONS Considerable countermeasures have slowed down the covid-19 outbreak in the Lombardy region. However, notwithstanding the long-lasting lockdown period, the epidemic is still not under control. The effective reproduction number, according to the model used in this work, is still greater than 1.0. Estimation of unascertained cases has important implications on continuing surveillance and interventions. https://www.medrxiv.org/content/10.1101/2020.04.12.20062919v1

NEWLY REGISTERED CLINICAL TRIALS

- Diabetes drugs are capturing some attention. Here is a new trial with dapagliflozin. This is an international, multicenter, parallel-group, randomized, double-blind, placebo controlled, study in hospitalized adult patients with COVID-19 in the US and other countries with high prevalence of COVID-19. The study is evaluating the effect of dapagliflozin 10 mg versus placebo, given once daily for 30 days in addition to background local standard of care therapy, in reducing disease progression, complications, and all-cause mortality. [**note: no sign of hydroxychloroquine in this trial.**] NCT04350593
- Here is a trial sponsored by a small German biotech company investigating the safety and efficacy of IFX-1, the company´s monoclonal anti-C5a antibody, in patients with severe COVID-19-induced pneumonia. The company has received initial positive human data from two initial

patients suffering from COVID-19-induced severe pneumonia who were treated with BDB-001, an anti-C5a antibody produced by BDB from the IFX-1 cell line, in China. This is a pragmatic, adaptive, open-label, randomized, multicenter phase II/III study consisting of two parts: Phase II and Phase III. In both study parts, patients will be randomized to two treatment arms (Arm A: best supportive care [BSC] + IFX-1; Arm B: BSC alone). After all patients are treated in Phase II, an interim analysis will be performed to assess the clinical benefit of the treatment using the assessed clinical parameters. NCT04333420

- This may be the first one from Poland!! Studies have shown that amiodarone and verapamil can interfere with coronavirus entry and amplification by blocking ion channels. ReCOVery-SIRIO is a randomized study to investigate amiodarone or verapamil compared with usual care in symptomatic patients hospitalized with confirmed COVID-19 infection. [**note: How can you go wrong, working at Nicolaus Copernicus University? I'm not a clinician; will amiodarone help counteract QT issues with hydroxychloroquine?**] NCT04351763
- No location listed for this trial. The main purpose of this study is to evaluate the activity of low dose oral selinexor (KPT-330) and to evaluate the clinical recovery, the viral load, length of hospitalization and the rate of morbidity and mortality in patients with severe COVID-19 compared to placebo. It's an FDA-approved anti-cancer drug. NCT04349098
- Here is a trial for CM4620-IE. CM4620-IE is a potent and selective small molecule CRAC channel inhibitor that prevents CRAC channel overactivation, which can cause pulmonary endothelial damage and cytokine storm in COVID-19. It has demonstrated clinical safety and potential efficacy in patients with hypoxemia secondary to systemic inflammatory response syndrome (SIRS) from acute pancreatitis. This open-label randomized controlled study will evaluate safety, efficacy, and the pharmacokinetic profile of CM4620-IE in patients with severe COVID-19 pneumonia. Forty patients on low flow oxygen and forty patients on high flow oxygen will receive 2.0 mg/kg of CM4620-IE by continuous IV infusion on Day 1, followed by 1.6 mg/kg for days 2 and 3. Another 20 patients of each will receive local standard of care only. The infusion of CM4620-IE will start within 8 hours from the time the patient or LAR provides informed consent. NCT04345614

CLINICAL TRIAL RESULTS

- Whoa Nellie, looks like men need to stay quarantined for a longer period of time. Here is a study from Mumbai, To determine whether males have delayed viral clearance after infection, we evaluated the time to clearance in symptomatic patients tested by serial oropharyngeal/nasopharyngeal swabs followed by RT-PCR at a reference lab in Mumbai, India. A total of 68 subjects with median age of 37 years (3-75 range) were examined and included 48 (71%) males and 20 (29%) females. We observed that females were able to achieve viral clearance significantly earlier than males, with a median difference of 2 days in achieving a negative PCR result (P value = 0.038). Furthermore, examination of 3 families with both male and female patients followed serially, demonstrated that female members of the same household cleared the SARS-CoV2 infection earlier in each family. To determine reasons for delayed clearance in males, we examined the expression patterns of the SARS-CoV2 receptor, Angiotensin-converting enzyme 2 (ACE2), in tissue specific repositories. We observed that the

testes was one of the highest sites of ACE2 expression in 3 independent RNA expression databases (Human Protein Atlas, FAMTOM5 and GETx). ACE2 was also determined to be highly expressed in testicular cells at the protein levels. Interestingly, very little expression of ACE2 was seen in ovarian tissue. Taken together, these observations demonstrate for the first time that male subjects have delayed viral clearance of SARS-CoV2. High expression of ACE2 in testes raises the possibility that testicular viral reservoirs may play a role in viral persistence in males and should be further investigated.
https://www.medrxiv.org/content/10.1101/2020.04.16.20060566v1

- I'm not sure I like this protective factor!!! A retrospective review of all COVID-19 infected patients treated at Wuhan Union Hospital from Feb 1 to Mar 20 was carried out. Continuous variables were described as mean, median, and interquartile range (IQR), while categorical variables were compared by X2 test or Fisher's exact test between COVID-19 infected patients with mycoplasma IgG (-) and mycoplasma IgG (+). Results: Statistically significant differences were shown in terms of laboratory test results. COVID-19 infected patients with mycoplasma IgG positivity had a higher lymphocyte count and percentage (p=0.026, p=0.017), monocyte count and percentage (p=0.028, p=0.006) and eosinophil count and percentage (p=0.039, p=0.007), and a lower neutrophil count and percentage (p=0.044, p=0.006) than COVID-19 infected patients without mycoplasma IgG. Other routine blood tests, including coagulation tests, blood biochemistry and infection-related biomarkers did not significantly differ except for thrombin time (p=0.001) and lactate dehydrogenase (p=0.008). Furthermore, requirement and use of a nasal catheter or oxygen mask was significantly lower in COVID-19 infected patients with mycoplasma IgG positivity (p=0.029). Conclusions: Our findings indicate that mycoplasma IgG positivity is a potential protective factor for SARS-CoV-2 infection. (**note: I absolutely will not enter any clinical trial that wants to make me inhale mycoplasma.)**
https://www.medrxiv.org/content/10.1101/2020.04.12.20060079v1
- More good work from the Bari Italy group (makes me want to visit the town). This describes the application of a rapid serological test of asymptomatic health workers. We screened 512 health workers of our Cancer Institute with rapid serological test Viva-Diag analyzing, with colorimetric test,IgG/IgM- COVID-19 associated. Five subjects (1%) resulted with Viva-Diag test not-negative for IgM. All of them had rt-PCR SARS-CoV-2 test negative while for 2 out of 5 cases, CLIA analysis confirmed positive IgM expression. In this original study on health workers we demonstrated that Viva-Diag is able to evidence subjects positive for IgM expression. However, discordant results with respect to rt-PCR and CLIA assays clearly refer to further studies to optimize the utilization of the serological test in asymptomatic and in at risk subjects.
https://www.medrxiv.org/content/10.1101/2020.04.15.20057786v1
- Here is data on the poor prognosis of cardiac arrest patients. To inform this debate, we report survival outcomes following cardiopulmonary resuscitation in a cohort of similar critically ill patients with pneumonia or sepsis who were receiving mechanical ventilation in an ICU at the time of arrest. The probability of survival without severe neurological disability (CPC of 1 or 2) ranged from less than 3% to over 22% across key patient subgroups, For patients with an initial rhythm of asystole or PEA, who were also receiving vasopressors at the time of arrest, fewer than 10% were discharged without severe neurological disability (CPC of 1 or 2), and this number dropped to less than 3% in patients over 80 years old. In contrast, survival rates were much higher in younger patients, patients with an initial rhythm of VF or pulseless VT, and in

patients receiving ventilatory support without vasopressors. Our findings suggest caution in universal resuscitation policies. Even in a cohort of critically ill patients on mechanical ventilation, survival outcomes following in-hospital resuscitation were not uniformly poor and varied markedly depending on age, co-morbidities and illness severity. We believe that these data can help inform discussions among patients, providers and hospital leaders regarding resuscitation policies and goals of care in the context of the COVID-19 pandemic. https://www.medrxiv.org/content/10.1101/2020.04.11.20060749v1

- Here is an interesting German study on early IgA profile and disease severity. Here, the kinetics of the development of SARS-CoV-2-specific antibody responses in relation to clinical features and dynamics of specific B-cell populations are reported. Immunophenotyping of B cells was performed by flow cytometry with longitudinally collected PBMCs. In parallel, serum samples were analyzed for the presence of SARS-CoV-2-specific IgA, IgG, and IgM antibodies using whole proteome peptide microarrays. Soon after disease onset in a mild case, we observed an increased frequency of plasmablasts concomitantly with a strong SARS-CoV-2-specific IgA response. In contrast, a case with more severe progression showed a delayed, but eventually very strong and broad SARS-CoV-2-specific IgA response. This case study shows that determining SARS-CoV-2-specific antibody epitopes can be valuable to monitor the specificity and magnitude of the early B-cell response, which could guide the development of vaccine candidates. Follow-up studies are required to evaluate whether the kinetics and strength of the SARS-CoV-2-specific IgA response could be potential prognostic markers of viral control. https://www.medrxiv.org/content/10.1101/2020.04.14.20059733v1
- Here is a dissenting voice on BCG vaccination!! The reason for the observed country-wise variability in incidence and severity of the COVID-19 outcome remains unknown. Few recent studies have suggested a positive protective correlation of the BCG vaccination policy of the countries with the observed COVID-19 severity. The current study was undertaken to reassess the existing data as of 4th April 2020. The incidence rates (cases per million population), Case Fatality Rates (CFR) and inherently more robust Infection Fatality Rates (IFR) were calculated across countries accounting for about 99% COVID-19 deaths. The initial scrutiny suggested a weaker association with BCG vaccination policy or BCG coverage, so positivity to the Tuberculin Sensitivity Test (TST)/ Interferon Gamma Release Assay (IGRA) as a measure of the potential protective effect of the resident populations exposure to *Mycobacterium spp.* whether from BCG vaccination or as a result of exposure to environmental mycobacteria was analyzed. The incidence rates (the number of cases per million population) decreased with an increase in % LTBI (TST/IGRA positivity) for the analyzed countries with R2 =0.6343, suggesting an exponentially negative covariation. However, the covariation of CFR estimates that ranged from 0.29% to 12.25 % (average 5.39%) among countries, was tenuous. Interim estimates of IFR (i-IFR), a more dependable measure for such studies, for the best and worst-case scenarios, i.e., i-IFR-l and i-IFR-h, predict on an average 20.57% to 30.15 % COVID-19 fatality rates globally, but individual country estimates display huge variation. Among countries accounting for 92.14% deaths (11 countries; top 20% countries included in current study) the estimate for lowest IFRs (i-IFR-l=4.16 (China) & i-IFR-h=4.61 (China)) and highest IFRs (i-IFR-l=96.39% (UK); & i-IFR-h=96.54% (UK)) displayed huge difference (average for the group: CFR=6.8 ± 3.6%; i-IFR-l=34.97 ± 30.55%; & i-IFR-h=44.20 ± 29.08%). Currently, the worst affected countries Italy (CFR=12.25%; i-IFR-l=42.63%; i-IFR-h=48.69%) and Spain (CFR=9.39%; i-IFR-l=26.85%; i-IFR-h=36.60%) would

seemingly cope with COVID-19 better than UK, Netherlands and USA while the countries Germany (CFR=1.40%; i-IFR-l=4.93%; i-IFR-h=17.49%) and Switzerland (CFR=3.01%; i-IFR-l=10.87%; i-IFR-h=16.23%) along with China could fare the best. The rest of the 80% countries (accounting for 6.74% deaths), seemed to have reduced mortality (CFR=2.45 ± 2.01; i-IFR-l= 30.62 ± 28.24%; i-IFR-h=40.99 ± 30.47%) with associated high % LTBI (17.28 ± 8.87) than top 20% countries. The inherent issues in the data set (e.g., heterogeneity, non-random sampling, different criteria of sampling and reporting, access to health care, genetic composition, underlying co-morbidities, etc) need to be taken into account for making informed decisions. https://www.medrxiv.org/content/10.1101/2020.04.11.20062232v1

DRUG DEVELOPMENT

- FINALLY SOME ENCOURAGING NEWS!! The Wuhan group offers some encouragement on the use of arbidol and oseltamivir. We have assembled a cohort consisting 504 hospitalized COVID-19. Information of patients characteristics and antiviral medication use during hospital stay is collected. The study objective is to evaluate the treatment efficacy of selected antiviral medications on mortality and lesion absorption based on chest CT scan. RESULTS The overall mortality rate was 15.67% in the cohort. Older age, lower SpO2 level, bigger lesion, early admission data, and the presence of pre-existing conditions were associated with higher mortality. After adjusting for sex, pre-existing condition, age, SpO2, lesion size, admission data, hospital, and anti-viral medications use, Arbidol and Oseltamivir use is associated with a reduction in mortality. The OR is 0.183 (95% CI, 0.075 to 0.446; p<0.001) for Arbidol and 0.220 (95% CI, 0.069 to 0.707; p=0.011) for Oseltamivir. Compared with patients taking neither Arbidol nor Oseltamivir, the OR is 0.253 (95% CI, 0.064 to 1.001; p=0.050) for patients taking Oseltamivir only; 0.190 (95% CI, 0.076 to 0.473; p<0.001) for patients taking Arbidol only; and 0.030 (95% CI, 0.003 to 0.310; p=0.003) for patients taking both, after adjusting for patients characteristics and Lopinavir/Ritonavir use. Similarly, Arbidol is also associated with faster lesion absorption after adjusting for patients characteristics as well as Oseltamivir and Lopinavir/Ritonavir use. CONCLUSIONS Arbidol is able to substantially associated with a reduction in mortality among hospitalized COVID-19 patients. The combination of Arbidol and Oselmativir may further associated with a reduction in mortality. *There is no proven treatment benefit of Lopinavir/Ritonavir.* (**note: the generic name for Arbidol is umifenovir and it's a broad-spectrum antiviral. AFIK, it is only approved in Russia and China for seasonal influenza.**] https://www.medrxiv.org/content/10.1101/2020.04.11.20056523v1 There is an Iranian group that is trialing this drug also but their protocol is complicated and involves lopinavir/ritonavir, hydroxychloroquine, and interferon-β 1a. NCT04350684
- And now more good news from Hubei province and Wuhan!!! Objective To investigate the efficacy and safety of recombinant human interferon alpha1b (rhIFN-α) nasal drops in healthy medical staff to prevent 2019 novel coronavirus disease (COVID-19). Methods A prospective, open-label study was conducted. Starting January 21, 2020, at Taihe Hospital in Shiyan City, Hubei Province, 2944 medical staff members were recruited and allocated into a low-risk group or a high-risk group according to whether they were directly exposed to the coronavirus. Participants in the low-risk group received rhIFN-α nasal drops (2-3 drops/nostril/time, 4

times/day) for 28 days; those in the high-risk group received rhIFN-α nasal drops combined with thymosin-α1 (1.6 mg, hypodermic injection, once a week). The primary outcome was new-onset COVID-19 over 28 days. The secondary outcome was new-onset fever or respiratory symptoms but with negative pulmonary images. The results were compared with the number of new cases in medical staff in the same areas of Hubei Province (including Wuhan) during the same period. Adverse reactions to interferon nasal drops were also observed. Results Among the 2944 subjects in our study, 2415 were included in the low-risk group, including 997 doctors and 1418 nurses with average ages of 37.38 and 33.56 years, respectively; 529 were included in the high-risk group, including 122 doctors and 407 nurses with average ages of 35.24 and 32.16 years, respectively. The 28-day incidence of COVID-19 was zero in both the high- and low-risk groups. The 28-day incidence of new-onset clinical symptoms with negative images for pneumonia was also zero in both the high- and low-risk groups. As controls, a total of 2035 medical personnel with confirmed COVID-19 pneumonia from the same area (Hubei Province) was observed between January 21 to February 23, 2020. There were no serious adverse effects in the 2944 subjects treated during the intervention period. Conclusion *In this investigator-initiated open-label study, we observed that rhIFN-α nasal drops can effectively prevent COVID-19 in treated medical personnel. Our results also indicate that rhIFN-α nasal drops have potential promise for protecting susceptible healthy people during the coronavirus pandemic.*
https://www.medrxiv.org/content/10.1101/2020.04.11.20061473v1

- The folks from PETA won't like this one!!! Researchers from The Netherlands have found an animal model that may help things out. The current pandemic coronavirus, SARS-CoV-2, was recently identified in patients with an acute respiratory syndrome, COVID-19. To compare its pathogenesis with that of previously emerging coronaviruses, we inoculated cynomolgus macaques with SARS-CoV-2 or MERS-CoV and compared the pathology and virology with historical reports of SARS-CoV infections. In SARS-CoV-2-infected macaques, virus was excreted from nose and throat in the absence of clinical signs, and detected in type I and II pneumocytes in foci of diffuse alveolar damage and in ciliated epithelial cells of nasal, bronchial, and bronchiolar mucosae. In SARS-CoV-infection, lung lesions were typically more severe, while they were milder in MERS-CoV infection, where virus was detected mainly in type II pneumocytes. These data show that SARS-CoV-2 causes COVID-19-like disease in macaques, and provides a new model to test preventive and therapeutic strategies.
https://science.sciencemag.org/content/early/2020/04/16/science.abb7314

DIAGNOSTIC DEVELOPMENT

- I think this is the first Scottish paper to make the newsletter. The extent of spread of SARS coronavirus 2 (SARS-CoV-2) in the UK and elsewhere is unknown because typically only symptomatic individuals are diagnosed. We performed a serological study of recent blood donors in Scotland to detect antibodies to SARS-CoV-2 as a marker of past infection. Methods. A pseudotyped SARS-CoV-2 virus microneutralisation assay was used to detect neutralising antibodies to SARS-CoV-2. The study group comprised samples from 1000 blood donors collected in Scotland during March, 2020. Controls were collected from 100 donors in Scotland during 2019. Findings. All samples collected on the 17th March, 2020 (n=500) were negative in the pseudotyped SARS-CoV-2 virus microneutralisation assay. Neutralising antibodies were

detected in 5 of the 500 samples collected 21st to 23rd March; one further sample was reactive in an anti-spike ELISA. Interpretation. Although we cannot use the rise in numbers seropositive to infer the contemporary seroprevalence or the growth rate of the epidemic, we note that they are consistent with frequency of reported diagnosed infections and SARS-CoV-2-associated deaths reported in that time period in Scotland, given that seroconversion takes up to 2-3 weeks. It should also be noted that blood donors are not representative of the general population; in particular, those with a history of recent respiratory infections are deferred. Finally, it is unknown what proportion of infected individuals seroconvert and become reactive in the assays used. Serial follow up studies are needed to track infection and seroconversion in this and other similar populations However, these data indicate that sero-surveys of blood banks can serve as a useful tool for tracking the emergence and progression of an epidemic like the current SARS-CoV-2 outbreak.
https://www.medrxiv.org/content/10.1101/2020.04.13.20060467v1

- From UC Irvine - The current practice for diagnosis of COVID-19, based on SARS-CoV-2 PCR testing of pharyngeal or respiratory specimens in a symptomatic patient at high epidemiologic risk, likely underestimates the true prevalence of infection. Serologic methods can more accurately estimate the disease burden by detecting infections missed by the limited testing performed to date. Here, we describe the validation of a coronavirus antigen microarray containing immunologically significant antigens from SARS-CoV-2, in addition to SARS-CoV, MERS-CoV, common human coronavirus strains, and other common respiratory viruses. A comparison of antibody profiles detected on the array from control sera collected prior to the SARS-CoV-2 pandemic versus convalescent blood specimens from virologically confirmed COVID-19 cases demonstrates complete discrimination of these two groups. This array can be used as a diagnostic tool, as an epidemiologic tool to more accurately estimate the disease burden of COVID-19, and as a research tool to correlate antibody responses with clinical outcomes. https://www.biorxiv.org/content/10.1101/2020.04.15.043364v1
- Kudos to the Mt. Sinai group!!! They know that high throughput serological testing is needed and they are developing the tools. While PCR-based assays are used for diagnosis, high through-put serologic methods are needed to detect antibodies for seroserveillance and for identification of seroconversion, potential plasma donors, and the nature of the immune response to this pathogen. Methods. A Luminex binding assay was used to assess the presence of antibodies in human sera from COVID-19-infected and -uninfected individuals specific for two recombinant proteins of SARS-CoV-2. Findings. Fluorochrome-labeled beads were coated with a recombinant soluble stabilized trimeric SARS-CoV-2 S protein ectodomain or its central portion, the receptor binding domain (RBD). Coated beads were incubated with sera, followed by incubation with biotinylated anti-human total Ig antibodies and phycoerythrin (PE)-labeled streptavidin. Readout using a Luminex analyzer clearly differentiated between sera of the infected and uninfected subject, delineating a wide range of serum antibody levels in infected subjects. Interpretation. Antibody assays of sera can identify individuals who are infected with SARS-CoV-2 and have seroconverted, as well as subjects who have been infected and recovered. The use of the Luminex binding Ab assay has the advantage that it can be run in approximately 2.5 hours, uses very little antigen, and permits a high through-put of samples/day.
https://www.medrxiv.org/content/10.1101/2020.04.14.20059501v1

>>

2020-04-18

Jeez Louise, there were a lot of abstracts today. Fortunately, only a couple of clinical trials worth mentioning (one is for all you self-isolationists and how to keep buff and trim – one good way is to not bake chocolate chip cookies).

Here's the music choice for today. She sure didn't make a convincing Maria but just maybe La Netrebko is better suited for German operetta. From an earlier stage in her career (I think it's at the Baden-Baden gala): https://www.youtube.com/watch?v=7tUq8Q_b8Lg

I'm moving this one up to the top for the beginning of your newsletter reading. It's importance is obvious and the researchers are first rate. Santa Clara county is the sixth largest by population in CA and also home to Stanford University. The researchers took an off the shelf test kit that is made in China and distributed by a Minneapolis company. The Stanford group did additional testing on lab specimens collected from patients with known SARS-CoV-2 infections that were treated locally (this test has not been approved by the FDA). Background Addressing COVID-19 is a pressing health and social concern. To date, many epidemic projections and policies addressing COVID-19 have been designed without seroprevalence data to inform epidemic parameters. We measured the seroprevalence of antibodies to SARS-CoV-2 in Santa Clara County. Methods On 4/3-4/4, 2020, we tested county residents for antibodies to SARS-CoV-2 using a lateral flow immunoassay. Participants were recruited using Facebook ads targeting a representative sample of the county by demographic and geographic characteristics. We report the prevalence of antibodies to SARS-CoV-2 in a sample of 3,330 people, adjusting for zip code, sex, and race/ethnicity. We also adjust for test performance characteristics using 3 different estimates: (i) the test manufacturer's data, (ii) a sample of 37 positive and 30 negative controls tested at Stanford, and (iii) a combination of both. Results The unadjusted prevalence of antibodies to SARS-CoV-2 in Santa Clara County was 1.5% (exact binomial 95CI 1.11-1.97%), and the population-weighted prevalence was 2.81% (95CI 2.24-3.37%). Under the three scenarios for test performance characteristics, the population prevalence of COVID-19 in Santa Clara ranged from 2.49% (95CI 1.80-3.17%) to 4.16% (2.58-5.70%). *These prevalence estimates represent a range between 48,000 and 81,000 people infected in Santa Clara County by early April, 50-85-fold more than the number of confirmed cases. Conclusions The population prevalence of SARS-CoV-2 antibodies in Santa Clara County implies that the infection is much more widespread than indicated by the number of confirmed cases. Population prevalence estimates can now be used to calibrate epidemic and mortality projections.* [**note: While I have suspected there were more infections that were not diagnosed, the magnitude of these numbers is somewhat shocking. We need more such testing to confirm that this is what is really going on. It may be that the CRF does drop dramatically downward. This study has been nationally reported. It is also a good example of not waiting around for FDA to bless a diagnostic test system. A good lab can double check the company's self validation.**] https://www.medrxiv.org/content/10.1101/2020.04.14.20062463v1 there is also a modeling study here: https://www.medrxiv.org/content/10.1101/2020.04.13.20064220v1 that makes the same argument about underestimation of cases.

Here is a nice story on OHDSI's achievements in a short period of time: https://www.ohdsi.org/88-hours/

Derek Lowe has a couple of very good blog posts, the first one has some updates on hydroxychloroquine and the second on remdesivir. Neither are encouraging and the breach of protocol by the Chicago

investigator is very troubling (as usual with Derek's posts it is always illuminating to read the comments. He notes that he is receiving a lot of hate mail from the hydroxychloroquine community):

https://blogs.sciencemag.org/pipeline/archives/2020/04/16/more-small-molecule-clinical-data-against-covid-19-as-of-april-16

https://blogs.sciencemag.org/pipeline/archives/2020/04/17/whats-happening-with-remdesivir

This really doesn't fit into one of my existing categories but it does issue an important warning: **get rid of your pet ferrets!!!** As the pandemic progresses, information about the modes of transmission of SARS-CoV-2 among humans is critical to apply appropriate infection control measures and to slow its spread. Here we show that SARS-CoV-2 is transmitted efficiently via direct contact and via the air (via respiratory droplets and/or aerosols) between ferrets. Intranasal inoculation of donor ferrets resulted in a productive upper respiratory tract infection and long-term shedding, up to 11 to 19 days post-inoculation. SARS-CoV-2 transmitted to four out of four direct contact ferrets between 1 and 3 days after exposure and via the air to three out of four independent indirect recipient ferrets between 3 and 7 days after exposure. The pattern of virus shedding in the direct contact and indirect recipient ferrets was similar to that of the inoculated ferrets and infectious virus was isolated from all positive animals, showing that ferrets were productively infected via either route. This study provides experimental evidence of robust transmission of SARS-CoV-2 via the air, supporting the implementation of community-level social distancing measures currently applied in many countries in the world and informing decisions on infection control measures in healthcare settings.
https://www.biorxiv.org/content/10.1101/2020.04.16.044503v1

Yesterday, I sent around a note about the effort that is beginning at the Foundation for the National Institutes of Health. This was the culmination of the effort mentioned in a Washington Post story that I linked to a couple of days ago. Here is the FNIH link: https://fnih.org/news/press-releases/nih-launches-partnership-to-speed-covid19-vaccines-treatments I have received some emails requesting my opinion of this. I am not going to say too much outside of what I've already noted in past newsletters. This is not the point in time to criticize any research effort (perhaps the large number of hydroxychloroquine trials might be an exception). I have a paper that will likely be completed this weekend about conducting clinical trials in a pandemic. Of course I don't have the cachet to even consider submitting it for publication in one of the medical journals so it will likely reside on my website for anyone to read. When I was at PhRMA we created some consortia that were moved over the FNIH. The most successful of those was the Observational Medical Outcomes Partnership (OMOP) that lives on as the Observational Health Data Sciences and Informatics (OHDSI). I was the PhRMA project manager for OMOP and help get the necessary start up funding from the PhRMA Board. It was successful as we had a sound business plan and lots of sweat equity from PhRMA company people from several disciplines. I picked the executive director who had a lot of industry experience in bioinformatics and carried the project forward for it's first three years to a point where it could morph into a self-standing collaboration of industry and academic investigators. That's all I'm going to say as I don't want to put my chances of being nominated to the COVID-19 Blue Ribbon Panel in jeopardy!!

Phew!!!!! This ended up as a much longer newsletter than I thought!! I love research progress but staring at a computer screen for 3 ½ hours now is tiring. Note there are some abstracts below that don't necessarily fit into the categories but are of interest.

Alan

SARS-CoV-2 (AKA, COVID-19): It's here; we know what to do; and we are doing it!

Stay Safe, Mask Up, & Wash Hands

MODELING

- Here is a German model looking at exit strategies from lockdown with a focus on Antibody Testing. A strategy is needed such that both the health system is not overloaded letting people die in an uncontrolled way and also such that the majority of people can get back their social contacts as soon as possible. We investigate the potential effects of a combination of measures such as continuation of hygienic constraints after leaving lockdown, isolation of infectious persons, repeated and adaptive short-term contact reductions and also large-scale use of antibody tests in order to know who can be assumed to be immune and participate at public life without constraints. We apply two commonly used modeling approaches: extended SEIR models formulated both as System Dynamics and Agent-Based Simulation, in order to get insight into the disease dynamics of a complete country like Germany and also into more detailed behavior of smaller regions. We confirm the findings of other models that without intervention the consequences of the pandemic can be catastrophic and we extend such findings with effective strategies to overcome the challenge. Based on the modeling assumptions it can be expected that repeated short-term contact reductions will be necessary in the next years to avoid overload of the health system and that on the other side herd immunity can be achieved and antibody tests are an effective way to mitigate the contact reductions for many. [**note: I'm pretty sure that I've been saying pretty much the same thing.**]
https://www.medrxiv.org/content/10.1101/2020.04.14.20063750v1
- Here is an important consideration for returning to work. The consequences of COVID-19 infection varies substantially based on individual social risk factors and predisposing health conditions. Understanding this variability may be critical for targeting COVID-19 control measures, resources and policies, including efforts to return people back to the workplace. We compiled individual level data from the National Health Information Survey and Quarterly Census of Earnings and Wages to estimate the number of at-risk workers for each US county and industry, accounting for both social and health risks. Nearly 80% of all workers have at least one health risk and 11% are over 60 with an additional health risk. We document important variation in the at-risk population across states, counties, and industries that could provide a strategic underpinning to a staged return to work.
https://www.medrxiv.org/content/10.1101/2020.04.13.20063776v1
- A group in Australia is critical of IHME model that has been used for the prediction of ventilator and hospital beds in the US. A recent model developed at the Institute for Health Metrics and Evaluation (IHME) provides forecasts for ventilator use and hospital beds required for the care of COVID19 patients on a state-by-state basis throughout the United States over the period March 2020 through August 2020 (See the related website https://covid19.healthdata.org/projections for interactive data visualizations). In addition, the manuscript and associated website provide projections of deaths per day and total deaths throughout this period for the entire US, as well as for the District of Columbia. This research

has received extensive attention in social media, as well as in the mass media. Moreover, this work has influenced policy makers at the highest levels of the United States government, having been mentioned at White House Press conferences, including March 31, 2020. In this paper, we evaluate the predictive validity of model forecasts for COVID19 outcomes as data become sequentially available, using the IHME prediction of daily deaths. We have found that the predictions for daily number of deaths provided by the IHME model have been highly inaccurate. The model has been found to perform poorly even when attempting to predict the number of next day deaths. In particular, the true number of next day deaths has been outside the IHME prediction intervals as much as 70% of the time. [**note: I include this with a degree of trepidation. The whole modeling enterprise has moved into the political realm and many overlook the underlying problem of knowns and unknowns (https://en.wikipedia.org/wiki/There_are_known_knowns). It's easy to be a Monday morning quarterback but far more difficult to make decision on the field in the midst of a "fog of war" (yes, your humble correspondent has read von Clausewitz several times!!! See what good stuff you learn here?**]
https://www.medrxiv.org/content/10.1101/2020.04.11.20062257v1

- *We know what to do and we are doing it!!! That's from my mantra and a Berkeley group shows that it is working!!* By the start of April 2020, the majority of people living in the United States were under orders to dramatically restrict their daily activities in order to reduce transmission of the virus that can cause COVID-19. These strong social distancing measures will be effective in controlling the spread of the virus only if they are able to reduce the amount of close interpersonal contact in a population. It is therefore crucial for researchers and policymakers to empirically measure the extent to which these policies have actually reduced interpersonal interaction. We created the Berkeley Interpersonal Contact Study (BICS) to help achieve this goal. Here, we report the first set of BICS results, based on data collected in the United States between March 22, 2020 and April 8, 2020. We find evidence that rates of interpersonal contact have greatly been reduced at all ages in the United States.
https://www.medrxiv.org/content/10.1101/2020.04.13.20064014v1
- This is probably better suited to this category and is may have interesting clinical implications. Our researchers looked at the ACE2 gene in more than 200,000 people, comparing their exact DNA sequences to see where there are differences among people. Variation in the DNA sequence of a gene is common and is sometimes meaningless. But other times, small changes in the DNA sequence can alter the protein that is made from that gene. In this case the ACE2 gene makes the ACE2 protein, which is what the SARS-CoV-2 virus interacts with. We found a lot of variation between individuals and checked to see if that variation coincided with any traits (i.e., people with variant X tend to have high blood pressure more often than people without variant X). All of the traits we looked at were non-COVID-19-related traits, meaning we haven't asked these people anything about COVID-19 yet (this is because these DNA sequences were collected before the pandemic). We found that there are a number of variations observed among people in a specific part of the ACE2 gene. These variations are expected to alter the shape or functionality of a specific part of the ACE2 protein: The part that interacts with the SARS-CoV-2 virus. We don't yet know what the real-life significance of this variation is, but it's possible that these variants decrease the protein's ability to interact with the SARS-CoV-2 virus, thus decreasing the person's likelihood of being infected. We can speculate that there will be a

spectrum of vulnerability to COVID-19 among people, where some people are more vulnerable than others, and that variants in this part of the ACE2 gene may be one of the reasons. The research we presented here shines a light on this part of the ACE2 gene and may give future researchers a direction to go in as they try to figure out what makes people vulnerable to COVID-19 and similar viruses. [**note: This would be a very good observational cohort study. I assume that patient samples are being collected for retrospective analysis. So many intriguing paths to wander down after we get through the pandemic situation.**]
https://www.biorxiv.org/content/10.1101/2020.04.07.030544v1

NEWLY REGISTERED CLINICAL TRIALS

- Hard to believe that nobody thought to give mefloquine a try. A Russian group has stepped up to fill this gap in our knowledge. Study of the effectiveness and safety of the drug Mefloquine, tablets 250 mg, produced by FSUE "SPC" Farmzaschita " FMBA of Russia (Russia), in comparison with the drug Hydroxychloroquine, tablets 200 mg, for the treatment of patients with coronavirus infection, in the "off-label" mode, to make a decision on the possibility of expanding the indications for use. NCT04347031
- Some of you have asked about trials that address the impact on self-imposed isolation. Well I have just the trial for you!! From Turkey: Both influenza and coronaviruses cause respiratory infections, which can lead to morbidity and mortality, especially in those who are immunocompromised or not immune to viruses (Zhu). Physical exercise has many effects on the human body, including the immune system. Moderate exercise appears to have a beneficial effect on immune function, which can protect against upper respiratory infections. Human being is a social entity by nature and social isolation can negatively affect individuals' psychology. There are many studies examining the effect of physical activity on the mental state of people. The World Health Organization (WHO) suggests individual protection measures such as establishing necessary hygienic conditions, ensuring social isolation and keeping immune system strong against the complications that may develop due to Coronavirus.Human being is a social entity by nature and social isolation can negatively affect individuals' psychology. There are many studies examining the effect of physical activity on the mental state of people. Different theories which claims the psychological improvements resulting from the increased levels of physical activity have also been proposed in the literature.Regular aerobic exercise and walking can not only improve the emotional state of the individuals, but may also affect the mental health by avoiding the negative thoughts and adapting to stress. The aim of this study is to increase the physical activity level, psychological condition and physical well-being with video-based exercises. [**note to Jane Fonda – get your old workout videos up on YouTube ASAP!!! Oh wait, some intrepid person has already done this: https://www.youtube.com/watch?v=L5kKJ7Qvaqw Time to rewatch Klute! I wish that they would put "They Shoot Horses Don't They" on TV but maybe it's too dark a movie for these times.**] NCT04335851

CLINICAL TRIAL RESULTS

- This is just an observation that was recently published in the Lancet on the smaller than expected number of asthmatics getting hospitalized: https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30167-3/fulltext [**note: as someone who had mild asthma and suffers seasonal allergies, I wonder what role elevated IgE levels might mean. Maybe an added layer of protection?**]
- Here is a meta-analysis of chloroquine and hydroxychloroquine trials. We searched PubMed, EMBASE, Cochrane Central, Web of Science, Clinical Trials Registries, CNKI, Wanfang Data, CQVIP, and Preprint Servers through April 4, 2020, for randomized controlled trials (RCTs) that examined the efficacy and safety of CQ and HCQ against viral infection. We analyzed pooled data on the overall efficacy, the relative risks over the placebo, and the prevalence of adverse events. Trial sequential analysis (TSA) was also performed to evaluate the random errors in the meta-analysis. Potential moderators of drug-placebo efficacy differences were analyzed by meta-regression. Results: The analysis included 11 RCTs with 2613 adult patients. Both the plasma viral load (standard mean difference: 0.29, 95% CI: -1.19 - 1.76, P = 0.70) and the improvement of clinical symptoms (odds ratio: 2.36, 95% CI: 0.81 - 6.92, P = 0.11) were not different between the intervention and placebo arm. There was significant heterogeneity for the efficacy assessment, which was primarily explained by the age of patients and the sample size. Compared to the placebo, CQ and HCQ had increased risk of mild adverse events (risk ratio: 1.51, 95% CI: 1.35 - 1.70, P < 0.05, TSA adjusted 95% CI: 1.31 - 2.19), which were statistically significant in nervous, integumentary, and gastrointestinal systems. The most common adverse events were observed in the nervous system, with the pooled prevalence of 31.4% (95% CI: 10.5% - 56.7%). Conclusions: Insufficient data were available to support the antiviral efficacy of CQ and HCQ due to the high heterogeneity caused by the age of patients. Mild side effects are expected for the current antiviral dose regimens of CQ and HCQ. Treatment outcomes may be enhanced by better-selected patients based on age and well-controlled adverse events. [**note: still a lot of unknown unknowns with this drug treatment; will we ever know the answer?**] https://www.medrxiv.org/content/10.1101/2020.04.13.20064295v1
- Not a result exactly but an example how hospitals with EHR systems can form a consortium. Our goal is to consolidate and leverage the largely untapped resource of clinical data from electronic health records of hospital systems in affected countries with the aim to better-define markers of organ injury to improve outcomes. METHODS: A consortium of international hospital systems of different sizes utilizing Informatics for Integrating Biology and the Bedside (i2b2) and Observational Medical Outcomes Partnership (OMOP) platforms was convened to address the COVID-19 epidemic. Over a course of two weeks, the group initially focused on admission comorbidities and temporal changes in key laboratory test values during infection. After establishing a common data model, each site generated four data tables of aggregate data as comma-separated values files. These non-interlinked files encompassed, for COVID-19 patients, daily case counts; demographic breakdown; daily laboratory trajectories for 14 laboratory tests; and diagnoses by diagnosis codes. RESULTS: 96 hospitals in the US, France, Italy, Germany, and Singapore contributed data to the consortium for a total of 27,927 COVID-19 cases and 187,802 performed laboratory values. Case counts and laboratory trajectories were concordant with existing literature. Laboratory test values at the time of viral diagnosis showed hospital-level differences that were equivalent to country-level variation across the consortium partners.

CONCLUSIONS: In under two weeks, we formed an international community of researchers to answer critical clinical and epidemiological questions around COVID-19. Harmonized data sets analyzed locally and shared as aggregate data has allowed for rapid analysis and visualization of regional differences and global commonalities. Despite the limitations of our datasets, we have established a framework to capture the trajectory of COVID-19 disease in various subsets of patients and in response to interventions. [**note: they are using the OMOP data model platform!!**] https://www.medrxiv.org/content/10.1101/2020.04.13.20059691v1

- Here is an interesting Italian case study of a patient with severe encephalopathy from SARS-CoV-2 infection. SARS-CoV-2 infection has the potential for targeting central nervous system and several neurological symptoms have been described in patients with severe respiratory distress. Here we described the case of an otherwise healthy 60-year old subject with SARS-CoV-2 infection but only mild respiratory abnormalities who developed severe progressive encephalopathy associated with mild pleocytosis and hyperproteinorrachia. MRI was negative whereas EEG showed theta waves on the anterior brain regions. Serum and CSF analyses excluded other known infectious or autoimmune disorders. The patient dramatically improved after high-doses steroid treatment suggesting an inflammatory-mediated brain involvement related to SARS-CoV-2 infection.
  https://www.medrxiv.org/content/10.1101/2020.04.12.20062646v1
- More data from China on the association between ABO blood groups and clinical outcomes. The correlations between pathogen susceptibility and blood type distribution have attracted attention decades ago. The current retrospective study aimed to examine the correlation between blood type distribution and SARS-CoV-2 infection, progression, and prognosis in patients with coronavirus disease 2019 (COVID-19). With 265 patients from multiple medical centers and two established cohorts, we found that the blood type A population was more sensitive to SARS-CoV-2. Moreover, the blood type distribution was not relevant to acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), and mortality in COVID-19 patients. These findings are indicative of coping with the great threat since it probed the relationship between blood types and ARDS, AKI, and mortality, in addition to susceptibility in COVID-19 patients. [**note: you type A individuals need to take special care out there.**]
  https://www.medrxiv.org/content/10.1101/2020.04.15.20063107v1
- This is petty intriguing in terms of whether neutralizing antibodies are important. Whether antibodies are important for the adaptive immune responses against SARS-CoV-2 infection needs to be determined. Here, 26 cases of COVID-19 in Jinan, China, were examined and shown to be mild or with common clinical symptoms and no cases of severe symptoms were found among these patients. A striking feature of some patients is that SARS-CoV-2 could exist in patients who have virus-specific IgG antibodies for a very long period, with one case for up to 36 days. One COVID-19 patient who did not produce any SARS-CoV-2-bound IgG successfully cleared SARS-CoV-2 after 46 days of illness, revealing that without antibody-mediated adaptive immunity, innate immunity may still be powerful enough to eliminate SARS-CoV-2. Overall, this report may provide a basis for further analysis of both innate and adaptive immunity in SARS-CoV-2 clearance, especially in non-severe cases. This study also has implications for understanding the pathogenesis and treatment of SARS-CoV-2.
  https://www.medrxiv.org/content/10.1101/2020.04.13.20040980v1

- Here is an important meta-analysis from Japan, South Korea, and China on the potential effectiveness and safety of antiviral agents in children with SARS-CoV-2. A total of 23 studies of indirect evidence with 6008 patients were included. The risks of bias in all studies were moderate to high in general. The effectiveness and safety of antiviral agents for children with COVID-19 is uncertain: For adults with COVID-19, lopinavir/ritonavir had no effect on mortality (risk ratio [RR]= 0.77, 95% confidence interval [CI] 0.45 to 1.30) and probability of negative PCR test (RR=0.98, 95 CI% 0.82 to 1.18). Arbidol had no benefit on probability of negative PCR test (RR=1.27, 95% CI 0.93 to 1.73). Hydroxychloroquine was not associated with increasing the probability of negative PCR result (RR=0.93, 95% CI 0.73 to 1.18). For adults with SARS, interferon was associated with reduced corticosteroid dose (weighted mean difference [WMD]=-0.14 g, 95% CI -0.21 to -0.07) but had no effect on mortality (RR=0.72, 95% CI 0.28 to 1.88); ribavirin did not reduce mortality (RR=0.68, 95% CI % 0.43 to 1.06) and was associated with high risk of severe adverse reactions; and oseltamivir had no effect on mortality (RR=0.87, 95% CI 0.55 to 1.38). Ribavirin combined with interferon was also not effective in adults with MERS and associated with adverse reactions. Conclusions: *There is no evidence showing the effectiveness of antiviral agents for children with COVID-19, and the clinical efficacy of existing antiviral agents is still uncertain. We do not suggest clinical routine use of antivirals for COVID-19 in children, with the exception of clinical trials.* [**note: I love international cooperation!!!**] https://www.medrxiv.org/content/10.1101/2020.04.13.20064436v1
- And following up on the previous post, here is a meta-analysis of clinical symptoms in children. We searched studies reporting clinical characteristics in children with COVID-19 published until March 31, 2020. We screened the literature, extracted the data and evaluated the risk of bias and quality of evidence of the included studies. We combined some of the outcomes (symptoms) in a single-arm meta-analysis using a random-effects model. Results: Our search retrieved 49 studies, including 25 case reports, 23 case series and one cohort study, with a total of 1667 patients. Our meta-analysis showed that most children with COVID-19 have mild symptoms. Eighty-three percent of the children were within family clusters of cases, and 19% had no symptoms. At least 7% with digestive symptoms. The main symptoms of children were fever (48%, 95% confidence interval [CI]: 39%, 56%) and cough (39%, 95% CI: 30%, 48%). The lymphocyte count was below normal level in only 15% [95% CI: 8%, 22%] of children which is different from adult patients. 66% [95% CI: 55%, 77%] of children had abnormal findings in CT imaging. Conclusions: Most children with COVID-19 have only mild symptoms, and many children are asymptomatic. Fever and cough are the most common symptoms in children. Vomiting and diarrhea were not common in children. The lymphocyte count is usually within the normal range in children. https://www.medrxiv.org/content/10.1101/2020.04.13.20064352v1
- More pediatric information, this time about the use of antibiotics. We searched Cochrane library, Medline, Embase, Web of Science, CBM, Wanfang Data and CNKI from their inception to March 31, 2020. In addition, we searched related studies on COVID-19 published before March 31, 2020 through Google Scholar. We evaluated the risk of bias of included studies, and synthesized the results using a qualitative synthesis. Results: Six studies met our inclusion criteria. Five studies on SARS showed an overall risk of death of 7.2% to 20.0%. One study of SARS patients who used macrolides, quinolones or beta lactamases showed that the mean duration of hospital stay was 14.2, 13.8 and 16.2 days, respectively, and their average duration of fever was 14.3, 14.0 and 16.2 days, respectively. One cohort study on MERS indicated that

macrolide therapy was not associated with a significant reduction in 90-day mortality (adjusted odds ratio [OR] 0.84, 95% confidence interval [CI] 0.47-1.51, P = 0.56) and improvement in MERS-CoV RNA clearance (adjusted hazard ratio [HR] 0.88, 95% CI 0.47, -1.64], P = 0.68). According to the findings of 33 studies, the proportion of antibiotics use ranged from 19.4% to 100.0% in children and 13.2% to 100.0% in adults, despite the lack of etiological evidence. The most commonly used antibiotics in adults were quinolones, cephalosporins and macrolides and in children meropenem and linezolid. Conclusions: The benefits of antibiotic agents for adults with SARS or MERS were questionable in the absence of bacterial coinfections. There is no evidence to support the use of antibiotic agents for children with COVID-19 in the absence of bacterial coinfection. https://www.medrxiv.org/content/10.1101/2020.04.13.20064402v1

DRUG DEVELOPMENT

- Here is the phenotype of SARS-CoV-2 specific T-cells in patients who progress to ARD. COVID-19 is associated with lymphopenia and cytokine storm, but no information is available on specific cellular immune responses to SARS-CoV-2. Here, we characterized SARS-CoV-2-specific CD4+ and CD8+ T-cells in patients with acute respiratory distress syndrome. The spike protein (S) proved a potent T-cell antigen and specific T-cells predominantly produced Th1 cytokines. These novel data are important in vaccine design and will facilitate evaluation of vaccine candidate immunogenicity. https://www.medrxiv.org/content/10.1101/2020.04.11.20062349v1
- *Stop the presses, here is perhaps the best drug re-purposing study that I have read!* It's a large group of investigators who did not only some careful *in silico* screening but also *in vitro* anti-viral work to identify new drugs. The emergence of novel SARS coronavirus 2 (SARS-CoV-2) in 2019 has triggered an ongoing global pandemic of severe pneumonia-like disease designated as coronavirus disease 2019 (COVID-19). To date, more than 2.1 million confirmed cases and 139,500 deaths have been reported worldwide, and there are currently no medical countermeasures available to prevent or treat the disease. As the development of a vaccine could require at least 12-18 months, and the typical timeline from hit finding to drug registration of an antiviral is >10 years, repositioning of known drugs can significantly accelerate the development and deployment of therapies for COVID-19. To identify therapeutics that can be repurposed as SARS-CoV-2 antivirals, we profiled a library of known drugs encompassing approximately 12,000 clinical-stage or FDAapproved small molecules. Here, we report the identification of 30 known drugs that inhibit viral replication. Of these, six were characterized for cellular dose-activity relationships, and showed effective concentrations likely to be commensurate with therapeutic doses in patients. These include the PIKfyve kinase inhibitor Apilimod, cysteine protease inhibitors MDL-28170, Z LVG CHN2, VBY-825, and ONO 5334, and the CCR1 antagonist MLN-3897. Since many of these molecules have advanced into the clinic, the known pharmacological and human safety profiles of these compounds will accelerate their preclinical and clinical evaluation for COVID-19 treatment. [**note: is there an infrastructure in place to bring these into the clinic within the next week? I don't think so.**]

DIAGNOSTIC DEVELOPMENT

- I really LOVE outside the box thinking!!! This group rapidly developed and validated multiple new 3D-printed nasopharyngeal swabs!! We participated in an unprecedentedly open and urgent iterative process to help develop and validate new swabs. Methods We tested prototypes for material suitability, collection sufficiency, PCR compatibility, and the likelihood that they could be mass-produced, individually packaged, and sterilized quickly. Suitable prototypes were selected for an ongoing IRB-approved clinical trial. Participants were outpatients suspected of COVID-19 who presented to our drive-through test station. Each participant was swabbed with a control swab followed by a prototype swab. For each prototype, at least 10 control-swab positive and 10 control-swab negative PCR results were collected. We measured concordance using Cohen's kappa, compared Ct values by Mann-Whitney U, and assessed staff preferences via written survey. Results We evaluated 45 materials and 150 designs from 23 individuals, laboratories, and companies. We have selected four so far for the clinical trial. Three have completed testing. For these, we obtained PCR results from control and prototype swabs from 230 people (74-79 pairs/prototype). Concordance was 0.85-0.89 on 10-19 control-swab positives and 58-67 control-swab negatives. Ct values were statistically indistinguishable from controls. Staff preferred two of the prototypes over the third but ultimately preferred the control swab most. The time elapsed between identification of the problem and development of a high-manufacturing-volume solution was three weeks. Conclusions Our experience provides lessons for how an open process can efficiently and effectively contribute to resolving a medical manufacturing crisis during a major pandemic. [**note to self: figure out how to send them a prize!**] https://www.medrxiv.org/content/10.1101/2020.04.14.20065094v1
- I include this one here as it's another great example of outside the box thinking!! He constructed a positive pressure hood from ubiquitous low cost materials. A positive pressure protective hood system was purposefully constructed only from materials commonly found worldwide, including bendable aluminum mesh, elastic head straps, velcro tape, a plastic sheet, a furnace filter and two computer central processing unit (CPU) cooling fans. The practical advantages of this system are that the materials are readily available in the inventories of most electronics and hardware outlets, ease of assembly (particularly if choosing to employ 3D printing for the fan enclosure and/or making several units at once with a defined workflow), and high probability of the materials being available in current or prospective personal protective equipment (PPE)-deplete regions. An experiment with identical fire detectors showed adequate inner isolation of the hood prototype from paper combustion particulates, which have a size range slightly smaller than putative coronavirus aerosols, for at least 90 seconds. The theoretical advantages of this system include significant reduction in healthcare provider exposure to coronavirus-containing respiratory fomites, respiratory droplets and aerosols (vs. traditional static masks and shields) during high risk procedures such as endotracheal intubation or routine care of an upright and coughing patient. Additionally, the assembly eliminates contact exposure to coronavirus fomites due to whole-head coverage from a hood system. [**note: this guy deserves a prize for ingenuity! I have three unused computer fans sitting around. I think a trip to the hardware store is in order to get some of the materials I'm missing. I see a DIY project this weekend!!**] https://www.medrxiv.org/content/10.1101/2020.04.14.20064808v1
- More DIY information, this time on cloth materials for mask making. Objectives: To examine the ability of fabrics which might be used to create homemade face masks to filter out ultrafine

(smaller than 1µm in diameter) particles. Method: Twenty commonly available fabrics and materials were evaluated for their ability to reduce air concentrations of ultrafine particles. Further assessment was made on the filtration ability of select fabrics while damp and of fabric combinations which might be used to construct homemade masks. Results: Single fabric layers blocked a range of ultrafine particles. When fabrics were layered, significantly more ultrafine particles were filtered. Several fabric combinations were successful in removing similar amounts of ultrafine particles when compared to an N95 mask and surgical mask. Conclusions: The current coronavirus pandemic has left many communities without access to commercial facemasks. Our findings suggest that face masks made from layered common fabric can help filter ultrafine particles and provide some protection for the wearer when commercial facemasks are unavailable. [**note: there is a neighborhood seamstress who makes wonderful masks. We have been using them and they are quite comfortable and snug enough.**] https://www.medrxiv.org/content/10.1101/2020.04.14.20065375v1

- The Swedes have also shown that rapid and massive testing is feasible by extraction free SARS-CoV-2 RT-qPCR. The most widely used method of COVID-19 diagnostics is a reverse transcription quantitative polymerase chain reaction (RT-qPCR) assay, detecting the presence of SARS-CoV-2 RNA in patient samples, typically from nasopharyngeal swabs. The RNA extraction is a major bottleneck in current COVID-19 testing, in terms of turn-around, logistics, component availability and cost, which delays or completely precludes COVID-19 diagnostics in many settings. Efforts to simplify the current methods are important, as increased diagnostic availability and efficiency is expected to benefit patient care and infection control. Here, we describe methods to circumvent RNA extraction in COVID-19 testing by performing RT-qPCR directly on heat-inactivated subject samples as well as samples lysed with readily available detergents. Our data, including cross-comparisons with clinically diagnosed patient samples, suggest that direct RT-qPCR is a viable option to extraction-based COVID-19 diagnostics. We argue that significant savings in terms of time and cost can be achieved by embracing RNA-extraction-free protocols, that feeds directly into the established PCR-based testing pipeline. This could aid the expansion of COVID-19 testing. https://www.medrxiv.org/content/10.1101/2020.04.17.20067348v1

>>

2020-04-19

Contest Alert!!!!!! Today's music selection is one that I often come back to, a performance of the Country classic 'Wabash Cannonbal;' it is a group of all-star singers and musicians, some contemporary and some from years past: https://www.youtube.com/watch?v=z7eTelcaf_M The song is introduced by two old clips by the legendary Roy Acuff before the scrim comes up and Ketch Secor of Old Crow Medicine Show starts the second verse. Ketch introduces the instrumental soloists, but the second vocal soloist is not named. To win the prize, your task is to identify the wonderful baritone who sings the Daddy Claxton verse. Hey, let's also add a Sunday morning bonus!!! Of course you guessed it, 'Sunday Morning Coming Down' from Kris Kristofferson's debut album: https://www.youtube.com/watch?v=vbqGWTxwZEA [**note: I certainly do not endorse cigarette smoking!**]

Before getting into the nitty gritty, I'll point you all to a fine SCIENCE article on how SARS-CoV-2 illness progresses: https://www.sciencemag.org/news/2020/04/how-does-coronavirus-kill-clinicians-trace-ferocious-rampage-through-body-brain-toes and here is an interesting editorial: https://advances.sciencemag.org/content/early/2020/04/16/sciadv.abc1518

Our neighborhood listserve was inundated yesterday with questions about SARS-CoV-2 cleaning products. Alcohol wipes and bottled isopropyl alcohol have disappeared from the shelves. Not to worry as I found the updated EPS list of cleaning products. While a 'sure thing' is usually statistically impossible, chances are quite good that you have one of the products (the list is 47 pages!!!): https://www.dec.ny.gov/docs/materials_minerals_pdf/covid19.pdf I'm constantly on the lookout for things to help the public health!!!

I've received some correspondence about the Internet debate over the validity of the Santa Clara county serology study that I posted yesterday. I always enjoy a good debate but this one is a little over the top. As you know, my views on testing are that we need much more than is presently being done. I'm not going to criticize independent efforts; having read the Stanford paper this is the type of work that more groups need to be doing. I hope the Mt. Sinai folks are using their test to profile outbreaks in NYC. I received a note from a reader yesterday alerting me to a letter to the New England Journal of Medicine that 15% of pregnant women presenting at Columbia U hospitals for routine deliveries are viral positive (https://www.nejm.org/doi/full/10.1056/NEJMc2009316). I'm sure the babies will be tested to see if the early research showing no maternal -> fetus transmission occurs holds up.

To show what can and should be done, Germany are beginning an ambitious project of serological testing: https://www.nytimes.com/2020/04/18/world/europe/with-broad-random-tests-for-antibodies-germany-seeks-path-out-of-lockdown.html [**notes: Yesterday I posted a link to a German paper describing an exit strategy based on serological testing. Hey, I just realized that I also have a PhD in chemistry just like Chancellor Merkel, unfortunately it's a little late for me to enter the presidential primary race but I'm younger than Biden and Sanders!**] This is in accord with where things should be going in this country. Here are Emanuel and Romer on testing: https://www.theatlantic.com/ideas/archive/2020/04/were-testing-the-wrong-people/610234/ I'll continue to post periodic notes on this topic as it is critical to the reopening of the US.

I have discussed and posted about models since this newsletter began. There is a very good column in the Washington Post today on this topic. https://www.washingtonpost.com/outlook/2020/04/14/coronavirus-models-ihme-ic/ is written in plain language, discussing both the Imperial College and IHME models (**I hope it is not behind the paywall**). Here is the money quote, "Epidemiology can be complicated, but it can also be simple. Debating the merits of different models rather than taking prompt action to slow the relentless march of the coronavirus is a deadly mistake. We need no model at all to look at the grim data points of Wuhan, China; Italy; Spain; Britain; and now New York. Models will play a huge role in planning future strategies after we have emerged from this initial crisis, and we will have better data to inform them. But for the next few weeks, our duty is to stop more of those grim data points from developing."

Fortunately, it was a light day for abstracts and clinical trials today.

MODELING

- I already ranted enough in the introductory section.

NEWLY REGISTERED CLINICAL TRIALS

- One reader asked about Vitamin D and I think I forgot to post this one the other day. Here is a French trial looking at high dose administration of the vitamin. Vitamin D is a secosteroid hormone produced by the skin during Summer exposure to UVB rays. Hypovitaminosis D is common in Winter (October to March) at Northern latitudes above 20 degrees North, and from April to September at Southern latitudes beyond 20 degrees below the equator. In the past, coronaviruses and influenza viruses have exhibited very high seasonality, with outbreaks occurring preferentially during the Winter. The Covid-19 pandemic is indeed more severe above Winter latitudes of 20 degrees, while it remains until now less severe in the Southern hemisphere, with a much lower number of deaths. Preclinical research suggests that the SARS-Cov-2 virus enters cells via the angiotensin converting enzyme 2 (ACE2). Coronavirus viral replication downregulates ACE2, thereby dysregulating the renin-angiotensin system (RAS) and leading to a cytokine storm in the host, causing acute respiratory distress syndrome (ARDS). Research also shows that vitamin D plays a role in balancing RAS and in reducing lung damage. On the contrary, chronic hypovitaminosis D induces pulmonary fibrosis through activation of RAS. Similarly, hypovitaminosis D has been strongly associated in the literature with ARDS, as well as with a pejorative vital prognosis in resuscitation but also in geriatric units, and with various comorbidities associated to deaths during SARS-Cov-2 infections. Conversely, vitamin D supplementation has been reported to increase immunity and to reduce inflammatory responses and the risk of acute respiratory tract infections. High-dose oral vitamin D3 supplementation has been shown to decrease short-term mortality in resuscitation patients with severe hypovitaminosis D (17% absolute risk reduction). It is considered safe to take oral vitamin D supplementation at doses up to 10,000 IU/day for short periods, particularly in older adults, i.e. a population that is mostly affected by hypovitaminosis D and who should receive at least 1,500 IU of vitamin D daily to ensure satisfactory vitamin D status. Vitamin D supplementation is mentioned as a potentially interesting treatment for SARS-Cov-2 infection but on a scientific basis with a low level of evidence until now. We hypothesize that high-dose vitamin D supplementation improves the prognosis of older patients diagnosed with COVID-19 compared to a standard dose of vitamin D. [**note to self: I need to figure out how many containers of yogurt I need to eat daily to get the vitamin D levels up**] NCT04344041

CLINICAL TRIAL RESULTS

- Here is another interesting finding from the intrepid Chinese investigators who genetically profiled the ACE2 receptor and the cellular protease TMPRSS2 showing human organs susceptible to SARS-CoV-2 infection. ACE2 is a receptor protein of SARS-CoV-2, and TMPRSS2 promotes virus proliferation and transmission. Some patients developed multiple organ dysfunction syndromes other than lungs. Therefore, studying the viral susceptibility of other organs is important for a deeper understanding of viral pathogenesis. Methods: The advantage

of scRNA-seq data is the identification of cell types by clustering the gene expression of cells. ACE2 and TMPRSS2 are highly expressed in AT2 of lungs, we compared the ACE2 and TMPRSS2 expression levels of cell types from 31 organs, with AT2 of lungs to evaluate the risk of the viral infection using scRNA-seq data. Findings: For the first time, we found the brain, gall bladder, and fallopian tube are vulnerable to COVID-19 infection. Besides, the nose, heart, small intestine, large intestine, esophagus, testis and kidney are also identified to be high-risk organs with high expression levels of ACE2 and TMPRSS2. Moreover, the susceptible organs are grouped into three risk levels based on the TMPRSS2 expression. As a result, the respiratory system, digestive system and reproductive system are at the top-risk level to COVID-19 infection. Interpretation: *This study provides evidence for COVID-19 infection in the human nervous system, digestive system, reproductive system, respiratory system, circulatory system and urinary system using scRNA-seq data, which helps for the clinical diagnosis and treatment of patients.* [**note: real time genetic information may prove useful in patient treatment.**]
https://www.biorxiv.org/content/10.1101/2020.04.16.045690v1

- First paper from the United Arab Emirates!! Here is a discussion of the regulation of angiotensin converting enzyme 2 (ACE2) in obesity. Obesity and diabetes are usually associated with dysregulated lipid synthesis and clearance which can initiate or aggravate pulmonary inflammation and injury. It has been shown that for viral entry into the host cell, SARS-CoV-2 utilizes the angiotensin converting enzyme 2 (ACE2) receptors present on the cells. We aimed to characterize how SARS-CoV-2 dysregulates lipid metabolism pathways in the host and the effect of dysregulated lipogenesis on the regulation of ACE2, specifically in obesity. In our study, through the re-analysis of publicly available transcriptomic data, we first found that lung epithelial cells infected with SARS-CoV-2 showed upregulation of genes associated with lipid metabolism, including the SOC3 gene which is involved in regulation of inflammation and inhibition of leptin signaling. This is of interest as viruses may hijack host lipid metabolism to allow completion of their viral replication cycles. Furthermore, a mouse model of diet-induced obesity showed a significant increase in Ace2 expression in the lungs which negatively correlated with the expression of genes that code for sterol response element binding proteins 1 and 2 (SREBP). Suppression of Srebp1 showed a significant increase in Ace2 expression in the lung. Together our results suggest that the dysregulated lipogenesis and the subsequently high ACE2 expression in obese patients might be the mechanism underlying the increased risk for severe complications in those patients when infected by SARS-CoV-2.
https://www.biorxiv.org/content/10.1101/2020.04.17.046938v1
- We old folks need to be aware that SARS-CoV-2 incubation times may be longer than for youngsters, at least this observational study from China is suggestive of this. Based on individual case data published online by 21 cities of China, we investigated a total of 136 COVID19 patients who traveled to Hubei from 21 cities of China between January 5 and January 31, 2020, remained there for 48 hours or less, and returned to these cities with onset of symptoms between January 10 and February 6, 2020. Among these patients, 110 were found to be aged 15 to 64, 22 aged 65 to 86, and 4 aged under 15. Findings: The differential incubation time histogram of the two age groups 15 to 64 and 65 to 86 are adequately fitted by the log normal model. For the 15 to 64 age group, the median incubation time of 7.00+1.10 - 0.9 days (uncertainties are 95 % CL) is broadly consistent with previous literature. For the 65-86 age group, the median is 10.9+2.7 - 2.0 days is statistically significantly longer. Moreover, for this

group, the 95 % confidence contour indicates the data cannot constrain the upper bound of the log normal parameters μ, σ by failing to close there; this is because the sample has a maximum incubation time of 17 days, beyond which we ran out of data even though the histogram has not yet peaked. Thus there is the potential of a much longer incubation time for the 65 to 86 age group than 10 to 14 days. Only a much larger sample can settle this. [**note: Channeling Ponce de Leon – please let me know where the Fountain of Youth is; I need to turn the clock back 50 years!]** https://www.medrxiv.org/content/10.1101/2020.04.14.20065896v1

DRUG DEVELOPMENT

- I don't think I've seen a paper discussing the SARS-CoV-2 spike protein as a therapeutic target. This paper indicates that it might be a useful one to look at drug binding. The causative virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), uses its spike (S) protein to gain entry into host cells. Therefore, the S protein presents a viable target to develop a directed therapy. Here, we deployed an integrated artificial intelligence with molecular dynamics simulation approach to provide new details of the S protein structure. Based on a comprehensive structural analysis of S proteins from SARS-CoV-2 and previous human coronaviruses, we found that the protomer state of S proteins is structurally flexible. Without the presence of a stabilizing beta sheet from another protomer chain, two regions in the S2 domain and the hinge connecting the S1 and S2 subunits lose their secondary structures. Interestingly, the region in the S2 domain was previously identified as an immunodominant site in the SARS-CoV-1 S protein. We anticipate that the molecular details elucidated here will assist in effective therapeutic development for COVID-19.
https://www.biorxiv.org/content/10.1101/2020.04.17.047548v1

DIAGNOSTIC DEVELOPMENT

- This Chinese study looks at the clinical development of neutralizing antibodies in inpatients and convalescent patients. A total of 117 blood samples were collected from 70 COVID-19 inpatients and convalescent patients. The presence of neutralizing antibody was determined with a modified cytopathogenic assay based on live SARS-CoV-2. The dynamics of neutralizing antibody levels at different with different clinical characteristics were analyzed. Results. The seropositivity rate reached up to 100.0% within 20 days since onset, and remained 100.0% till day 41-53. The total GMT was 1:163.7 (95% CI, 128.5 to 208.6), and the antibody level was highest during day 31-40 since onset, and then decreased slightly. Individual differences in changes of antibody levels were observed among 8 representative convalescent patients. In multivariate GEE analysis, patients at age of 31-60 and 61-84 had a higher antibody level than those at age of 16-30 (β=1.0518, P=0.0152; β=1.3718, P=0.0020). Patients with a worse clinical classification had a higher antibody titer (β=0.4639, P=0.0227). Conclusions. The neutralizing antibodies were detected even at the early stage of disease, and a significant response showed in convalescent patients. Moreover, changes on antibody levels ware individual specific.
https://www.medrxiv.org/content/10.1101/2020.04.15.20065623v1