2020-10-26

Welcome to Week 32!

This popped up on my YouTube feed yesterday, a wonderful 'World Opera Day' concert. It starts off with the choral movement of Beethoven's 9th symphony in Tokyo and moves on from there. The filmed piece from Petra Jordan is lovely. I celebrate all these artists!!!: https://www.youtube.com/watch?v=BVBDDakOGlY Music can revive the soul and that is Act 1. Here are the links to the others: Act 2: https://www.youtube.com/watch?v=2tuqfIlS6Fw, Act 3: https://www.youtube.com/watch?v=jKMZlIBX4Gs and Act 4: https://www.youtube.com/watch?v=OO2QbIOurB4

The Washington Post offers suggestions to get through the upcoming holidays. Families are in a quandary about setting up visits. Let us not forget the stress on other family members of a COVID-19 patient. Here is a link about what is happening within the Vice President's office staff and the statement by President Trump's Chief of Staff. This is totally unsurprising to me. Germany's national disease control center was attacked with an incendiary device. A large city in western China had an asymptomatic outbreak of COVID-19. 4.7 million residents are being tested. Good news from the UK as the health secretary expects the AstraZeneca/Oxford vaccine to be rolled out in early 2021. There is data of immune response in elderly trial subjects. More good news, this time from Australia as the lockdown in Melbourne is being lifted as there are no cases of COVID-19. This one will disturb the anti-mask folks; Kansas counties with mask mandates are seeing new infections at half the rate of the rest of the state. MASK UP.

The New York Times continues to document how hospitals are being overrun with COVID-19 cases. College budgets and programs are being slashed. The Times also covers the outbreak of COVID-19 in Vice President Pence's staff. Even Fox News presenters may have been exposed to the virus. For those still going into office buildings, the elevator ride may be the scariest part of your work day.

STAT have a first person opinion by a physician who has symptoms of a 'long-hauler.' Here is a nice video on how the new mRNA COVID-19 vaccines work.

Monday's are slow and the low number of papers reflects this. All the more time to watch the wonderful opera selections!

MODELING

- We employ individual-based Monte Carlo computer simulations of a stochastic SEIR model variant on a two-dimensional Newman--Watts small-world network to investigate the control of epidemic outbreaks through periodic testing and isolation of infectious individuals, and subsequent quarantine of their immediate contacts. Using disease parameters informed by the COVID-19 pandemic, *we investigate the effects of various crucial mitigation features on the epidemic spreading: fraction of the infectious population that is identifiable through the tests; testing frequency; time delay between testing and isolation of positively tested individuals; and the further time delay until quarantining their contacts as well as the quarantine duration. We thus determine the required ranges for these intervention parameters to yield effective control of the disease through both considerable delaying the epidemic peak and massively reducing the total number of sustained infections*. [**note: as my loyal readers know, I love Monte Carlo**

simulations (and also the Monty Hall problem that is totally unrelated other than the first name) and usually cite these papers. This one is useful in that it looks at containment requirements for containing the spread of SARS-CoV-2. You need to download and read this one. The graphs are very useful.]
https://www.medrxiv.org/content/10.1101/2020.10.21.20217331v1

- Background: Recent studies have reported numerous significant predictors for adverse outcomes in COVID-19 disease. However, there have been few simple clinical risk score for prompt risk stratification. The objective is to develop a simple risk score for severe COVID-19 disease using territory-wide healthcare data based on simple clinical and laboratory variables. Methods: Consecutive patients admitted to Hong Kong public hospitals between 1st January and 22nd August 2020 diagnosed with COVID-19, as confirmed by RT-PCR, were included. The primary outcome was composite intensive care unit admission, need for intubation or death with follow-up until 8th September 2020. Results: COVID-19 testing was performed in 237493 patients and 4445 patients (median age 44.8 years old, 95% CI: [28.9, 60.8]); 50% male) were tested positive. Of these, 212 patients (4.8%) met the primary outcome. *A risk score including the following components was derived from Cox regression: gender, age, hypertension, stroke, diabetes mellitus, ischemic heart disease/heart failure, respiratory disease, renal disease, increases in neutrophil count, monocyte count, sodium, potassium, urea, alanine transaminase, alkaline phosphatase, high sensitive troponin-I, prothrombin time, activated partial thromboplastin time, D-dimer and C-reactive protein, as well as decreases in lymphocyte count, base excess and bicarbonate levels. The model based on test results taken on the day of admission demonstrated an excellent predictive value. Incorporation of test results on successive time points did not further improve risk prediction. Conclusions: A simple clinical score accurately predicted severe COVID-19 disease, even without including symptoms, blood pressure or oxygen status on presentation, or chest radiograph results*. [**note: here is some useful information from Hong Kong using population-based administrative data to model severe COVID-19.**
https://www.medrxiv.org/content/10.1101/2020.10.21.20217380v1
- Recently, the World Health Organization (WHO) in a brief report about the status of environmental surveillance for SARS-CoV-2 indicated that 'approaches are needed that can be applied in lower-resource settings, where a greater proportion of the population is not connected to sewers and instead uses pit toilets or septic tanks. Possibilities include testing surface water contaminated by sewage'. In this study we measured SARS-CoV-2 RNA from a surface water source in a low-income settlement. We observe for this community that measurements of SARS-CoV-2 concentrations in surface water contaminated by sewage can be considered as an estimation of changes in COVID-19 prevalence on a population level. [**note: this is from Argentina and is an example of how viral surveillance in a low resource community can help out in monitoring for SARS-CoV-2 spread.**]
https://www.medrxiv.org/content/10.1101/2020.10.21.20215434v1
- We model the propagation of an infection, in a population, as a simplified age-dependent branching process. We analytically estimate the fraction of population, needed to be infected or immuned, to achieve herd immunity for an infection. We calculate this estimation as a function of the incubation period of the contagion, contact probability among the infected and susceptible population, and the probability of disease transmission from an infected to a susceptible individual. *We show how herd immunity is strongly dependent on the incubation*

period, and it may be extremely difficult to achieve herd immunity in case of large incubation period. We derive the distribution of generation time from basic principles, which, by far, has been assumed in an ad hoc manner in epidemiological studies. We quantify the success probability of quarantine measures before achieving herd immunity, and discuss a novel method for designing effective quarantine measures in the absence of any pharmaceutical interventions. We also compare the effectiveness of an early imposition against a delayed imposition of lockdown, of the same duration, in mitigating infection from a population. [**note: this Univ of Leeds researchers provides a model for herd immunity and the success probability of quarantine measures. Second only to Monte Carlo, stochastic models are my cup of tea. This paper was a sober reminder of how much calculus I've forgotten over the years. If you have the math skills this is an intriguing paper!**]
https://www.medrxiv.org/content/10.1101/2020.10.22.20216481v1

- In response to the SARS-CoV-2 pandemic, unprecedented policies of travel restrictions and stay-at-home orders were enacted around the world. Ultimately, the public's response to announcements of lockdowns - defined here as restrictions on both local movement or long distance travel - will determine how effective these kinds of interventions are. Here, we measure the impact of the announcement and implementation of lockdowns on human mobility patterns by analyzing aggregated mobility data from mobile phones. *We find that following the announcement of lockdowns, both local and long distance movement increased. To examine how these behavioral responses to lockdown policies may contribute to epidemic spread, we developed a simple agent-based spatial model. We find that travel surges following announcements of lockdowns can increase seeding of the epidemic in rural areas, undermining the goal of the lockdown of preventing disease spread. Appropriate messaging surrounding the announcement of lockdowns and measures to decrease unnecessary travel are important for preventing these unintended consequences of lockdowns*. [**note: this is from the Harvard School of Public Health and shows how travel behavior undermines containment of SARS-CoV-2.**]
https://www.medrxiv.org/content/10.1101/2020.10.22.20217752v1
- Within-household transmission of SARS-CoV-2 infection has been identified as one of the main sources of spread of COVID-19 after lockdown restrictions and self-isolation guidelines are implemented. Secondary attack rates among household contacts are estimated to be five to ten times higher than among non-household contacts, but it is unclear which individuals are more prone to transmit infection within their households. METHODS: Using address matching, a cohort was assembled of all laboratory-confirmed cases of COVID-19 residing in private households in Ontario, Canada. Descriptive analyses were performed to compare characteristics of cases in households that experienced secondary transmission versus those that did not. Logistic regression models were fit to determine index case characteristics and neighbourhood characteristics associated with transmission. FINDINGS: Between January and July, 2020, there were 26,152 cases of COVID-19 residing in 21,226 households. Longer testing delays (≥5 days versus 0 days OR=3.02, 95% CI: 2.53 - 3.60) and male sex (OR=1.28, 95% CI: 1.18 - 1.38) were associated with greater odds of household secondary transmission, while being a healthcare worker (OR=0.56, 95% CI: 0.50 - 0.62) was associated with lower odds of transmission. Neighbourhoods with larger average economic family size and a higher proportion of households with multiple persons per room were also associated with greater odds of transmission. INTERPRETATION*: It is important for individuals to get tested for SARS-CoV-2*

infection as soon as symptoms appear, and to isolate away from household contacts; this is particularly important in neighbourhoods with large family sizes and/or crowded households. [**note: this is from Ontario and looks at the characteristics associated with household transmission of SARS-CoV-2 in the province.**] https://www.medrxiv.org/content/10.1101/2020.10.22.20217802v1

NEWLY REGISTERED CLINICAL TRIALS

- I checked yesterday!

CLINICAL TRIAL RESULTS

- Patients with coronavirus disease 2019 (COVID-19) predominantly have a respiratory tract infection with various symptoms and high mortality is associated with respiratory failure second to severe disease. The risk factors leading to severe disease remain unclear. Here, we reanalyzed a published single-cell RNA-Seq (scRNA-Seq) dataset and found that bronchoalveolar lavage fluid (BALF) of patients with severe disease compared to those with mild disease contained decreased TH17 type cells, decreased IFNA1 expressing cells with lower expression of toll-like receptor 7 (TLR7) and TLR8, increased IgA expressing B cells, and increased hyperactive epithelial cells (and/or macrophages) expressing matrix metalloproteinases (MMPs), Hyaluronan synthase 2 (HAS2), and Plasminogen activator inhibitor-1 (PAI-1), which may together contribute to the pulmonary pathology in severe COVID-19. *We propose IFN-I (and TLR7/TLR8) and PAI-1 as potential biomarkers to predict the susceptibility to severe COVID19*. {**note: form Univ of New Mexico, more information on dysregulation of pulmonary response and possible biomarkers for severe COVID-19.**] https://www.biorxiv.org/content/10.1101/2020.10.23.353177v1

DRUG DEVELOPMENT

- Nothing new.

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Nothing new.

DIAGNOSTIC DEVELOPMENT

- Nothing new.

>>

2020-10-27

I featured Hilary Hahn back in May playing the Bach concerto for two violins. Here is a piece considerably later than the Bach, the Sibelius violin concerto: https://www.youtube.com/watch?v=DpbTHQn7RP8 We saw her play this piece with the Baltimore Symphony maybe seven years ago at the Strathmore Concert Hall right up the road from us in Bethesda.

The Washington Post reports that Boston wastewater testing is pointing to a surge in COVID-19 infections, not the news we wanted to read about. Chicago Mayor Lightfoot wants regional action to stop the case swell in the Midwest. Hospitals are again receiving high cases of COVID-19 patients. A

British study shows that antibodies to SARS-CoV-2 wane with time. This would not be unusual and does not imply that immune memory is lost. Airlines are playing hardball if passengers won't wear masks. Half of South Dakota's prison population test positive for COVID-19. Here is a dancing event in South Carolina that did not end well. The Lilly monoclonal antibody does not appear to help patients with severe COVID-19 and the clinical trial in those patients will end. While disappointing, this is not all that surprising as many patients with severe COVID-19 produce antibodies to the virus but the immune system dysfunction is what causes problems. We still are in need of a therapeutic approach for cytokine storm. Public transportation or ride share, what is the right choice?

The New York Times has a sobering story on why the City's recovery will be difficult. El Paso has instituted a curfew to help stem COVID-19 case. Among healthcare workers, nurses are most at risk for contacting COVID-19. The virus outlook worsens. Russia implements a nationwide mask mandate. The Times also reports on the halted Lilly monoclonal antibody trial.

Tony Fauci weighs in on COVID-19 vaccines.

STAT asks why isn't routine COVID-19 testing happening in prisons and immigrant detention centers? This article discusses what colleges that are currently doing distance learning need to do to open successfully in early 2021. As you know I am following Purdue University and it looks like there was an uptick in positive COVID-19 tests in the recent week with a rate of 4.07%. I hope they get this under control! Being a good engineering school, I wonder if they are testing sewage effluents.

The Atlantic has an interesting article on the difference between feeling safe and being safe.

Nature have an interesting paper on the Spike mutation D614G which is the major strain circulating now. *D614G enhances replication on human lung epithelial cells and primary human airway tissues through an improved infectivity of virions. Hamsters infected with the G614 variant produced higher infectious titers in the nasal washes and trachea, but not lungs, confirming clinical evidence that the D614G mutation enhances viral loads in the upper respiratory tract of COVID-19 patients and may increases transmission. Sera from D614-infected hamsters exhibit modestly higher neutralization titers against G614 virus than against D614 virus, indicating that (i) the mutation may not reduce the ability of vaccines in clinical trials to protect against COVID-19 and (ii) therapeutic antibodies should be tested against the circulating G614 virus. Together with clinical findings, our work underscores the importance of this mutation in viral spread, vaccine efficacy, and antibody therapy*.

Medscape report on how CDC will monitor COVID-19 vaccine recipients.

MODELING

- Background The course of coronavirus disease 2019 (COVID-19) seems to be aggravated by air pollution, and some industrial chemicals, such as the perfluorinated alkylate substances (PFASs), are immunotoxic and may contribute as well. Methods From Danish biobanks, we obtained plasma samples from 323 subjects aged 30-70 years with known SARS-CoV-2 infection. The PFAS concentrations measured at the background exposures included five PFASs known to be immunotoxic. Register data was obtained to classify disease status, other health information, and demographic variables. We used ordinal and ordered logistic regression analyses to determine associations between PFAS concentrations and disease outcome. Results Plasma-PFAS concentrations were higher in males, in subjects with Western European background, and

tended to increase with age, but were not associated with the presence of chronic disease. Of the study population, 108 (33%) had not been hospitalized, and of those hospitalized, 53 (16%) had been in intensive care or were deceased. Among the five PFASs considered, perfluorobutanoic acid (PFBA) showed an odds ratio (OR) of 2.19 (95% confidence interval, CI, 1.39-3.46) for increasing severities of the disease, although the OR decreased to 1.77 (95% CI, 1.09, 2.87) after adjustment for age, sex, sampling site and interval between blood sampling and diagnosis. Conclusions *Measures of individual exposures to immunotoxic PFASs included PFBA that accumulates in the lungs. Elevated plasma-PFBA concentrations were associated with an increased risk of more severe course of CIVID-19. Given the low background exposure levels in this study, the role of PFAS exposure in COVID-19 needs to be ascertained in populations with elevated exposures*. {**note: this is from Denmark shows a potential linkage of a class of air pollutants with severe COVID-19]**
https://www.medrxiv.org/content/10.1101/2020.10.22.20217562v1

- Background Beginning in early February 2020, COVID-19 spread across the state of Georgia leading to 258,354 cumulative cases as of August 25, 2020. The time scale of spreading (i.e., serial interval) and magnitude of spreading (i.e., Rt or reproduction number) for COVID-19, were observed to be heterogenous by demographic characteristics, region and time period. In this study, we examined the COVID-19 transmission in the state of Georgia, United States. Methods During February 1-July 13, 2020, we identified 4080 transmission pairs using contact information from reports of COVID-19 cases from the Georgia Department of Public Health. We examined how various transmission characteristics were affected by disease symptoms, demographics (age, gender, and race), and time period (during shelter-in-place and after reopening). In addition, we estimated the time course of reproduction numbers during early February-mid-June for all 159 counties in the state of Georgia, using a total of 118,491 reported COVID-19 cases. Findings Over this period, the serial interval appeared to decrease from 5.97 days in February-April to 4.40 days in June-July. With regard to age, transmission was assortative and patterns of transmission changed over time. COVID-19 mainly spread from adults to all age groups; transmission among and between children and the elderly was found less frequently. Younger adults (20-50 years old) were involved in the majority of transmissions occurring during or after reopening subsequent to the shelter-in-place period. By mid-July, two waves of COVID-19 transmission were apparent, separated by the shelter-in-place period in the state of Georgia. Counties around major cities and along interstate highways had more intense transmission. Interpretation *The transmission of COVID-19 in the state of Georgia had been heterogeneous by area and changed over time. The shelter-in-place was not long enough to sufficiently suppress COVID-19 transmission in densely populated urban areas connected by major transportation links. Studying local transmission patterns may help in predicting and guiding states in prevention and control of COVID-19 according to population and region*. [**note: this is from Emory Univ and studies transmission of COVID-19 in the state of Georgia. It's perhaps the best single study of a state that I've seen.]**
https://www.medrxiv.org/content/10.1101/2020.10.22.20217661v1
- What is hardly known in the studies of the COVID-19 global pandemic crisis is the impact of general lockdown during the first wave of COVID-19 pandemic both public health and economic system. The main goal of this study is a comparative analysis of some European countries with a longer and shorter period of national lockdown during the first wave of COVID-19 from March to August 2020. *Findings suggests that: a) countries with shorter period of lockdown have a*

variation of confirmed cases/population (%) higher than countries with longer period of lockdown; b) countries with shorter period of lockdown have average fatality rate (5.45%) lower than countries with longer period of lockdown (12.70%), whereas variation of fatality rate from August to March 2020 suggests a higher reduction in countries with longer period of lockdown (-1.9% vs 0.72%). However, Independent Samples Test and the Mann-Whitney test reveal that the effectiveness of longer period of lockdown versus shorter one on public health is not significant. In addition, the COVID-19 pandemic associated with longer period of lockdown has a higher negative impact on economic growth with consequential social issues in countries. Results of the impact of COVID-19 lockdowns on public health and economies of some leading countries in Europe, during the first wave of the COVID-19 pandemic, can provide vital information to design effective containment strategies in future waves of this pandemic to minimize the negative effects in society. [**note: this is from Italy looks at the impact of lockdown during the first wave of COVID-19. The interesting finding here is that longer lockdowns don't appear to have a significant effect on public health. Obviously, if we did much more testing we could do targeted remediation to control the virus.**]
https://www.medrxiv.org/content/10.1101/2020.10.22.20217695v1

- While some countries adapted draconic measures, which have been perceived controversial others pursued a strategy aiming for herd immunity. The latter is even more controversial and has been called unethical by the WHO Director-General. Inevitably, without proper control measure, viral diversity increases and multiple infectious exposures become common, when the pandemic reaches its maximum. This harbors not only a potential threat overseen by simplified theoretical arguments in support of herd immunity, but also deserves attention when assessingresponse measures to increasing numbers of infection. Methods and findings: We extend the simulation model underlying the pandemic preparedness web interface CovidSim 1.1 (http://covidsim.eu/) to study the hypothetical effect of increased morbidity and mortality due to 'multi infections', either acquired at by successive infective contacts during the course of one infection or by a single infective contact with a multi-infected individual. The simulations are adjusted to reflect roughly the situation in the East Coast of the USA. We assume a phase of general contact reduction ('lockdown') at the beginning of the epidemic and additional case-isolation measures. *We study the hypothetical effects of varying enhancements in morbidity and mortality, different likelihoods of multi-infected individuals to spread multi infections and different susceptibility to multi infectious in different disease phases. It is demonstrated that multi infections lead to a slight reduction in the number of infections, as these are more likely to get isolated due to their higher morbidity. However, the latter substantially increases the number of deaths. Furthermore, simulations indicate that a potential second lockdown can substantially decrease the epidemic peak, the number of multi-infections and deaths. Conclusions: Enhanced morbidity and mortality due to multiple disease exposure is a potential threat in the COVID-19 pandemic that deserves more attention. Particularly it underlines another facet questioning disease management strategies aiming for herd immunity* [**note: here is an interesting paper on herd immunity and the potential for increased mortality.**]
https://www.medrxiv.org/content/10.1101/2020.10.22.20217638v1
- In Italy, 311364 cases and 35851 deaths of people who tested positive for SARS-CoV-2 were registered as of September 29th, 2020. To avoid the spreading of the virus, mathematical models predicting the course of infection spread1 become the basis to plan stringent

countermeasures. We applied a published algorithm to real data up to September 27th, modeling two scenarios where predicted and real data were compared: a conservative scenario with a lockdown still ongoing and a scenario reflecting what actually happened in Italy, where the lockdown has been removed. *Results revealed that the number of individuals in life-threatening condition is much lower than predicted, as well as the number of symptomatic individuals. Contrarily, the number of asymptomatic individuals is much higher than predicted. This suggest that human beings are not passive victims, but active fighters able to change the course of the infection creating adaptive strategies against the infection spread*. [**note: here is an interesting paper from Italy on the importance of the human factor during the pandemic. I am not sure I would term things 'successful' as the authors have.**]
https://www.medrxiv.org/content/10.1101/2020.10.22.20215277v1

- Coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), exhibits high levels of mortality and morbidity and has dramatic consequences on human live, sociality and global economy. Neutralizing antibodies constitute a highly promising approach for treating and preventing infection by this novel pathogen. In the present study, we characterized and further evaluated the recently identified human monoclonal MD65 antibody for its ability to provide protection against a lethal SARS-CoV-2 infection of K18-hACE2 transgenic mice. 75% of the untreated mice succumbed 6-9 days post-infection while administration of the MD65 antibody as late as 3 days after exposure, rescued all infected animals. The data unprecedentedly demonstrate, the therapeutic value of human monoclonal antibodies as a life-saving treatment of severe COVID-19 infection. [**note: here is an Israeli monoclonal antibody.**]
https://www.biorxiv.org/content/10.1101/2020.10.26.354811v1
- SARS-CoV-2-neutralizing antibodies are promising therapeutics for COVID-19. However, little is known about the mechanisms of action of these antibodies or their effective dosing windows. We report the discovery and development of SC31, a potent SARS-CoV-2 neutralizing IgG1 antibody, originally isolated from a convalescent patient at day 27 after the onset of symptoms. Neutralization occurs via a binding epitope that maps within the ACE2 interface of the SARS-CoV-2 Spike protein, conserved across all common circulating SARS-CoV-2 mutants. In SARS-CoV-2 infected K18-human ACE2 transgenic mice, SC31 demonstrated potent survival benefit by dramatically reducing viral load concomitant with attenuated pro-inflammatory responses linked to severe systemic disease, such as IL-6. Comparison with a Fc-null LALA variant of SC31 demonstrated that optimal therapeutic efficacy of SC31 requires intact Fc-mediated effector functions that can further induce an IFNγ-driven anti-viral immune response. Dose-dependent efficacy for SC31 was observed down to 5mg/kg when dosed before the activation of lung inflammatory responses. Importantly, despite FcγR binding, no evidence of antibody dependent enhancement was observed with the Fc-competent SC31 even at sub-therapeutic doses. Therapeutic efficacy was confirmed in SARS-CoV-2-infected hamsters, where SC31 again significantly reduced viral load, decreased lung lesions and inhibited progression to severe disease manifestations. This study underlines the potential for significant COVID-19 patient benefit for the SC31 antibody that justifies rapid advancement to the clinic, as well as highlighting the importance of appropriate mechanistic and functional studies during development. [**note: this mAb comes from Singapore.**]
https://www.biorxiv.org/content/10.1101/2020.10.26.355107v1

- SARS-CoV-2 is causing a second outbreak so the hope for its complete eradication is far from happening. In the absence of effective vaccines, it is mandatory to find effective treatments with low adverse effects able to treat hospitalized patients with COVID-19 disease. In this work, we determined the existence of SARS-CoV-2 specific T cells within the CD45RA- T memory cells from the blood of convalescent donors. Memory T cells can respond quickly to the infection and provide long-term immune protection to reduce the severity of the COVID-19 symptoms. Also, CD45RA- memory T cells confer protection from other pathogens the donors encountered in their life. This is vital to clear other secondary infections usually developed in hospitalized COVID-19 patients. SARS-CoV-2 specific memory T cells were found within all the CD45RA- subsets CD3+, CD4+, CD8+, and in the central memory and effector memory subpopulations. The procedure to obtain the cells is feasible, easy to implement for small scale manufacture, quick and cost-effective involving minimal manipulation, and without GMP condition requirements. This biobank of specific SARS-CoV-2 memory T cells would be immediately available off-the-shelf to treat moderate/severe cases of COVID-19 increasing the therapeutic options available for these patients. [**note: this is from Spain and represents a different therapeutic approach using memory T cells.]**
  https://www.biorxiv.org/content/10.1101/2020.10.23.352294v1

NEWLY REGISTERED CLINICAL TRIALS

- I check this on Sunday.

CLINICAL TRIAL RESULTS

- Only the news article on the Eli Lilly monoclonal antibody is relevant.

DRUG DEVELOPMENT

- The SARS-Cov-2 pandemic is triggering a global health emergency alert, and recent research is indicating the relevance of aerosols in the spread of SARS-CoV-2. Thus, in this study antiseptic mouthwashes based on the actives chlorhexidine (CHX) and octenidine (OCT) were investigated regarding their efficacy against SARS-CoV-2 using EN 14476. Based on the requirement of EN 14476 (i.e. reduction of viral titer by ≥ 4 log 10), the OCT-based formulation was effective within only 15 sec against SARS-CoV-2, and thus constitutes an interesting candidate for future clinical studies to prove its effectiveness in a potential prevention of SARS-CoV-2 transmission by aerosols. [**note: this is from Germany and looks at mouthwash efficacy.**]
  https://www.biorxiv.org/content/10.1101/2020.10.25.354571v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Nothing new.

DIAGNOSTIC DEVELOPMENT

- Monocyte CD169 upregulation has been reported as a marker of viral infections, we evaluated a flow cytometry three-color rapid assay of whole blood monocyte CD169 for CoVID-19 screening. Outpatients (n=177) with confirmed CoVID-19 infection, comprising 80 early-stage (≤14 days after symptom onset), 71 late-stage (≥15 days), and 26 asymptomatic patients received whole blood CD169 testing in parallel with SARS-CoV-2 RT-PCR. Upregulation of monocyte CD169

without polymorphonuclear neutrophil CD64 changes was the primary endpoint. Sensitivity was 98% and 100% in early-stage and asymptomatic patients respectively, specificity was 50% and 84%. Rapid whole blood monocyte CD169 evaluation was highly sensitive when compared with RT-PCR, especially in early-stage, asymptomatic patients whose RT-PCR tests were not yet positive. *Diagnostic accuracy, easy finger prick sampling and minimal time-to-result (15-30 minutes) rank whole blood monocyte CD169 upregulation as a potential screening and diagnostic support for CoVID-19. Secondary endpoints were neutrophil CD64 upregulation as a marker of bacterial infections and monocyte HLA-DR downregulation as a surrogate of immune fitness, both assisting with adequate and rapid management of non-CoVID cases*. {**note: this is a rapid test for a presumptive marker for COVID-19.**]
https://www.medrxiv.org/content/10.1101/2020.10.22.20215749v1

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

2020-10-28

Here is another Wigmore Hall recital. The pianist is Russian pianist Pavel Kolesnikov. This is the first time I've heard him, and he is quite good. In looking at some reviews, his programs are always structured with a variety of different composer's works. In this recital there is Scriabin, Liszt, Schubert and Beethoven: https://www.youtube.com/watch?v=RNQYEKPLE4A

The Washington Post has a wellness column on the collision of pandemic depression with seasonal depression. This is wearing on all of us. There was a good video roundtable discussion of how to safely reopen schools and business. Admiral Giroir gave a very good presentation. Here is an in depth story of the Kansas nursing home that saw all of the residents contract COVID-19. It was heavily fined by CMS as a result of improper actions to control virus outbreak within the facility. Chicago is closing indoor dining at restaurants and bars this Friday because of the large outbreak. Things are trending in the wrong direction for Pennsylvania. Why aren't people wearing masks? Here is what people are buying during the pandemic. The boom in home cooking is seeing spices jump off grocery shelves. YIKES!!!!! Melbourne's 111-day lockdown had consequences. SUNY students will need a negative COVID-19 test before they can leave for Thanksgiving; this is a good idea. Congrats to Sanofi and GSK who will supply 200 million vaccines to the global effort. Northern Virginia is working on plans to return kids to school. More Western states are stupidly joining California to review COVID-19 vaccines. Let the FDA do its job.

The New York Times asks a good question, 'When Will the Children Visit?' Holding school classes outside is one good approach (as long as the weather holds up). Science labs and hubs may be coming to Manhattan! Pfizer will not have results of their COVID-19 vaccine by the end of the month. Some college towns are seeing COVID-19 cases drop. CDC notes that most Americans have been wearing masks since the spring. The Times also covers the Melbourne lockdown ending. Newark NJ is shutting down.

STAT wants to know how homebound older individuals will get vaccinated for COVID-19.

The Lancet has a commentary on lessons from Sweden, where can older adults shelter from COVID-19? Here is an important paper on defining what constitutes an efficacious COVID-19 vaccine. There will be challenges.

Medscape points to an article that HCQ fails to protect medical workers in a study from Univ of Minnesota.

There are a lot of papers today!!!

MODELING

- We assess the economic value of screening testing programs as a policy response to the ongoing COVID-19 pandemic. We find that the fiscal, macroeconomic, and health benefits of rapid SARS-CoV-2 screening testing programs far exceed their costs, with the ratio of economic benefits to costs typically in the range of 4-15 (depending on program details), not counting the monetized value of lives saved. Unless the screening test is highly specific, however, the signal value of the screening test alone is low, leading to concerns about adherence. Confirmatory testing increases the net economic benefits of screening tests by reducing the number of healthy workers in quarantine and by increasing adherence to quarantine measures. The analysis is undertaken using a behavioral SIR model for the United States with 5 age groups, 66 economic sectors, screening and diagnostic testing, and partial adherence to instructions to quarantine or to isolate. [**note: this is a paper from three economists who look at the benefits of screening tests. Of course this is obvious to those of use who have been advocating big testing programs!!!!**] https://www.medrxiv.org/content/10.1101/2020.10.22.20217984v1
- Background: School reopened in August-September 2020 and their effect on COVID-19 infections is unclear. Methods: We examined Coronavirus Disease-19 incidence following school reopening in Florida. Results: We found that counties teaching physically had 1.2-fold incidence increase in elementary schools and 1.3-fold increase in high schools, while counties teaching remotely had no increase. Conclusions: *Our results suggest that counties teaching physically could consider teaching remotely, especially in high school, until it is safe to teach physically*. [**note: here is data on COVID-19 cases in Florida schools after reopening. No surprise here but it would be interesting to know what the background rate change was in the community rather than just age groups.**] https://www.medrxiv.org/content/10.1101/2020.10.24.20218321v1
- Estimating the case fatality ratio (CFR) for COVID-19 is an important aspect of public health. However, calculating CFR accurately is problematic early in a novel disease outbreak, due to uncertainties regarding the time course of disease and difficulties in diagnosis and reporting of cases. In this work, we present a simple method for calculating the case fatality ratio using only public case and death data over time by exploiting the correspondence between the time distributions of cases and deaths. The time-shifted distribution (TSD) analysis generates two parameters of interest: the delay time between reporting of cases and deaths and the case fatality ratio. These parameters converge reliably over time once the exponential growth phase has finished. Analysis is performed for early COVID 19 outbreaks in many countries, and we discuss corrections to CFR values using excess-death and seroprevalence data to estimate the infection fatality ratio (IFR). While CFR values range from 0.2-20% in different countries, estimates for IFR are mostly around 0.5-0.8% for countries that experienced moderate outbreaks and 1-3% for severe outbreaks. The simplicity and transparency of TSD analysis enhance its usefulness in characterizing a new disease as well as the state of the health and

reporting systems. [**note: here is paper from Australia that estimates the Case Fatality Rate for various countries based on a time shifted distribution analysis. These are high because of inadequate testing to know the total number who are infected. The authors note that the Infection Fatality Rate is the key number and they see variability here as well. Until we have a good number for total infections, models will only get us so far. I'm still sticking with a value between 0.3-0.6%**] https://www.medrxiv.org/content/10.1101/2020.10.25.20216671v1

- Wastewater-based epidemiology (WBE) is a great approach that enables us to comprehensively monitor the community to determine the scale and dynamics of infections in a city, particularly in metropolitan cities with a high population density. Therefore, we monitored the time course of the SARS-CoV-2 RNA concentration in raw sewage in the Frankfurt metropolitan area, the European financial center. To determine the SARS-CoV-2 concentration in sewage, we continuously collected samples from two wastewater treatment plant (WWTP) influents (Niederrad and Sindlingen) serving the Frankfurt metropolitan area and performed RT-qPCR analysis targeting three genes (N gene, S gene, and ORF1ab gene). In August, a resurgence in the SARS-CoV-2 RNA load was observed, reaching 3 x 10^13 copies/day, which represents similar levels compared to April with approx. 2 x 10^14 copies/day. This corresponds to an also continuous increase again in COVID-19 cases in Frankfurt since August, with an average of 28.6 incidences, compared to 28.7 incidences in April. Different temporal dynamics were observed between different sampling points, indicating local dynamics in COVID-19 cases within the Frankfurt metropolitan area. The SARS-CoV-2 load to the WWTP Niederrad ranged from approx. 4 x 10^11 to 1 x 10^15 copies/day, the load to the WWTP Sindlingen from approx. 1 x 10^11 to 2 x 10^14 copies/day, which resulted in a preceding increase in these loading in July ahead of the weekly averaged incidences. *The study shows that WBE has the potential as early warning system for SARS-CoV-2 infections and as monitoring system to identify global hotspots of COVID* 19. [**note: here is a wastewater study from Frankfurt Germany.]** https://www.medrxiv.org/content/10.1101/2020.10.26.20215020v1
- Background As many countries seek to slow the spread of COVID-19 without reimposing national restrictions, it has become important to track the disease at a local level to identify areas in need of targeted intervention. Methods We performed modelling on longitudinal, self-reported data from users of the COVID Symptom Study app in England between 24 March and 29 September, 2020. Combining a symptom-based predictive model for COVID-19 positivity and RT-PCR tests provided by the Department of Health we were able to estimate disease incidence, prevalence and effective reproduction number. Geographically granular estimates were used to highlight regions with rapidly increasing case numbers, or hotspots. Findings More than 2.6 million app users in England provided 115 million daily reports of their symptoms, and recorded the results of 170,000 PCR tests. On a national level our estimates of incidence and prevalence showed similar sensitivity to changes as two national community surveys: the ONS and REACT studies. On a geographically granular level, our estimates were able to highlight regions before they were subject to local government lockdowns. Between 12 May and 29 September we were able to flag between 35-80% of regions appearing in the Government's hotspot list. Interpretation *Self-reported data from mobile applications can provide a cost-effective and agile resource to inform a fast-moving pandemic, serving as an independent and complementary resource to more traditional instruments for disease surveillance*. [**note: I was waiting for some data on a mobile phone app!!!! This one from Zoe Global appears to work. The big issue is**

getting people to use them.]
https://www.medrxiv.org/content/10.1101/2020.10.26.20219659v1

- Identifying linked cases of infection is a key part of the public health response to viral infectious disease. Viral genome sequence data is of great value in this task, but requires careful analysis, and may need to be complemented by additional types of data. The Covid-19 pandemic has highlighted the urgent need for analytical methods which bring together sources of data to inform epidemiological investigations. We here describe A2B-COVID, an approach for the rapid identification of linked cases of coronavirus infection. *Our method combines knowledge about infection dynamics, data describing the movements of individuals, and novel approaches to genome sequence data to assess whether or not cases of infection are consistent or inconsistent with linkage via transmission. We apply our method to analyse and compare data collected from two wards at Cambridge University Hospitals, showing qualitatively different patterns of linkage between cases on designated Covid-19 and non-Covid-19 wards. Our method is suitable for the rapid analysis of data from clinical or other potential outbreak settings*. [**note: here is another UK paper that outlines an approach for the rapid identification of linked cases of viral infection.]** https://www.medrxiv.org/content/10.1101/2020.10.26.20219642v1
- This project's aim was to generate an unbiased estimate of the incidence of SARS-CoV-2 infection in four urban counties in Utah. A multi-stage sampling design was employed to randomly select community-representative participants 12 years and over. Between May 4 and June 30, 2020, surveys were completed and sera drawn from 8,108 individuals belonging to 5,125 households. A qualitative chemiluminescent microparticle immunoassay was used to detect the presence of IgG antibody to SARS-CoV-2. The overall prevalence of IgG antibody to SARS-CoV-2 was estimated at 0.8%. *The estimated seroprevalence-to-case count ratio was 2.4, corresponding to a detection fraction of 42%. Only 0.2% of individuals who had a nasopharyngeal swab collected were reverse transcription polymerase chain reaction (RT-PCR) positive. The prevalence of antibodies to SARS-CoV-2 in Utah urban areas between May and June was low and the prevalence of positive RT-PCR even lower. The detection fraction for COVID-19 in Utah was comparatively high. Probability-based sampling provides an effective method for robust estimates of community-based SARS-CoV-2 seroprevalence and detection fraction among urban populations in Utah*. [**note: here is a Utah group that developed a probability based sample model to assess seroprevalence in urban populations. During the time period studied, infection rate was low.**] https://www.medrxiv.org/content/10.1101/2020.10.26.20219907v1

NEWLY REGISTERED CLINICAL TRIALS

- You need to wait until Sunday.

CLINICAL TRIAL RESULTS

- To examine the association between dexamethasone use and mortality among hospitalized patients for COVID-19. Design: Multicenter observational retrospective cohort study. Setting: Greater Paris University hospitals, France. Participants: 12,217 adults hospitalized with COVID-19 between 24 January and 20 May 2020, including 171 patients (1.4%) who received dexamethasone orally or by intravenous perfusion during the visit. Data source: Assistance Publique-Hôpitaux de Paris Health Data Warehouse. Main outcome measures: The primary endpoint was time to death. We compared this endpoint between patients who received

dexamethasone and those who did not in time-to-event analyses adjusting for sex, age, obesity, current smoking status, any medical condition associated with increased COVID-19-related mortality, and clinical and biological severity of COVID-19 at admission, while stratifying by the need of respiratory support (i.e., oxygen or intubation). The primary analysis was a multivariable Cox model and the secondary analysis used a univariate Cox regression in a matched analytic sample. Results: Among patients who required respiratory support, the end-point event of death occurred in 10 patients (15.9%) who received dexamethasone and 298 patients (26.4%) who did not. In this group of patients, there was a significant association between dexamethasone use and reduced mortality in both the crude, unadjusted analysis (hazard ratio (HR), 0.40; 95% CI, 0.18 to 0.87, p=0.021) and the adjusted multivariable analysis (HR, 0.46; 95% CI, 0.22 to 0.96, p=0.039). In the sensitivity analysis, the univariate Cox regression model in the matched analytic sample yielded a same tendency, albeit non-significant (HR, 0.31; 95% CI, 0.08 to 1.14, p=0.077). Among patients without respiratory support, the end-point event of death occurred in 14 patients (13.0%) who received dexamethasone and 1,086 patients (10.0%) who did not. In this group of patients, there was no significant association between dexamethasone use and the endpoint. When examining the association between the cumulative dose of dexamethasone received during the visit and the endpoint, we found that the administration of a cumulative dose between 60 mg to 150 mg among patients who required respiratory support was significantly associated with a lower risk of death in the crude, unadjusted analysis (HR, 0.28; SE, 0.58, p=0.028), the adjusted multivariable analysis (HR, 0.24; SE, 0.65, p=0.030), and in the univariate Cox regression model in the matched analytic sample (HR, 0.32; SE, 0.58, p=0.048), whereas no significant association was observed with a different dose. Among patients without respiratory support, there was no significant association between the cumulative dose of dexamethasone and the endpoint in the crude and in the adjusted multivariable analyses. Conclusions: *In this observational study involving patients with Covid-19 who had been admitted to the hospital, dexamethasone use administered either orally or by intravenous injection at a cumulative dose between 60 mg and 150 mg was associated with decreased mortality among those requiring respiratory support*. [**note: this is an observational study on mortality in patients receiving dexamethasone. It's from the greater Paris area and the steroid did reduce mortality among patients requiring ventilation.**] https://www.medrxiv.org/content/10.1101/2020.10.23.20218172v1

- To examine the association between hydroxyzine use and mortality in patients hospitalized for COVID-19, based on its anti-inflammatory and antiviral properties. Design: Multicenter observational retrospective cohort study. Setting: Greater Paris University hospitals, France. Participants: 7,345 adults hospitalized for COVID-19 between 24 January and 1 April 2020, including 138 patients (1.9%) who received hydroxyzine during the visit at a mean dose of 49.8 mg (SD=51.5) for an average of 22.4 days (SD=25.9). Data source: Assistance Publique-Hopitaux de Paris Health Data Warehouse. Main outcome measures: The study endpoint was death. We compared this endpoint between patients who received hydroxyzine and those who did not in time-to-event analyses adjusting for patient characteristics (such as age, sex, and comorbidities), clinical and biological markers of disease severity, and use of other medications. The primary analysis was a multivariable Cox model with inverse probability weighting. Sensitivity analyses included a multivariable Cox model and a univariate Cox regression model in a 1:1 ratio matched analytic sample. Results: Over a mean follow-up of 20.3 days (SD=27.5), 994 patients (13.5%)

had a primary end-point event. The primary multivariable analysis with inverse probability weighting showed a significant association between hydroxyzine use and reduced mortality (HR, 0.42; 95% CI, 0.25 to 0.71; p=0.001) with a significant dose-effect relationship (HR, 0.10; 95% CI, 0.02 to 0.45; p=0.003). This association was similar in sensitivity analyses. In secondary analyses conducted among subsamples of patients, we found a significant association between hydroxyzine use and a faster decrease in biological inflammatory markers associated with COVID-19-related mortality, including neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-C-reactive protein ratio (LCRP), and circulating interleukin 6 levels (IL-6) (all p<0.016), with a significant dose-effect relationship for NLR and LCRP (both p<0.037). Conclusions: *In this retrospective observational study, hydroxyzine use was associated with reduced mortality in patients hospitalized for COVID-19. This association may be partially mediated by specific anti-inflammatory properties of H1 antihistamines. Double-blind controlled randomized clinical trials of hydroxyzine for COVID-19 are needed to confirm these results*. [**note: here's an old drug with a possible repurpose for COVID-19. Data again is from France. The drug is still used in the US for treating severe cases of poison ivy.]**
https://www.medrxiv.org/content/10.1101/2020.10.23.20154302v1

- Early identification of symptoms and comorbidities most predictive of COVID-19 is critical to identify infection, guide policies to effectively contain the pandemic, and improve health systems' response. Here, we characterised socio-demographics and comorbidity in 3,316,107 persons tested and 219,072 persons tested positive for SARS-CoV-2 since January 2020, and their key health outcomes in the month following the first positive test. Routine care data from primary care electronic health records (EHR) from Spain, hospital EHR from the United States (US), and claims data from South Korea and the US were used. The majority of study participants were women aged 18-65 years old. Positive/tested ratio varied greatly geographically (2.2:100 to 31.2:100) and over time (from 50:100 in February-April to 6.8:100 in May-June). Fever, cough and dyspnoea were the most common symptoms at presentation. Between 4%-38% required admission and 1-10.5% died within a month from their first positive test. Observed disparity in testing practices led to variable baseline characteristics and outcomes, both nationally (US) and internationally. *Our findings highlight the importance of large scale characterization of COVID-19 international cohorts to inform planning and resource allocation including testing as countries face a second wave*. [**note: this is a very large project that arose out of the OHDSI work that I have referred to in the past. They look at 30 day outcomes of over 3.3M people tested for COVID-19.**] https://www.medrxiv.org/content/10.1101/2020.10.25.20218875v1
- Information on COVID-19 in representative community surveillance is limited, particularly regarding cycle threshold (Ct) values (a proxy for SARS-CoV-2 viral load) and symptoms. Methods: We included all positive nose and throat swabs between 26 April-11 October 2020 from the UK national COVID-19 Infection Survey, tested by RT-PCR for the N, S and ORF1ab genes. We investigated predictors of median Ct value using quantile regression. Results: 1892(0.22%) of 843,851 results were positive, 1362(72%), 185(10%) and 345(18%) for 3, 2 or 1 genes respectively. Ct for different genes were strongly correlated (rho=0.99) with overall median Ct 26.2 (IQR 19.7-31.1; range 10.3-37.6), corresponding to ~2,500 dC/ml (IQR 80-240,000). Ct values were independently lower in those reporting symptoms, with more genes detected, and in first (vs. subsequent) positives per-participant, with no evidence of independent effects of sex, ethnicity, age, deprivation or other test characteristics (p>0.20).

Whilst single-gene positives without reported symptoms almost invariably had Ct>30, triple-gene positives without reported symptoms had widely varying Ct. Incorporating pre-test probability and Ct values, 1547(82%) and 112(6%) positives had higher or lower supporting evidence for genuine infection. *Ct values, symptomatic percentages and supporting evidence changed over time. With lower positivity in the summer, there were proportionally more lower evidence positives, and higher evidence positives had higher Ct values (p<0.0001), suggesting lower viral burden. Declines in mean/median Ct values were apparent throughout August and preceded increases in positivity rates. Conclusions: Community SARS-CoV-2 infections show marked variation in viral load. Ct values could be a useful epidemiological early-warning indicator*. [**note: another large observational study from the UK. This one looks at viral load in community cases.**]

- COVID-19 patients suffer from the lack of curative therapy. Hence, there is an urgent need to try repurposed old drugs on COVID-19. Methods: Randomized controlled study on 70 COVID-19 patients (48 mild-moderate, 11 severe, and 11 critical patients) treated with 200ug/kg PO of Ivermectin per day for 2-3 days along with 100mg PO doxycycline twice per day for 5-10 days plus standard therapy; the second arm is 70 COVID-19 patients (48 mild-moderate and 22 severe and zero critical patients) on standard therapy. The time to recovery, the progression of the disease, and the mortality rate were the outcome-assessing parameters. Results: among all patients and among severe patients, 3/70 (4.28%) and 1/11 (9%), respectively progressed to a more advanced stage of the disease in the Ivermectin-Doxycycline group versus 7/70 (10%) and 7/22 (31.81%), respectively in the control group (P>0.05). The mortality rate was 0/48 (0%), 0/11 (0%), and 2/11 (18.2%) in mild-moderate, severe, and critical COVID-19 patients, respectively in Ivermectin-Doxycycline group versus 0/48 (0%), and 6/22 (27.27%) in mild-moderate and severe COVID-19 patients, respectively in standard therapy group (p=0.052). Moreover, the mean time to recovery was 6.34, 20.27, and 24.13 days in mild-moderate, severe, and critical COVID-19 patients, respectively in Ivermectin-Doxycycline group versus 13.66 and 24.25 days in mild-moderate and severe COVID-19 patients, respectively in standard therapy group (P<0.01). Conclusions: Ivermectin with doxycycline reduced the time to recovery and the percentage of patients who progress to more advanced stage of disease; in addition, Ivermectin with doxycycline reduced mortality rate in severe patients from 22.72% to 0%; however, 18.2% of critically ill patients died with Ivermectin and doxycycline therapy. Taken together, the earlier administered Ivermectin with doxycycline, the higher rate of successful therapy. [**note: this is the first ivermectin trial that I've seen data on. The trial is from Iraq and the number of trial subjects is quite small. There are some confounding variables here and those interested should read the paper. I'm not yet convinced the ivermectin is a reliable therapy.**] https://www.medrxiv.org/content/10.1101/2020.10.26.20219345v1
- Objectives To determine clinical course and outcomes in rheumatic disease patients with coronavirus disease 2019 (COVID-19) and compare results to uninfected patients. Methods We conducted a case cohort study of autoimmune disease patients with COVID-19 (confirmed by severe acute respiratory syndrome coronavirus 2 PCR) from 02/01/2020 to 07/31/2020 and compared them in a 1:3 ratio with uninfected patients who were matched based on race, age, sex, and comorbidity index. Patient demographics, clinical course, and outcomes were compared among these patient groups. Results A total of 70 rheumatic disease patients with COVID-19 (mean age, 56.6 years; 64% African American) were identified. The 34 (49%) patients

who were hospitalized used oral glucocorticoids more frequently (p<0.01). All 10 patients on anti-TNFα medications were treated as outpatients (p<0.01). Those hospitalized with COVID-19 more often required ICU admission (17 (50%) vs 27 (26%), OR=2.78 (95% CI: 1.24 to 6.20)) and intubation (10 (29%) vs 6 (6%), OR=6.67 (95% CI: 2.20 to 20.16)) than uninfected patients. They also had higher mortality rates (6 (18%) vs 3 (3%), OR=7.21 (95% CI: 1.70 to 30.69)). Of the six COVID-19 patients who died, one was of African ancestry (p=0.03). Conclusions *Rheumatic disease patients infected with COVID-19 were more likely to require ICU admission, ventilation, and died more frequently versus uninfected patients with autoimmune disease. Patients on anti-TNFα medications were hospitalized less frequently while those on chronic glucocorticoids were hospitalized more frequently. These findings have important implications for medication choice in rheumatic disease patients during the ongoing spread of COVID-19*. [**note: this is from Emory Univ and looks at outcomes on patients being already treated for rheumatic diseases.**]
https://www.medrxiv.org/content/10.1101/2020.10.26.20219154v1

- OBJECTIVE It is important to know if mortality among hospitalised covid-19 patients has changed as the pandemic has progressed. The aim of this study was to describe the dynamics of mortality among patients hospitalised for covid-19 in a nationwide study. DESIGN Nationwide observational cohort study of all patients hospitalised in Sweden 1 March to 30 June 2020 with SARS-CoV-2 RNA positivity 14 days before to 5 days after admission, and a discharge code for covid-19. SETTING All hospitals in Sweden. PARTICIPANTS 15 761 hospitalised patients with covid-19, with data compiled by the Swedish National Board of Health and Welfare. MAIN OUTCOME MEASURES Outcome was 60-day all-cause mortality. Patients were stratified according to month of hospital admission. Poisson regression was used to estimate the relative risk of death by month of admission, adjusting for pre-existing conditions, age, sex, care dependency, and severity of illness (Simplified Acute Physiology, version 3), for patients in intensive care units (ICU). RESULTS *The overall 60-day mortality was 17.8% (95% confidence interval (CI), 17.2% to 18.4%), and it decreased from 24.7% (95% CI, 23.0% to 26.5%) in March to 13.3% (95% CI, 12.1% to 14.7%) in June. Adjusted relative risk (RR) of death was 0.56 (95% CI, 0.51 to 0.63) for June, using March as reference. Corresponding RR for patients not admitted to ICU and those admitted to ICU were 0.60 (95% CI, 0.53 to 0.67) and 0.61 (95% CI, 0.48 to 0.79), 3 respectively. The proportion of patients admitted to ICU decreased from 19.5% (95% CI, 17.9% to 21.0%) in the March cohort to 11.0% (95% CI, 9.9% to 12.2%) in the June cohort. CONCLUSIONS There was a gradual decline in mortality from March to June 2020 in Swedish hospitalised covid-19 patients, which was independent of pre-existing conditions, age, and sex. Future research is needed to explain the reasons for this decline. The changing covid-19 mortality should be taken into account when management and results of studies from the first pandemic wave are evaluated.* [**note: this is a nationwide mortality study of hospitalized patients in Sweden. It shows a gradual decline in mortality over the period studied. I believe this is what other countries have observed.**]
https://www.medrxiv.org/content/10.1101/2020.10.27.20220061v1
- Introduction At present, there are no data regarding the incidence and clinical course of COVID-19 among professional soccer players, and the studies examining putative complications of COVID-19 infections are probabilistic. Thus, examining the incidence of COVID-19 and various aspects of its clinical course in a group of adult professional soccer players would be of great practical interest. Methods The incidence, clinical course, and severity of COVID-19 infection, as

well as the duration of treatment and return to play were studied by the questioning of the team physicians and medical records assessment in the group of adult professional soccer players representing the clubs of the Russian Premier-League (RPL) during the period of championship resumption from 01.04.2020 until 20.09.2020. *Results COVID-19 infection was detected in 103 soccer players in the course of COVID-19 screening. This number comprises 14.5% of all soccer players which were on the rosters of RPL soccer teams and which were subject to regular COVID-19 testing. The asymptomatic course was observed in 43.7% of cases (n=45). These players were isolated and their clinical condition was monitored closely. Clinical symptoms were observed in 56.3% of cases (n=58), the most common symptoms being fatigue, headache, fever, and anosmia. Conclusions COVID-19 infection was commonly diagnosed among adult professional soccer players continuously residing in Russia. However, the majority of infections had a mild course and did not impair return to regular exercise*. [**note: I post this one because soccer is the only sport that I follow these days. Here is a study of soccer players in the Russian Premier League.**]
https://www.medrxiv.org/content/10.1101/2020.10.27.20220400v1

DRUG DEVELOPMENT

- The spread of SARS-CoV-2 has caused a global pandemic that has affected almost every aspect of human life. The development of an effective COVID-19 vaccine could limit the morbidity and mortality caused by infection, and may enable the relaxation of social distancing measures. Age is one of the most significant risk factors for poor health outcomes after SARS-CoV-2 infection, therefore it is desirable that any new vaccine candidates should elicit a robust immune response in older adults. Here, we test the immunogenicity of the adenoviral vectored vaccine ChAdOx1 nCoV-19 (AZD-1222) in aged mice. We find that a single dose of this vaccine induces cellular and humoral immunity in aged mice, but at a reduced magnitude than in younger adult mice. Furthermore, we report that a second dose enhances the immune response to this vaccine in aged mice, indicating that a prime-boost strategy may be a rational approach to enhance immunogenicity in older persons. [**note: here is a study on the AstraZeneca/Oxford vaccine and how a booster shot improves immunogenicity. The human trials are using a booster vaccine approach.**] https://www.biorxiv.org/content/10.1101/2020.10.27.357426v1
- Immunomodulatory agents dexamethasone and colchicine, antiviral drugs remdesivir, favipiravir and ribavirin, as well as antimalarial drugs chloroquine phosphate and hydroxychloroquine are currently used in the combat against COVID-19. However, whether some of these drugs have clinical efficacy for COVID-19 is under debate. Moreover, these drugs are applied in COVID-19 patients with little knowledge of genetic biomarkers, which will hurt patient outcome. To answer these questions, we designed a screen approach that could employ genome-wide sgRNA libraries to systematically uncover genes crucial for these drugs' action. Here we present our findings, including genes crucial for the import, export, metabolic activation and inactivation of remdesivir, as well as genes that regulate colchicine and dexamethasone's immunosuppressive effects. *Our findings provide preliminary information for developing urgently needed genetic biomarkers for these drugs. Such biomarkers will help better interpret COVID-19 clinical trial data and point to how to stratify COVID-19 patients for proper treatment with these drugs*. [**note: here is a Chinese study on how genetic determinants of drug efficacy can be revealed by CRISPR screens.**] https://www.biorxiv.org/content/10.1101/2020.10.26.356279v1

- The outbreak of coronavirus disease 2019 (COVID-19) rapidly spreads across worldwide and becomes a global pandemic. Remdesivir is the only COVID-19 treatment approved by U.S. Food and Drug Administration (FDA); however, its effectiveness is still under questioning as raised by the results of a large WHO Solidarity Trial. Herein, we report that the parent nucleotide of remdesivir, GS-441524, potently inhibits the replication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Vero E6 and other cells. It exhibits good plasma distribution and longer half-life (t1/2=4.8h) in rat PK study. GS-441524 is highly efficacious against SARS-CoV-2 in AAV-hACE2 transduced mice and murine hepatitis virus (MHV) in mice, reducing the viral titers in CoV-attacked organs, without noticeable toxicity. Given that GS-441524 was the predominant metabolite of remdesivir in the plasma, the anti-COVID-19 effect of remdesivir may partly come from the effect of GS-441524. Our results also supported that GS-441524 as a promising and inexpensive drug candidate in the treatment of COVID-19 and future emerging CoVs diseases. [**note: here is a Chinese paper on remdesivir action which is likely a result of the metabolite I don't think this is news and there were some other papers noting this as well.**] https://www.biorxiv.org/content/10.1101/2020.10.26.353300v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Background We aimed to further characterize and analyze in depth intra-host variation and founder variants of SARS-CoV-2 worldwide up until August 2020, by examining in excess of 94,000 SARS-CoV-2 viral sequences in order to understand SARS-CoV-2 variant evolution, how these variants arose and identify any increased mortality associated with these variants. Methods and Findings We combined worldwide sequencing data from GISAID and Sequence Read Archive (SRA) repositories and discovered SARS-CoV-2 hypermutation occurring in less than 2% of COVID19 patients, likely caused by host mechanisms involved APOBEC3G complexes and intra-host microdiversity. Most of this intra-host variation occurring in SARS-CoV-2 are predicted to change viral proteins with defined variant signatures, demonstrating that SARS-CoV-2 can be actively shaped by the host immune system to varying degrees. At the global population level, several SARS-CoV-2 proteins such as Nsp2, 3C-like proteinase, ORF3a and ORF8 are under active evolution, as evidenced by their increased πN/πS ratios per geographical region. Importantly, two emergent variants: V1176F in co-occurrence with D614G mutation in the viral Spike protein, and S477N, located in the Receptor Binding Domain (RBD) of the Spike protein, are associated with high fatality rates and are increasingly spreading throughout the world. The S477N variant arose quickly in Australia and experimental data support that this variant increases Spike protein fitness and its binding to ACE2. Conclusions SARS-CoV-2 is evolving non-randomly, and human hosts shape emergent variants with positive fitness that can easily spread into the population. We propose that V1776F and S477N variants occurring in the Spike protein are two novel mutations occurring in SARS-CoV-2 and may pose significant public health concerns in the future. [**note: viruses mutate as this paper documents. Whether the mutations will lead to improved infectivity and/or mortality is still an open question.**] https://www.medrxiv.org/content/10.1101/2020.10.23.20218511v1
- Background The prevalence and persistence of antibodies following a peak SARS-CoV-2 infection provides insights into its spread in the community, the likelihood of reinfection and potential for some level of population immunity. Methods Prevalence of antibody positivity in England, UK (REACT2) with three cross-sectional surveys between late June and September 2020. 365104

adults used a self-administered lateral flow immunoassay (LFIA) test for IgG. A laboratory comparison of LFIA results to neutralization activity in panel of sera was performed. Results There were 17,576 positive tests over the three rounds. Antibody prevalence, adjusted for test characteristics and weighted to the adult population of England, declined from 6.0% [5.8, 6.1], to 4.8% [4.7, 5.0] and 4.4% [4.3, 4.5], a fall of 26.5% [-29.0, -23.8] over the three months of the study. There was a decline between rounds 1 and 3 in all age groups, with the highest prevalence of a positive result and smallest overall decline in positivity in the youngest age group (18-24 years: -14.9% [-21.6, -8.1]), and lowest prevalence and largest decline in the oldest group (75+ years: -39.0% [-50.8, -27.2]); there was no change in antibody positivity between rounds 1 and 3 in healthcare workers (+3.45% [-5.7, +12.7]). The decline from rounds 1 to 3 was largest in those who did not report a history of COVID-19, (-64.0% [-75.6, -52.3]), compared to -22.3% ([-27.0, -17.7]) in those with SARS-CoV-2 infection confirmed on PCR. *Discussion These findings provide evidence of variable waning in antibody positivity over time such that, at the start of the second wave of infection in England, only 4.4% of adults had detectable IgG antibodies using an LFIA. Antibody positivity was greater in those who reported a positive PCR and lower in older people and those with asymptomatic infection. These data suggest the possibility of decreasing population immunity and increasing risk of reinfection as detectable antibodies decline in the population*. [**note: this is the UK antibody decay paper that was reported in the news. What we really need to know if whether there is immune memory.**]
https://www.medrxiv.org/content/10.1101/2020.10.26.20219725v1

- Infection of human cells by the SARS-CoV2 relies on its binding to a specific receptor and subsequent fusion of the viral and host cell membranes. The fusion peptide (FP), a short peptide segment in the spike protein, plays a central role in the initial penetration of the virus into the host cell membrane, followed by the fusion of the two membranes. Here, we use an array of molecular dynamics (MD) simulations taking advantage of the Highly Mobile Membrane Mimetic (HMMM) model, to investigate the interaction of the SARS-CoV2 FP with a lipid bilayer representing mammalian cellular membranes at an atomic level, and to characterize the membrane-bound form of the peptide. Six independent systems were generated by changing the initial positioning and orientation of the FP with respect to the membrane, and each system was simulated in five independent replicas. In 60% of the simulations, the FP reaches a stable, membrane-bound configuration where the peptide deeply penetrated into the membrane. Clustering of the results reveals two major membrane binding modes, the helix-binding mode and the loop-binding mode. *Taken into account the sequence conservation among the viral FPs and the results of mutagenesis studies establishing the role of specific residues in the helical portion of the FP in membrane association, we propose that the helix-binding mode represents more closely the biologically relevant form. In the helix-binding mode, the helix is stabilized in an oblique angle with respect to the membrane with its N-terminus tilted towards the membrane core. Analysis of the FP-lipid interactions shows the involvement of specific residues of the helix in membrane binding previously described as the fusion active core residues. Taken together, the results shed light on a key step involved in SARS-CoV2 infection with potential implications in designing novel inhibitors*. [**note: here is a paper from Univ of Illinois on the binding of SARS-CoV-2 and how a fusion peptide facilitates this.]**
https://www.biorxiv.org/content/10.1101/2020.10.27.357350v1

- During the evolution of SARS-CoV-2 in humans a D614G substitution in the spike (S) protein emerged and became the predominant circulating variant (S-614G) of the COVID-19 pandemic. However, whether the increasing prevalence of the S-614G variant represents a fitness advantage that improves replication and/or transmission in humans or is merely due to founder effects remains elusive. Here, we generated isogenic SARS-CoV-2 variants and demonstrate that the S-614G variant has (i) enhanced binding to human ACE2, (ii) increased replication in primary human bronchial and nasal airway epithelial cultures as well as in a novel human ACE2 knock-in mouse model, and (iii) markedly increased replication and transmissibility in hamster and ferret models of SARS-CoV-2 infection. *Collectively, our data show that while the S-614G substitution results in subtle increases in binding and replication in vitro, it provides a real competitive advantage in vivo, particularly during the transmission bottle neck, providing an explanation for the global predominance of S-614G variant among the SARS-CoV-2 viruses currently circulating*. [**note: here: is a Swiss study on how the Spike D614G variant confers enhanced replication and transmissibility.**] https://www.biorxiv.org/content/10.1101/2020.10.27.357558v1
- Cytokine storm resulting from a heightened inflammatory response is a prominent feature of severe COVID-19 disease. This inflammatory response results from assembly/activation of a cell-intrinsic defense platform known as the inflammasome. We report that the SARS-CoV-2 viroporin encoded by ORF3a activates the NLRP3 inflammasome, the most promiscuous of known inflammasomes. ORF3a triggers IL-1 beta expression via NFkB, thus priming the inflammasome while also activating it via ASC-dependent and -independent modes. *ORF3a-mediated inflammasome activation requires efflux of potassium ions and oligomerization between NEK7 and NLRP3. With the selective NLRP3 inhibitor MCC950 able to block ORF3a-mediated inflammasome activation and key ORF3a residues needed for virus release and inflammasome activation conserved in SARS-CoV-2 isolates across continents, ORF3a and NLRP3 present prime targets for intervention*. [**note: here is an interesting paper from Univ of Florida that may point to how the inflammatory pathway gets triggered by SARS-CoV-2. It looks like we are getting closer to a genetic understanding of what might trigger cytokine storm.**] https://www.biorxiv.org/content/10.1101/2020.10.27.357731v1
- Activation of the RIG-I-like receptors, RIG-I and MDA5, establishes an antiviral state by upregulating interferon (IFN)-stimulated genes (ISGs). Among these is ISG15 whose mechanistic roles in innate immunity still remain enigmatic. Here we report that ISGylation is essential for antiviral IFN responses mediated by the viral RNA sensor MDA5. ISG15 conjugation to the caspase activation and recruitment domains of MDA5 promotes the formation of higher-order assemblies of MDA5 and thereby triggers activation of innate immunity against a range of viruses including coronaviruses, flaviviruses and picornaviruses. *The ISG15-dependent activation of MDA5 is antagonized through direct de-ISGylation mediated by the papain-like protease (PLpro) of SARS-CoV-2, a recently emerged coronavirus that causes the COVID-19 pandemic. Our work demonstrates a crucial role for ISG15 in the MDA5-mediated antiviral response, and also identifies a novel immune evasion mechanism of SARS-CoV-2, which may be targeted for the development of new antivirals and vaccines to combat COVID-19*. [**note: This may be an important finding but there are some subtilties that I don't fully understand.** 😉] https://www.biorxiv.org/content/10.1101/2020.10.26.356048v1

DIAGNOSTIC DEVELOPMENT

- Nothing today.

>>

2020-10-29

I cannot believe that Yo-Yo Ma has not been featured in this newsletter! I did have some clips of the Silk Road Ensemble that he founded but not of Ma as a solicit! This will be remedied right now! Though there are lots of clips around, I particularly like the Bach cello suite #1. Here is the music video he did with the prelude to the suite: https://www.youtube.com/watch?v=1prweT95Mo0 Here is the full suite from a live London Proms recital: https://www.youtube.com/watch?v=rGgG-0lOJjk I am constantly amazed at Bach's inventiveness.

The Washington Post covers new state restrictions on gatherings. A UN report urges prioritizing school reopenings and catch-up classes. Hard to disagree with that. Some in China are getting early doses of a COVID-19 vaccine. Imperial College researchers suggest 100,000 people are being infected with SARS-CoV-2 each day in the UK. This is not the trajectory we wanted to see. Here are the best days to book flights during the Thanksgiving holiday. Tony Fauci expresses support for a national mask mandate.

The New York Times reports on the drop of COVID-19 death rates as an understanding of the disease has improved. There are still too many hospitalizations. The Netherlands has been hard hit in the second wave. Superspreading events on Long Island raise concerns. Being young and jobless in Europe during a pandemic is difficult.

The Atlantic's Ed Yong talks about the pandemic and the election. (I tend to stay away from posting about the election as it would drive me crazy but Yong is such a good science writer and has covered the pandemic since the beginning that this one is worth reading. My only other comment is, VOTE!!!)

The National Academies of Sciences, Engineering and Medicine have published "Evidenced-Based Practice for Public Health Emergency Preparedness and Response." This is a free download for those interested.

STAT discuss when COVID-19 vaccines will be available. Can we make enough of the new monoclonal antibodies? Here is an opinion piece on monitoring COVID-19 vaccine safety based n the H1N1 experience.

The Lancet have a view point on catecholamine physiology and the implications for patients with COVID-19.

JAMA have an insight paper from some Stanford researchers on school reopenings and the community during the pandemic. The CDC reported increases in HCQ prescriptions early in the pandemic based on rudimentary evidence.

Kaiser Health News discuss Americans expectations from a COVID-19 vaccine.

The New England Journal of Medicine also has a paper on evaluating and deploying a COVID-19 vaccine. Here is a discussion of no-fault compensation for vaccine injury. Here is some good news from Iceland! Humoral immune response to SARS-CoV-2 appears to be pretty good in a study of over 30K people in the country and follow up four months later. *Our results indicate that antiviral antibodies against SARS-CoV-2 did not decline within 4 months after diagnosis. We estimate that the risk of death from infection*

was 0.3% and that 44% of persons infected with SARS-CoV-2 in Iceland were not diagnosed by qPCR. Here is an editorial on this paper.

Derek Lowe provide commentary on the difficulty of unpacking the recent data on monoclonal antibodies.

MODELING

- A variant of SARS-CoV-2 emerged in early summer 2020, presumably in Spain, and has since spread to multiple European countries. The variant was first observed in Spain in June and has been at frequencies above 40% since July. Outside of Spain, the frequency of this variant has increased from very low values prior to 15th July to 40-70% in Switzerland, Ireland, and the United Kingdom in September. It is also prevalent in Norway, Latvia, the Netherlands, and France. Little can be said about other European countries because few recent sequences are available. Sequences in this cluster (20A.EU1) differ from ancestral sequences at 6 or more positions, including the mutation A222V in the spike protein and A220V in the nucleoprotein. *We show that this variant was exported from Spain to other European countries multiple times and that much of the diversity of this cluster in Spain is observed across Europe. It is currently unclear whether this variant is spreading because of a transmission advantage of the virus or whether high incidence in Spain followed by dissemination through tourists is sufficient to explain the rapid rise in multiple countries*. [**note: where would be without genetic fingerprint analysis? Here is work showing how a variant first found in Spain traveled through Europe this past summer.**] https://www.medrxiv.org/content/10.1101/2020.10.25.20219063v1
- As economic woes of the COVID-19 pandemic deepen, strategies are being formulated to avoid the need for prolonged stay-at-home orders, while implementing risk-based quarantine, testing, contact tracing and surveillance protocols. Given limited resources and the significant economic, public health and operational challenges of the current 14-day quarantine recommendation, it is vital to understand if more efficient but equally effective quarantine and testing strategies can be deployed. To this end, we developed a mathematical model to quantify the probability of post-quarantine transmission that varied across a range of possible quarantine durations, timings of molecular testing, and estimated incubation periods. We found that a 13-day quarantine with testing on entry, a nine-day quarantine with testing on exit, and an eight-day quarantine with testing on both entry and exit each provide equivalent or lower probability of post-quarantine transmission compared to a 14-day quarantine with no testing. *We found that testing on exit from quarantine is more effective in reducing probability of post-quarantine transmission than testing upon entry. When conducting a single test, testing on exit was most effective for quarantines of six days or shorter, while testing on day six or seven is optimal for longer quarantines. Optimal timing of testing during quarantine will reduce the probability of post-quarantine transmission, as false-positive results become less likely, enabling case isolation. Based on 4,040 SARS CoV-2 RT-PCR tests, an exit test 96 hours after the start of quarantine for an offshore oil rig population was demonstrated to identify all known asymptomatic cases that previously tested negative at entry, and-moreover-successfully prevented an expected seven or more offshore transmission events, each a serious concern for initiating rapid spread and a disabling outbreak in the close quarters of an offshore rig. This successful outcome highlights the*

importance of context-specific guidelines for the duration of quarantine and timing of testing that can minimize economic impacts, disruptions to operational integrity, and COVID-related public health risks. [**note: here is model of optimizing quarantine and testing strategies.]** https://www.medrxiv.org/content/10.1101/2020.10.27.20211631v1

- Many European countries underwent an unexpected spectacular boost of the daily reported new COVID-19 cases between September 20th and October 18th, imposing in emergency new confinement rules in order to prevent hospitals saturation. *The present study shows no correlation between the country COVID-19 boost date and its 2 weeks preceding temperature, but shows an impressive correlation with the country latitude. As the daily UV insolation earlier decreases in autumn for higher latitudes, this is an additional observation supporting the impact of low vitamin blood D level on the respiratory impairment in COVID-19 disease*. [**note: here is a paper that looks at the large increase in European viral cases from mid-September to mid-October; it correlates with latitude but not temperature. I don't know about the Vitamin D statement.**] https://www.medrxiv.org/content/10.1101/2020.10.28.20221176v1

NEWLY REGISTERED CLINICAL TRIALS

- You were expecting to see something in this space?😉

CLINICAL TRIAL RESULTS

- Background SARS-CoV-2 is a novel coronavirus that has rapidly expanded to become a pandemic, resulting in millions of deaths worldwide. The cytokine storm is caused by the release of inflammatory agents and results in a physiologic disruption. Tocilizumab is an IL-6 receptor antagonist with the ability to suppress the cytokine storm in critically ill patients infected with SARS-CoV-2. Methods This was a multi-center study of patients infected with SARS-CoV-2, admitted between 3/13/20 and 4/16/20, requiring mechanical ventilation. Parameters that were evaluated included age, sex, race, usage of steroids, inflammatory markers, and comorbidities. Early dosing was defined as a tocilizumab dose administered prior to or within one (1) day of intubation. Late dosing was defined as a dose administered greater than one (1) day after intubation. A control group that was treated only with standard of care, and without tocilizumab, was utilized for comparison (untreated). Findings We studied 118 patients who required mechanical ventilation. Eighty-one (81) received tocilizumab, compared to 37 who were untreated. Early tocilizumab therapy was associated with a statistically significant decrease in mortality as compared to patients who were untreated (p=0.003). *Dosing tocilizumab late was associated with an increased mortality compared to the untreated group (p=0.006). Interpretation Early tocilizumab administration was associated with decreased mortality in critically ill SARS-Co-V-2 patients, but a potential detriment was suggested by dosing later in a patient's course*. [**note: more information that tocilizumab may work on severe COVID-19 if administered early on.**] https://www.medrxiv.org/content/10.1101/2020.10.27.20211433v1
- Objective: We evaluated the impact of COVID-19 pandemic on childhood asthma outcomes. Design: The PeARL multinational cohort included children with asthma and non-asthmatic controls recruited during the COVID-19 pandemic and compared current disease activity with data available from the previous year. Setting: Pediatric outpatient clinics. Participants: The study included 1,054 children with asthma and 505 non-asthmatic controls, aged between 4-18 years, from 25 pediatric departments, from 15 countries globally. Exposures: COVID-19

pandemic first wave, starting from the date of the first fatality in the respective country. Main outcomes and measures: We assessed the pandemic's impact on the frequency of respiratory infections, emergency presentations and hospital admissions in asthmatic versus non-asthmatic participants, controlling for confounding factors including the pandemic's duration and the frequency of such acute events during 2019. Using paired analyses, we evaluated the impact of the pandemic on the annualized frequency of asthma attacks and the previously mentioned acute events, asthma control, and pulmonary function in children with asthma, compared to their baseline disease activity, during the preceding year. Results: During the pandemic, children with asthma experienced fewer upper respiratory tract infections, episodes of pyrexia, emergency visits, hospital admissions, asthma attacks and hospitalizations due to asthma, in comparison to the preceding year. Sixty-six percent of asthmatic children had improved asthma control while in 33% the improvement exceeded the minimally clinically important difference. Pre-bronchodilatation FEV1 and peak expiratory flow rate were also improved during the pandemic. When compared to non-asthmatic controls, children with asthma were not found to be at increased risk of LRTIs, episodes of pyrexia, emergency visits or hospitalizations during the pandemic. However, an increased risk of URTIs emerged. Conclusions and relevance: *Childhood asthma outcomes, including control, were improved during the first wave of the COVID-19 pandemic, probably because of reduced exposure to asthma triggers and increased treatment adherence. The decreased frequency of acute episodes does not support the notion that childhood asthma may be a risk factor for COVID-19. Furthermore, the potential for improving childhood asthma outcomes through environmental control becomes apparent*. [**note: here is another good piece of collaborative research. This is a look at childhood asthma and outcomes during the pandemic Perhaps the lack of environmental triggers was responsible.}** https://www.medrxiv.org/content/10.1101/2020.10.27.20219436v1

DRUG DEVELOPMENT

- Spanish flu and other influenza outbreaks, the recent Zika epidemics, and the ongoing COVID-19 pandemic are the most profound examples of severe widespread diseases that are caused by RNA viruses. Perhaps less well-known yet dangerous RNA viruses cause deadly diseases such as polio, Ebola, measles, rubella, yellow fever, dengue fever, etc. To combat a particular viral disease by diminishing its spread and number of fatal cases, effective vaccines and antivirals are indispensable. Therefore, quick access to the means of discovery of new treatments for any epidemic outbreak is of great interest and *in vitro*, biochemical assays are the basis of drug discovery. The recent outbreak of the coronavirus pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) demands an affordable and reliable assay for testing antivirals. Here, we developed a quick and inexpensive high-throughput fluorescent assay to test inhibitors of viral proteases. Accordingly, we employed this assay to sample inhibitors for papain-like protease from SARS-CoV-2. In addition, we validated this assay for screening inhibitors of flaviviral protease from the tick-borne encephalitis virus to emphasize a broad range of applications of our approach. This fluorescent high-throughput assay is based on fluorescent energy transfer (FRET) between two distinct fluorescent proteins (eGFP and mCherry) connected via a substrate polypeptide. When the substrate is cleaved, FRET is abolished and the change in fluorescence corresponds to reaction progress. Our data show that this assay can be used for testing the inhibitors in the 96 or 384 well plates format with robust

and reproducible outcomes. [**note: this is a nifty approach to high throughput screening for inhibitors of proteases from RNA viruses. There were folks in our research lab at Cornell that did this stuff when I was a post-doc]**
https://www.biorxiv.org/content/10.1101/2020.10.27.357418v1

- Currently, the FDA has approved remdesivir, an inhibitor of SARS-CoV-2 replication, to treat COVID-19, though very recent data from WHO showed little if any COVID19 protective effect. Here we report that ethacridine, a safe and potent antiseptic use in humans, effectively inhibits SARS-CoV-2, at very low concentrations (EC50 ~ 0.08 µM). *Ethacridine was identified through a high-throughput screening of an FDA-approved drug library in living cells using a fluorescent assay. Interestingly, the main mode of action of ethacridine is to inactivate virus particles, preventing binding to the host cells. Thus, our work has identified a potent drug with a distinct mode of action against SARS-CoV-2.* [**note: from UCSF, another drug with inhibitory activity against the virus in a cell infection model. This is an interesting compound and I did not know that it is used as a second trimester abortifacient. The inhibitory concentration is among the lowest I have seen.**] https://www.biorxiv.org/content/10.1101/2020.10.28.359042v1
- Background: saliva is established to contain high counts SARS-CoV-2 virus and contact with saliva droplets, contaminated surfaces or airborne particles are sources of viral transmission. The generation of infective aerosols during clinical procedures is of particular concern. Therefore, a fuller understanding of the potential of mouthwash to reduce viral counts and modulate the risk of transmission in medical professional and public context is an important research topic. Method: *we determined the virucidal activity of four anti-bacterial mouthwashes against a surrogate for SARS-CoV-2, Human CoV-SARS 229E, using a standard ASTM suspension test, with dilution and contact times applicable to recommended mouthwash use. Results: the mouthwash formulated with 0.07% Cetylpyridinium Chloride exhibited virucidal effects providing a ≥3.0 log reduction HCoV-229E viral count. Mouthwashes containing 15.7% ethanol, 0.2% zinc sulphate heptahydrate and a mix of enzymes and proteins did not demonstrate substantive virucidal activity in this test. Conclusion: mouthwash containing 0.07% Cetylpyridinium Chloride warrants further laboratory and clinical assessment to determine their potential benefit in reducing the risk of SARS-CoV-2*. [**note: this research on mouthwash utility is from Unilever**]
https://www.biorxiv.org/content/10.1101/2020.10.28.359257v1
- 5-amino levulinic acid (5-ALA) is a naturally synthesized amino acid and has been used for multiple purposes including as an anticancer therapy and as a dietary supplement due to its high bioavailability. In this study, we demonstrated that 5-ALA treatment potently inhibited infection of SARS-CoV-2, a causative agent of COVID-19. The antiviral effects could be detected in both human and non-human cells, without significant cytotoxicity. Therefore, 5-ALA is a candidate as an oral antiviral drug for COVID-19. [**note: another drug with *in vitro* activity against SARS-CoV-2.**] https://www.biorxiv.org/content/10.1101/2020.10.28.355305v1
- Extracellular vesicles (EVs) emerge as essential mediators of intercellular communication. DNA vaccines encoding antigens presented on EVs efficiently induce T-cell responses and EV-based vaccines containing the Spike (S) proteins of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) are highly immunogenic in mice. Thus, EVs may serve as vaccine platforms against emerging diseases, going beyond traditional strategies, with the antigen displayed identically to the original protein embedded in the viral membrane and presented as such to the immune system. *Compared to their viral and pseudotyped counterparts, EV-based vaccines overcome*

many safety issues including pre-existing immunity against these vectors. Here, we applied our technology in natural EV's engineering, to express the S proteins of SARS-CoV-2 embedded in the EVs, which mimic the virus with its fully native spikes. Immunizations with a two component CoVEVax vaccine, comprising DNA vector (DNA$^{S\text{-}EV}$) primes, allowing in situ production of Spike harbouring EVs, and a boost using S-EVs produced in mammalian cells, trigger potent neutralizing and cellular responses in mice, in the absence of any adjuvants. CoVEVax would be the prototype of vaccines, where the sole exchange of the envelope proteins on EVs leads to the generation of new vaccine candidates against emerging viruses. [**note: here is a new approach to a COVID-19 vaccine from the French company, Ciloa**]
https://www.biorxiv.org/content/10.1101/2020.10.28.357137v1

- An inactivated virus formulated vaccines such as Hepatitis A, inactivated polio, and influenza has been proven to be a reliable approach for immunization for long years. In this pandemic, we produced an inactivated SARS-CoV-2 vaccine candidate by modification of the oldest but the most experienced method that can be produced quickly and tested easily rather than the recombinant vaccines. Here, we optimized an inactivated virus vaccine which includes the gamma irradiation process for the inactivation as an alternative to classical chemical inactivation methods so that there is no extra purification required. Also, we applied the vaccine candidate (OZG-38.61.3) using the intradermal route in mice which decreased the requirement of a higher concentration of inactivated virus for proper immunization unlike most of the classical inactivated vaccine treatments. *Thus, the novelty of our vaccine candidate (OZG-38.61.3) is a non-adjuvant added, gamma-irradiated, and intradermally applied inactive viral vaccine. We first determined the efficiency and safety dose (either 1013 or 1014 viral copy per dose) of the OZG-38.61.3 in Balb/c mice. Next, to test the immunogenicity and protective efficacy of the OZG-38.61.3, we immunized human ACE2-encoding transgenic mice and infected them with a dose of infective SARS-CoV-2 virus for the challenge test. We showed that the vaccinated mice showed lowered SARS-CoV-2 viral copy number in oropharyngeal specimens along with humoral and cellular immune responses against the SARS-CoV-2, including the neutralizing antibodies similar to those shown in Balb/c mice without substantial toxicity. This study encouraged us towards a new promising strategy for inactivated vaccine development (OZG-38.61.3) and the Phase 1 clinical trial for the COVID-19 pandemic*. [**note: add Turkey to the list of countries developing a COVID-19 vaccine! These researchers use gamma irradiation to inactivate the virus.]**
https://www.biorxiv.org/content/10.1101/2020.10.28.356667v1
- Here, we show that the maduramycin and CP-80,219 aglycone polyether ionophores exhibit effective broad-spectrum antiviral activity, against various viruses, including Japanese encephalitis virus (JEV), Dengue virus (DENV), Zika virus (ZIKV), and Chikungunya virus (CHIKV), while also exhibiting promising activity against PR8 influenza virus and SARS-CoV-2. Moreover, liposome-encapsulated maduramycin and CP-80,219 provide full protection for mice from infection with JEV in vivo. *Mechanistic studies suggest that aglycone polyether ionophores primarily inhibit the viral replication step without blocking endosome acidification to promote the fusion between viral and cellular membranes. The successful application of liposomes containing aglycone polyether ionophores in JEV-infected mice offers hope to the development of broad-spectrum antiviral drugs like penicillin back to 1940s*. [**note: another possible drug approach using aglycone polyether ionophores. I'm not sure I buy the comparison to penicillin**

development but would love to be proven wrong.]
https://www.biorxiv.org/content/10.1101/2020.10.27.354563v1

-

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- We hereby describe a large-scale community effort to build an open-access, interoperable, and computable repository of COVID-19 molecular mechanisms - the COVID-19 Disease Map. We discuss the tools, platforms, and guidelines necessary for the distributed development of its contents by a multi-faceted community of biocurators, domain experts, bioinformaticians, and computational biologists. We highlight the role of relevant databases and text mining approaches in enrichment and validation of the curated mechanisms. We describe the contents of the map and their relevance to the molecular pathophysiology of COVID-19 and the analytical and computational modelling approaches that can be applied to the contents of the COVID-19 Disease Map for mechanistic data interpretation and predictions. We conclude by demonstrating concrete applications of our work through several use cases. [**note: major shout out to all these researchers and there are a lot of them. They have created a COVID-19 disease map of all the known virus-host interaction mechanisms. Collaborative efforts such as this one continue to impress!!!!!**]
https://www.biorxiv.org/content/10.1101/2020.10.26.356014v1
- Immune dysregulation characterized by altered innate cytokine responses is thought to contribute to the pathology of COVID-19 patients, which is a testimony of the fundamental role of the innate immune response against SARS-CoV-2. Here, we further characterized the host cell antiviral response against SARS-CoV-2 by using primary human airway epithelia and immortalized model cell lines. We mainly focused on the type I and III interferon (IFN) responses, which lead to the establishment of an antiviral state through the expression of IFN-stimulated genes (ISGs). Our results demonstrate that both primary airway epithelial cells and model cell lines elicit a robust immune response characterized by a strong induction of type I and III IFN through the detection of viral pathogen molecular patterns (PAMPs) by melanoma differentiation associated gene (MDA)-5. *However, despite the high levels of type I and III IFNs produced in response to SARS-CoV-2 infection, the IFN response was unable to control viral replication, whereas IFN pre-treatment strongly inhibited viral replication and de novo production of infectious virions. Taken together, these results highlight the complex and ambiguous interplay between viral replication and the timing of IFN responses*. [**note: here is more information on how the virus interferes with the immune response in this case interferon production.**] https://www.biorxiv.org/content/10.1101/2020.10.28.358945v1
- Here, we performed global proteomic analysis of the virus-host interface in a newly established panel of phenotypically diverse, SARS-CoV-2-infectable human cell lines representing different body organs. This revealed universal inhibition of interferon signaling across cell types following SARS-CoV-2 infection. We performed systematic analyses of the JAK-STAT pathway in a broad range of cellular systems, including immortalized cell lines and primary-like cardiomyocytes, and found that several pathway components were targeted by SARS-CoV-2 leading to cellular desensitization to interferon. *These findings indicate that the suppression of interferon signaling is a mechanism widely used by SARS-CoV-2 in diverse tissues to evade antiviral innate immunity, and that targeting the viral mediators of immune evasion may help block virus replication in*

patients with COVID-19. [**note: more information on how SARS-CoV-2 disrupts interferon response in host cells.**] https://www.biorxiv.org/content/10.1101/2020.10.27.358259v1

- Genome-wide CRISPR/Cas9 knock-out genetic screens are powerful approaches to unravel new regulators of viral infections. With the aim of identifying new cellular inhibitors of HIV-1, we have developed a strategy in which we took advantage of the ability of type 1 interferon (IFN) to potently inhibit HIV-1 infection, in order to create a cellular environment hostile to viral replication. This approach led to the identification of the DEAD-box RNA helicase DDX42 as an intrinsic inhibitor of HIV-1. Depletion of endogenous DDX42 using siRNA or CRISPR/Cas9 knock-out increased HIV-1 infection, both in model cell lines and in physiological targets of HIV-1, primary CD4+ T cells and monocyte-derived macrophages (MDMs), and irrespectively of the IFN treatment. Similarly, the overexpression of a dominant-negative mutant of DDX42 positively impacted HIV-1 infection, whereas wild-type DDX42 overexpression potently inhibited HIV-1 infection. *The positive impact of endogenous DDX42 depletion on HIV-1 infection was directly correlated to an increase in viral DNA accumulation. Interestingly, proximity ligation assays showed that DDX42, which can be mainly found in the nucleus but is also present in the cytoplasm, was in the close vicinity of HIV-1 Capsid during infection of primary monocyte-derived macrophages. Moreover, we show that DDX42 is also able to substantially decrease infection with other retroviruses and retrotransposition of long interspersed elements-1 (LINE-1). Finally, we reveal that DDX42 potently inhibits other pathogenic viruses, including Chikungunya virus and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2*). [**note: this is a human enzyme and I don't know how it could be mobilized to help inhibit the virus. It's an interesting finding in any event.**] https://www.biorxiv.org/content/10.1101/2020.10.28.359356v1

DIAGNOSTIC DEVELOPMENT

- Nothing today.

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

2020-10-30

The late Beethoven String Quartets are among the most sublime compositions regardless of genre. I have heard most of them in recital from various groups and they never fail to move me. Here is a performance of #15 in A minor op. 132 by the Esmé Quartet: https://www.youtube.com/watch?v=adKab_1S0ug The performance venue is Priesterseminar Church Brixen which is in the Italian Alps region. This is just a wonderful performance!

The Washington Post covers problems in the RV manufacturing hub of Elkhart, IN. The Maryland Superintendent of Education wants kids back in school. CDC is asking states to be ready for receiving COVID-19 vaccine by November 15. This is a tough ask because of the ultra-cold temperatures needed for storing the Pfizer vaccine (if that is the one that gets the go-ahead). Fitness trackers may help predict COVID-19 infections. Here is what is missing from pandemic-era travel. Who would have thought there was a government funded ad campaign to 'defeat despair' arising from the pandemic? I am sad they disqualified J Lo! What's up with Idaho's Lt. Governor?

The New York Times reports this has been the worst week for COVID-19 cases. Schools in Europe are staying open during this viral outbreak wave. Remdesivir may only be a mediocre drug. Los Angeles schools may stay remote until January.

The New England Journal of Medicine has results of the ongoing Eli Lilly monoclonal antibody trial. "In this interim analysis of a phase 2 trial, one of three doses of neutralizing antibody LY-CoV555 appeared to accelerate the natural decline in viral load over time, whereas the other doses had not by day 11." This is somewhat disappointing and Derek Lowe has more to say about this and also the Regeneron data which to date have only come out in press releases. As Clara Peller so famously said, "show me the beef!"

Science has an unflattering article on the remdesivir approval process.

STAT have an interview with Brown University's Ashish Jha on all things COVID-19 related.

The Lancet have a commentary on some of the uncertainties regarding dexamethasone use for COVID-19. Here is an editorial on issues related to aerosol transmission.

Nature have a summary of why schools are probably not COVID-19 hotspots.

After the deluge of papers the past three days, today the reading is on the light side.

MODELING

- No models today.

NEWLY REGISTERED CLINICAL TRIALS

- Wait for it!

CLINICAL TRIAL RESULTS

- The management of pneumonia caused by SARS-CoV-2 should rely on early recognition of the risk for progression to severe respiratory failure (SRF) and its prevention. We investigated if early suPAR (soluble urokinase plasminogen activator receptor)-guided anakinra treatment could prevent COVID-19-assocated SRF. Methods In this open-label prospective trial, 130 patients admitted with SARS-CoV-2 pneumonia SARS-CoV-2 and suPAR levels ≥6 µg/l were assigned to subcutaneous anakinra 100mg once daily for 10 days. The primary outcome was the incidence of SRF at day 14. Secondary outcomes were 30-day mortality, changes in sequential organ failure assessment (SOFA) score, of cytokine-stimulation pattern and of circulating inflammatory mediators. Equal number of propensity score-matched comparators for comorbidities, severity on admission and standard-of care (SOC) were studied. Results The incidence of SRF was 22.3% (95% CI, 16.0-30.2%) among anakinra-treated patients and 59.2% (95% CI, 50.6-67.3%; P: 4.6 x 10-8) among SOC comparators (hazard ratio, 0.30; 95%CI, 0.20-0.46). 30-day mortality was 11.5% (95% CI, 7.1-18.2%) and 22.3% (95% CI, 16.0-30.2%) respectively (hazard ratio 0.49; 95% CI 0.25-0.97%; P: 0.041). *Anakinra treatment was associated with decrease in SOFA score and in circulating interleukin (IL)-6, sCD163 and sIL2-R; the serum IL-10/IL-6 ratio on day 7 was inversely associated with the change in SOFA score. Duration of stay*

at the intensive care unit and at hospital was shortened compared to the SOC group; the cost of hospitalization was decreased. Conclusions Early suPAR-guided anakinra treatment is associated with decrease of the risk for SRF and restoration of the pro- /anti-inflammatory balance. [**note: this is the first set of results that I have seen for anakinra. I think the trials are largely outside the US. I will need to see some more confirmatory data before passing judgment on this observed treatment effect.**]
https://www.medrxiv.org/content/10.1101/2020.10.28.20217455v1

DRUG DEVELOPMENT

- We have previously reported that the SARS-CoV-2 neutralizing antibody, STI-2020, potently inhibits cytopathic effects of infection by genetically diverse clinical SARS-CoV-2 pandemic isolates in vitro, and has demonstrated efficacy in a hamster model of COVID-19 when administered by the intravenous route immediately following infection. We now have extended our in vivo studies of STI-2020 to include disease treatment efficacy, profiling of biodistribution of STI-2020 in mice when antibody is delivered intranasally (IN) or intravenously (IV), as well as pharmacokinetics in mice following IN antibody administration. Importantly, SARS-CoV-2-infected hamsters were treated with STI-2020 using these routes, and treatment effects on severity and duration of COVID-19-like disease in this model were evaluated. In SARS-CoV-2 infected hamsters, treatment with STI-2020 12 hours post-infection using the IN route led to a decrease in severity of clinical disease signs and a more robust recovery during 9 days of infection as compared to animals treated with an isotype control antibody. *Treatment via the IV route using the same dose and timing regimen resulted in a decrease in the average number of consecutive days that infected animals experienced weight loss, shortening the duration of disease and allowing recovery to begin more rapidly in STI-2020 treated animals. Following IN administration in mice, STI-2020 was detected within 10 minutes in both lung tissue and lung lavage. The half-life of STI-2020 in lung tissue is approximately 25 hours. We are currently investigating the minimum effective dose of IN-delivered STI-2020 in the hamster model as well as establishing the relative benefit of delivering neutralizing antibodies by both IV and IN routes.* [**note: here is animal data on the Sorrento monoclonal antibody that I previous cited a paper on. The see protective effects via IV or intranasal delivery.**]
https://www.biorxiv.org/content/10.1101/2020.10.28.359836v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Dysfunctional immune response in the COVID-19 patients is a recurrent theme impacting symptoms and mortality, yet the detailed understanding of pertinent immune cells is not complete. We applied single-cell RNA sequencing to 284 samples from 205 COVID-19 patients and controls to create a comprehensive immune landscape. Lymphopenia and active T and B cell responses were found to coexist and associated with age, sex and their interactions with COVID-19. *Diverse epithelial and immune cell types were observed to be virus-positive and showed dramatic transcriptomic changes. Elevation of ANXA1 and S100A9 in virus-positive squamous epithelial cells may enable the initiation of neutrophil and macrophage responses via the ANXA1-FPR1 and S100A8/9-TLR4 axes. Systemic up-regulation of S100A8/A9, mainly by megakaryocytes and monocytes in the peripheral blood, may contribute to the cytokine storms frequently observed in severe patients. Our data provide a rich resource for understanding the pathogenesis*

and designing effective therapeutic strategies for COVID-19. [**note: this is an effort from a very large Chinese group that may contribute to the knowledge of cytokine storm.**] https://www.biorxiv.org/content/10.1101/2020.10.29.360479v1

- While SARS-CoV-2 infection has pleiotropic and systemic effects in some patients, many others experience milder symptoms. We sought a holistic understanding of the severe/mild distinction in COVID-19 pathology, and its origins. We performed a whole-blood preserving single-cell analysis protocol to integrate contributions from all major cell types including neutrophils, monocytes, platelets, lymphocytes and the contents of serum. *Patients with mild COVID-19 disease display a coordinated pattern of interferon-stimulated gene (ISG) expression across every cell population and these cells are systemically absent in patients with severe disease. Severe COVID-19 patients also paradoxically produce very high anti-SARS-CoV-2 antibody titers and have lower viral load as compared to mild disease. Examination of the serum from severe patients demonstrates that they uniquely produce antibodies with multiple patterns of specificity against interferon-stimulated cells and that those antibodies functionally block the production of the mild disease-associated ISG-expressing cells. Overzealous and auto-directed antibody responses pit the immune system against itself in many COVID-19 patients and this defines targets for immunotherapies to allow immune systems to provide viral defense*. [**note: this is from UCSF and looks at protective immune states in severe COVID-19. It may be that auto-directed antibodies interfere with the immune system response.**] https://www.biorxiv.org/content/10.1101/2020.10.28.359935v1
- Currently, there is a critical shortage of proven treatment options and an urgent need to understand the pathogenesis of multi-organ failure and lung damage. Cytokine storm is associated with severe inflammation and organ damage during COVID-19. However, a detailed molecular pathway defining this cytokine storm is lacking, and gaining mechanistic understanding of how SARS-CoV-2 elicits a hyperactive inflammatory response is critical to develop effective therapeutics. Of the multiple inflammatory cytokines produced by innate immune cells during SARS-CoV-2 infection, we found that the combined production of TNF-α and IFN-γ specifically induced inflammatory cell death, PANoptosis, characterized by gasdermin-mediated pyroptosis, caspase-8-mediated apoptosis, and MLKL-mediated necroptosis. Deletion of pyroptosis, apoptosis, or necroptosis mediators individually was not sufficient to protect against cell death. However, cells deficient in both RIPK3 and caspase-8 or RIPK3 and FADD were resistant to this cell death. Mechanistically, the STAT1/IRF1 axis activated by TNF-α and IFN-γ co-treatment induced iNOS for the production of nitric oxide. Pharmacological and genetic deletion of this pathway inhibited pyroptosis, apoptosis, and necroptosis in macrophages. Moreover, inhibition of PANoptosis protected mice from TNF-α and IFN-γ-induced lethal cytokine shock that mirrors the pathological symptoms of COVID-19. In vivo neutralization of both TNF-α and IFN-γ in multiple disease models associated with cytokine storm showed that this treatment provided substantial protection against not only SARS-CoV-2 infection, but also sepsis, hemophagocytic lymphohistiocytosis, and cytokine shock models, demonstrating the broad physiological relevance of this mechanism. *Collectively, our findings reveal that blocking the COVID-19 cytokine-mediated inflammatory cell death signaling pathway identified in this study may benefit patients with COVID-19 or other cytokine storm-driven syndromes by limiting inflammation and tissue damage. The findings also provide a molecular and mechanistic description for the term cytokine storm. Additionally, these results open new avenues for the*

treatment of other infectious and autoinflammatory diseases and cancers where TNF-α and IFN-γ synergism play key pathological roles. [**note: this is from St. Judes and provides more information on cytokine storm and a new way to possibly block it from happening.**] https://www.biorxiv.org/content/10.1101/2020.10.29.361048v1

- Our understanding of the coronavirus disease-19 (COVID-19) immune response is almost exclusively derived from studies that examined blood. To gain insight in the pulmonary immune response we analysed BALF samples and paired blood samples from 17 severe COVID-19 patients. Macrophages and T cells were the most abundant cells in BALF. In the lungs, both CD4 and CD8 T cells were predominantly effector memory cells and expressed higher levels of the exhaustion marker PD-1 than in peripheral blood. *Prolonged ICU stay associated with a reduced proportion of activated T cells in peripheral blood and even more so in BALF. T cell activation in blood, but not in BALF, was higher in fatal COVID-19 cases. Increased levels of inflammatory mediators were more pronounced in BALF than in plasma. In conclusion, the bronchoalveolar immune response in COVID-19 has a unique local profile that strongly differs from the immune profile in peripheral blood*. [**note: more on the immune response from The Netherlands. There is a lot of information being generated and I hope this does lead to new therapeutic modalities.**] https://www.biorxiv.org/content/10.1101/2020.10.29.360586v1
- A major goal of current SARS-CoV-2 vaccine efforts is to elicit antibody responses that confer protection. Mapping the epitope targets of the SARS-CoV-2 antibody response is critical for innovative vaccine design, diagnostics, and development of therapeutics. Here, we developed a phage display library to map antibody binding sites at high resolution within the complete viral proteomes of all human-infecting coronaviruses in patients with mild or moderate/severe COVID-19. *The dominant immune responses to SARS-CoV-2 were targeted to regions spanning the Spike protein, Nucleocapsid, and ORF1ab. Some epitopes were identified in the majority of samples while others were rare, and we found variation in the number of epitopes targeted by different individuals. We also identified a set of cross-reactive sequences that were bound by antibodies in SARS-CoV-2 unexposed individuals. Finally, we uncovered a subset of enriched epitopes from commonly circulating human coronaviruses with significant homology to highly reactive SARS-CoV-2 sequences.* [**note: more good stuff from the Hutch in Seattle. Here is a refined epitope map and how it also relates to common circulating coronaviruses. I continue to wonder if Spike only vaccines are the best approach given there are signs that the Nucleocapsid protein may be an epitope and this paper also the ORF1ab.**] https://www.biorxiv.org/content/10.1101/2020.10.29.360800v1

DIAGNOSTIC DEVELOPMENT

- Current transmission rates of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are still increasing and many countries are facing second waves of infections. Rapid SARS-CoV-2 whole genome sequencing (WGS) is often unavailable but could support public health organizations and hospitals in monitoring and determining transmission links. Here we report a novel reverse complement polymerase chain reaction (RC-PCR) technology for WGS of SARS-CoV-2. This technique is unique as it enables library preparation in a single PCR saving time, resources and enables high throughput screening. A total of 173 samples tested positive for SARS-CoV-2 between March and September 2020 were included. *RC-PCR WGS applicability for outbreak analysis in public health service and hospital settings was tested on six predefined*

clusters containing samples of healthcare workers and patients. RC-PCR resulted in WGS data for 146 samples. It showed a genome coverage of up to 98,2% for samples with a maximum Ct value of 32. Three out of six suspected clusters were fully confirmed, while in other clusters four healthcare workers were not associated. Importantly, a previously unknown chain of transmission was confirmed in the public health service samples. These findings confirm the reliability and applicability of the RC-PCR technology for SARS-CoV-2 sequencing in outbreak analysis and surveillance. [**note: this is from The Netherlands and does whole genome sequencing to analyze outbreaks.**]
https://www.biorxiv.org/content/10.1101/2020.10.29.360578v1

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

2020-10-31

Happy Halloween!!!!!👻👹👽💀

I find Antonin Dvorak an interesting composer. He was a romantic but also incorporated folk tunes in to his music. Small ensemble works such as the piano trios and string quartets are always a delight to hear. Here is the Dvorak Serenade for Strings from the Concertgebouw:
https://www.youtube.com/watch?v=CRcbDMg56yg

The Washington Post covers the pandemic's effect on the top end hotels in the city. Regeneron has paused the trial of its monoclonal antibody drug in the sickest COVID-19 patients. New York and Los Angeles are permitting restaurants to add COVID-19 recovery charges to patron's bills. Government scientists are pushing back! The current outbreak is just NOT good. Hawaii is open for travel; unfortunately it is a long plane ride from where I live. Here is an article on the German concert experiment that I've cited in the past.

The New York Times points to an ignominious record. A new CDC report shows how fast the virus spreads within household even when the first case is a child. HERE is the CDC Report (it's a short but important read) and has implications for school reopenings. Speaking about schools, New York has a plan for opening schools in hard hit areas. College health officers are setting up Thanksgiving plans, and it's not turkey talk. Here is a really cool video on why masks work!! MASK UP or stay home!!!!

My Yahoo Newsfeed points to a study showing brain abnormalities in COVID-19 patients. Older males seem more at risk (YIKES!)

The Lancet have a news article on the UK proposal for COVID-19 vaccine human challenge trials. There is also a short commentary on wastewater tracking for rapid identification of COVID-19 in schools.

JAMA have an interesting and somewhat counterintuitive paper on association of construction work with risks of COVID-19 infection in Texas. *This decision analytical model of COVID-19 found that resuming construction work during shelter-in-place orders was associated with increased hospitalization risks in the construction workforce and increase transmission in the surrounding community. Based on COVID-19 hospitalization data through August 20, 2020, construction workers had a nearly 5-fold increased risk of hospitalization in central Texas compared with other occupational categories*. [**note: I would have thought this group might be 'safer' because it is not close quarters work and much of it is in open air environment.**]

Medscape points to confounding studies on famotidine as the latest observational report shows no treatment effect and possibly worse 30-day mortality. Here is an article on COVID-19 convalescents who retest positive in a follow up study. It is unclear whether these individuals are capable of viral transmission as this study did not find any family members who were infected.

MODELING

- Importance: This study assessed the longitudinal impact of new COVID-19 cases when a mask ordinance was implemented in 2 of a 5-county Midwestern U.S. metropolitan region over a 3-month period of time. Reduction in case growth was significant and reduced infection inequities by race and population density. Objective: The objective of this study was to assess the impact that a mandatory mask wearing requirement had on the rate of COVID-19 infections by comparing counties with a mandatory policy with those neighboring counties without a mandatory masking policy. Design: This was a quasi-experimental longitudinal study conducted over the period of June 12-September 25, 2020. Setting: This study was a population-based study. Data were abstracted from local health department reports of COVID-19 cases. Participants: Raw cases reported to the county health departments and abstracted for this study; census-level data were synthesized to address county-level population, income and race. Intervention(s) (for clinical trials) or Exposure(s) (for observational studies): The essential features of this intervention was an instituted mask mandate that occurred in St. Louis City and St. Louis County over a 12 week period. Main Outcome(s) and Measure(s): The primary study outcome measurement was daily COVID-19 infection growth rate. The mask mandate was hypothesized to lower daily infection growth rate. Results: Over the 15-week period, the average daily percent growth of reported COVID-19 cases across all five counties was 1.81% (sd 1.62%). The average daily percent growth in incident COVID-19 cases was similar between M+ and M- counties in the 3 weeks prior to implementation of mandatory mask policies (0.90% [sd 0.68] vs. 1.27% [sd 1.23%], respectively, p=0.269). Crude modeling with a difference-in-difference indicator showed that after 3 weeks of mask mandate implementation, M+ counties had a daily percent COVID-19 growth rate that was 1.32 times lower, or a 32% decrease. At 12 weeks post-mask policy implementation, the average daily COVID-19 case growth among M- was 2.42% (sd 1.92), and was significantly higher than the average daily COVID case growth among M+ counties (1.36% (sd 0.96%)) (p<0.001). A significant negative association was identified among counties between percent growth of COVID-19 cases and percent racial minorities per county (p<0.001), as well as population density (p<0.001). Conclusions and Relevance: *These data demonstrate that county-level mask mandates were associated with significantly lower incident COVID-19 case growth over time, compared to neighboring counties that did not implement a mask mandate. The results highlight the swiftness of how a mask ordinance can impact the trajectory of infection rate growth. Another notable finding was that following implementation of mask mandates, the disparity of infection rate by race and population density was no longer significant, suggesting that regional-level policies can not only slow the spread of COVID-19, but simultaneously create more equal environment*. [**note: MASKS WORK – end of story**] https://www.medrxiv.org/content/10.1101/2020.10.28.20221705v1
- Human travel is one of the primary drivers of infectious disease spread. Models of travel are often used that assume the amount of travel to a specific destination decays as cost of travel

increases and higher travel volumes to more populated destinations. Trip duration, the length of time spent in a destination, can also impact travel patterns. *We investigated the spatial distribution of travel conditioned on trip duration and find distinct differences between short and long duration trips. In short-trip duration travel networks, trips are skewed towards urban destinations, compared with long-trip duration networks where travel is more evenly spread among locations. Using gravity models imbedded in simulations of disease transmission, we show that pathogens with shorter generation times exhibit initial patterns of spatial propagation that are more predictable among urban locations, whereas longer generation time pathogens have more diffusive patterns of spatial spread reflecting more unpredictable disease dynamics*. [**note: here is another model looking at trip duration and disease spread.**] https://www.medrxiv.org/content/10.1101/2020.10.27.20215566v1

- Nearly all mass gathering events (MGEs) worldwide have been banned since the outbreak of SARS-CoV-2 as they are supposed to pose a considerable risk for transmission of COVID-19*. We investigated transmission risk of SARS-CoV-2 by droplets and aerosols during an experimental indoor MGE (using N95 masks and contact tracing devices) and conducted a simulation study to estimate the resulting burden of disease under conditions of controlled epidemics. The number of exposed contacts was <10 for scenarios with hygiene concept and good ventilation, but substantially higher otherwise. Of subsequent cases, 0%-23% were attributable to MGEs. Overall, the expected additional effect of indoor MGEs on burden of infections is low if hygiene concepts are applied and adequate ventilation exists*. [**note: from Germany, this one looks at the risk of indoor sports and culture events.]** https://www.medrxiv.org/content/10.1101/2020.10.28.20221580v1

NEWLY REGISTERED CLINICAL TRIALS

- Tomorrow you will get your wish!

CLINICAL TRIAL RESULTS

- **Objectives** To characterize the demographics, comorbidities, symptoms, in-hospital treatments, and health outcomes among children/adolescents diagnosed or hospitalized with COVID-19. Secondly, to describe health outcomes amongst children/adolescents diagnosed with previous seasonal influenza. **Design** International network cohort. **Setting** Real-world data from European primary care records (France/Germany/Spain), South Korean claims and US claims and hospital databases. **Participants** Diagnosed and/or hospitalized children/adolescents with COVID-19 at age <18 between January and June 2020; diagnosed with influenza in 2017-2018. **Main outcome measures** Baseline demographics and comorbidities, symptoms, 30-day in-hospital treatments and outcomes including hospitalization, pneumonia, acute respiratory distress syndrome (ARDS), multi-system inflammatory syndrome (MIS-C), and death. **Results** A total of 55,270 children/adolescents diagnosed and 3,693 hospitalized with COVID-19 and 1,952,693 diagnosed with influenza were studied. Comorbidities including neurodevelopmental disorders, heart disease, and cancer were all more common among those hospitalized vs diagnosed with COVID-19. The most common COVID-19 symptom was fever. Dyspnea, bronchiolitis, anosmia and gastrointestinal symptoms were more common in COVID-19 than influenza. In-hospital treatments for COVID-19 included repurposed medications (<10%), and adjunctive therapies: systemic corticosteroids (6.8% to 37.6%), famotidine (9.0% to 28.1%), and antithrombotics such

as aspirin (2.0% to 21.4%), heparin (2.2% to 18.1%), and enoxaparin (2.8% to 14.8%). Hospitalization was observed in 0.3% to 1.3% of the COVID-19 diagnosed cohort, with undetectable (N<5 per database) 30-day fatality. Thirty-day outcomes including pneumonia, ARDS, and MIS-C were more frequent in COVID-19 than influenza. **Conclusions** *Despite negligible fatality, complications including pneumonia, ARDS and MIS-C were more frequent in children/adolescents with COVID-19 than with influenza. Dyspnea, anosmia and gastrointestinal symptoms could help differential diagnosis. A wide range of medications were used for the inpatient management of pediatric COVID-19*. [**note: more from the OHDSI group of researchers. Here is a large look at children and adolescents with COVID-19 and influenza. While mortality in the age cohort is low, other side effects from COVID-19 are more frequent than those from influenza.**]
https://www.medrxiv.org/content/10.1101/2020.10.29.20222083v1

DRUG DEVELOPMENT

- The rapid development of safe and effective vaccines against SARS CoV−2 is the need of the hour for the coronavirus outbreak. Here, we have developed PRAK−03202, the world's first triple antigen VLP vaccine candidate in a highly characterized S. cerevisiae−based D−Crypt™ platform, which induced SARS CoV−2 specific neutralizing antibodies in BALB/c mice. Immunizations using three different doses of PRAK−03202 induces antigen specific (Spike, envelope and membrane proteins) humoral response and neutralizing potential. PBMCs from convalescent patients, when exposed to PRAK−03202, showed lymphocyte proliferation and elevated IFN-γ levels suggestive of conservation of epitopes and induction of T helper 1 (Th1)−biased cellular immune responses. These data support the clinical development and testing of PRAK−03202 for use in humans. [**note: this is an interesting vaccine candidate from India using a triple antigen approach in a yeast production system. I still wonder if these approaches will lead to better immune response than a single antigen vaccine.**]
https://www.biorxiv.org/content/10.1101/2020.10.30.360115v1
- Antibody engineering technologies face increasing demands for speed, reliability and scale. We developed CeVICA, a cell-free antibody engineering platform that integrates a novel generation method and design for camelid heavy-chain antibody VHH domain-based synthetic libraries, optimized *in vitro* selection based on ribosome display and a computational pipeline for binder prediction based on CDR-directed clustering. We applied CeVICA to engineer antibodies against the Receptor Binding Domain (RBD) of the SARS-CoV-2 spike proteins and identified >800 predicted binder families. Among 14 experimentally-tested binders, 6 showed inhibition of pseudotyped virus infection. *Antibody affinity maturation further increased binding affinity and potency of inhibition. Additionally, the unique capability of CeVICA for efficient and comprehensive binder prediction allowed retrospective validation of the fitness of our synthetic VHH library design and revealed direction for future refinement. CeVICA offers an integrated solution to rapid generation of divergent synthetic antibodies with tunable affinities* in vitro *and may serve as the basis for automated and highly parallel antibody generation*. [**note: these Broad Inst scientists come up with a cell-free antibody engineering platform that rapidly generates SARS-CoV-2 neutralizing antibodies.**]
https://www.biorxiv.org/content/10.1101/2020.10.29.361287v1

- Herein we provide a living summary of the data generated during the COVID Moonshot project focused on the development of SARS-CoV-2 main protease (Mpro) inhibitors. Our approach uniquely combines crowdsourced medicinal chemistry insights with high throughput crystallography, exascale computational chemistry infrastructure for simulations, and machine learning in triaging designs and predicting synthetic routes. This manuscript describes our methodologies leading to both covalent and non-covalent inhibitors displaying protease IC50 values under 150 nM and viral inhibition under 5 uM in multiple different viral replication assays. Furthermore, we provide over 200 crystal structures of fragment-like and lead-like molecules in complex with the main protease. *Over 1000 synthesized and ordered compounds are also reported with the corresponding activity in Mpro enzymatic assays using two different experimental setups. The data referenced in this document will be continually updated to reflect the current experimental progress of the COVID Moonshot project, and serves as a citable reference for ensuing publications. All of the generated data is open to other researchers who may find it of use*. [**note: a big shout out to this group for establishing 'The COVID Moonshot Consortium!' Here is an open source approach to Mpro inhibitors.**]
  https://www.biorxiv.org/content/10.1101/2020.10.29.339317v1
- Increasing evidence shows that both natural and synthetic antimicrobial peptides (AMPs), also referred to as Host Defense Proteins/Peptides (HDPs), can inhibit SARS-CoV-2, paving the way for the potential clinical use of these molecules as therapeutic options. In this manuscript, we describe the potent antiviral activity exerted by brilacidin−a de novo designed synthetic small molecule that captures the biological properties of HDPs−on SARS-CoV-2 in a human lung cell line (Calu-3) and a monkey cell line (Vero). These data suggest that SARS-CoV-2 inhibition in these cell culture models is primarily a result of the impact of brilacidin on viral entry and its disruption of viral integrity. Brilacidin has demonstrated synergistic antiviral activity when combined with remdesivir. Collectively, our data demonstrate that brilacidin exerts potent inhibition of SARS-CoV-2 and thus supports brilacidin as a promising COVID-19 drug candidate. Highlights: Brilacidin potently inhibits SARS-CoV-2 in an ACE2 positive human lung cell line. Brilacidin achieved a high Selectivity Index of 426 (CC_{50}=241µM/IC_{50}=0.565µM). Brilacidin's main mechanism appears to disrupt viral integrity and impact viral entry. Brilacidin and remdesivir exhibit excellent synergistic activity against SARS-CoV-2. Significance Statement: SARS-CoV-2, the emergent novel coronavirus, has led to the current global COVID-19 pandemic, characterized by extreme contagiousness and high mortality rates. There is an urgent need for effective therapeutic strategies to safely and effectively treat SARS-CoV-2 infection. We demonstrate that brilacidin, a synthetic small molecule with peptide-like properties, is capable of exerting potent in vitro antiviral activity against SARS-CoV-2, both as a standalone treatment and in combination with remdesivir, which is currently the only FDA-approved drug for the treatment of COVID-19. [**note: this compound was first developed at Univ of Pennsylvania almost 20 years ago. It seems to have interesting anti-microbial properties but the clinical development appears to have sputtered. Innovation Pharmaceuticals is the third company to develop this drug. We will see if this has any use for treating COVID-19.]**
  https://www.biorxiv.org/content/10.1101/2020.10.29.352450v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- In March 2020, the first cases of COVID-19 were reported in South Africa. The epidemic spread very fast despite an early and extreme lockdown and infected over 600,000 people, by far the highest number of infections in an African country. To rapidly understand the spread of SARS-CoV-2 in South Africa, we formed the Network for Genomics Surveillance in South Africa (NGS-SA). Here, we analyze 1,365 high quality whole genomes and identify 16 new lineages of SARS-CoV-2. Most of these unique lineages have mutations that are found hardly anywhere else in the world. *We also show that three lineages spread widely in South Africa and contributed to ~42% of all of the infections in the country. This included the first identified C lineage of SARS-CoV-2, C.1, which has 16 mutations as compared with the original Wuhan sequence. C.1 was the most geographically widespread lineage in South Africa, causing infections in multiple provinces and in all of the eleven districts in KwaZulu-Natal (KZN), the most sampled province. Interestingly, the first South-African specific lineage, B.1.106, which was identified in April 2020, became extinct after nosocomial outbreaks were controlled. Our findings show that genomic surveillance can be implemented on a large scale in Africa to identify and control the spread of SARS-CoV-2*. [**note: here is interesting genomic analysis of the SARS-CoV-2 outbreak in South Africa. New lineages not found before appeared and three of them spread rapidly. The first line that was identified in April 2020 disappeared.**]
  https://www.medrxiv.org/content/10.1101/2020.10.28.20221143v1
- Background: Multiple candidates of COVID-19 vaccines have entered Phase III clinical trials in the United States (US). There is growing optimism that social distancing restrictions and face mask requirements could be eased with widespread vaccine adoption soon. Methods: We developed a dynamic compartmental model of COVID-19 transmission for the four most severely affected states (New York, Texas, Florida, and California). We evaluated the vaccine effectiveness and coverage required to suppress the COVID-19 epidemic in scenarios when social contact was to return to pre-pandemic levels and face mask use was reduced. Daily and cumulative COVID-19 infection and death cases were obtained from the Johns Hopkins University Coronavirus resource center and used for model calibration. Results: Without a vaccine, the spread of COVID-19 could be suppressed in these states by maintaining strict social distancing measures and face mask use levels. But relaxing social distancing restrictions to the pre-pandemic level without changing the current face mask use would lead to a new COVID-19 outbreak, resulting in 0.8-4 million infections and 15,000-240,000 deaths across these four states over the next 12 months. In this scenario, introducing a vaccine would partially offset this negative impact even if the vaccine effectiveness and coverage are relatively low. However, if face mask use is reduced by 50%, a vaccine that is only 50% effective (weak vaccine) would require coverage of 55-94% to suppress the epidemic in these states. A vaccine that is 80% effective (moderate vaccine) would only require 32-57% coverage to suppress the epidemic. In contrast, if face mask usage stops completely, a weak vaccine would not suppress the epidemic, and further major outbreaks would occur. A moderate vaccine with coverage of 48-78% or a strong vaccine (100% effective) with coverage of 33-58% would be required to suppress the epidemic. Delaying vaccination rollout for 1-2 months would not substantially alter the epidemic trend if the current interventions are maintained. Conclusions: *The degree to which the US population can relax social distancing restrictions and face mask use will depend greatly on the effectiveness and coverage of a potential COVID-19 vaccine if future epidemics are to be prevented. Only a highly effective vaccine will enable the US population to return to life as it was*

before the pandemic. [**note: another model today, this one looks at the pandemic in the US in context of a potential vaccine and implications for social distancing and face mask use. This is a useful paper to read.**] https://www.medrxiv.org/content/10.1101/2020.10.28.20221234v1

- Multiple studies have shown loss of SARS-CoV-2 specific antibodies over time after infection, raising concern that humoral immunity against the virus is not durable. If immunity wanes quickly, millions of people may be at risk for reinfection after recovery from COVID-19. However, memory B cells (MBC) could provide durable humoral immunity even if serum neutralizing antibody titers decline. We performed multi-dimensional flow cytometric analysis of S protein receptor binding domain (S-RBD)-specific MBC in cohorts of ambulatory COVID-19 patients with mild disease, and hospitalized patients with moderate to severe disease, at a median of 54 (39-104) days after onset of symptoms. *We detected S-RBD-specific class-switched MBC in 13 out of 14 participants, including 4 of the 5 participants with lowest plasma levels of anti-S-RBD IgG and neutralizing antibodies. Resting MBC (rMBC) made up the largest proportion of S-RBD-specific class-switched MBC in both cohorts. FCRL5, a marker of functional memory when expressed on rMBC, was dramatically upregulated on S-RBD-specific rMBC. These data indicate that most SARS-CoV-2-infected individuals develop S-RBD-specific, class-switched MBC that phenotypically resemble germinal center-derived B cells induced by effective vaccination against other pathogens, providing evidence for durable B cell-mediated immunity against SARS-CoV-2 after recovery from mild or severe COVID-19 disease*. [**note: This is from Johns Hopkins and while it is a small group it points to durable humoral immunity. We need more confirmatory data but I look at this as a good thing!]**
  https://www.medrxiv.org/content/10.1101/2020.10.28.20220996v1
- Seasonal coronaviruses (OC43, 229E, NL63 and HKU1) are endemic to the human population, regularly infecting and reinfecting humans while typically causing asymptomatic to mild respiratory infections. It is not known to what extent reinfection by these viruses is due to waning immune memory or antigenic drift of the viruses. Here, we address the influence of antigenic drift on immune evasion of seasonal coronaviruses. *We provide evidence that at least two of these viruses, OC43 and 229E, are undergoing adaptive evolution in regions of the viral spike protein that are exposed to human humoral immunity. This suggests that reinfection may be due, in part, to positively-selected genetic changes in these viruses that enable them to escape recognition by the immune system. It is possible that, as with seasonal influenza, these adaptive changes in antigenic regions of the virus would necessitate continual reformulation of a vaccine made against them*. [**note: this paper looks at antigenic drift of the receptor binding protein of seasonal coronaviruses. It is possible this will have an impact on changes to SARS-CoV-2.]** https://www.biorxiv.org/content/10.1101/2020.10.30.352914v1
- SARS-CoV-2 exhibits significant experimental and clinical gastrointestinal, renal, and cardiac muscle tropisms responsible for local tissue-specific and systemic pathophysiology capriciously occurring in about half of COVID-19 patients. The underlying COVID-19 mechanisms engaged by these extra-pulmonary organ systems are largely unknown. We approached this knowledge gap by recognizing that neutral amino acid transporter B^0AT1 (alternately called NBB, B, B^0 in the literature) is a common denominator expressed nearly exclusively by three particular cell types: intestinal epithelia, renal proximal tubule epithelium, and cardiomyocytes. B^0AT1 provides uptake of glutamine and tryptophan. The gut is the main depot expressing over 90% of the body's entire pool of SARS-CoV-2 receptor angiotensin converting enzyme-2 (ACE2) and B^0AT1.

Recent cryo-EM studies established that ACE2 forms a thermodynamically favored dimer-of-heterodimers complex with B^0AT1 assembled in the form of a dimer of two ACE2:B^0AT1 heterodimers anchored in plasma membranes. Prior epithelial cell studies demonstrated ACE2 chaperone trafficking of B^0AT1. This contrasts with monomeric expression of ACE2 in lung pneumocytes, in which B^0AT1 is undetectable. The cell types in question also express a disintegrin and metalloproteinase-17 (ADAM17) known to cleave and shed the ectodomain of monomeric ACE2 from the cell surface, thereby relinquishing protection against unchecked renin-angiotensin-system (RAS) events of COVID 19. The present study employed molecular docking modeling to examine the interplaying assemblage of ACE2, ADAM17 and B^0AT1. We report that in the monomer form of ACE2, neck region residues R652-N718 provide unimpeded access to ADAM17 active site pocket, but notably R708 and S709 remained >10-15 Å distant. In contrast, interference of ADAM17 docking to ACE2 in a dimer-of-heterodimers arrangement was directly correlated with the presence of a neighboring B^0AT1 subunit complexed to the partnering ACE2 subunit of the 2ACE2:2B^0AT1 dimer of heterodimers, representing the expression pattern putatively exclusive to intestinal, renal and cardiomyocyte cell types. The monomer and dimer-of-heterodimers docking models were not influenced by the presence of SARS-CoV-2 receptor binding domain (RBD) complexed to ACE2. *The results collectively provide the underpinnings for understanding the role of B^0AT1 involvement in COVID-19 and the role of ADAM17 steering ACE2 events in intestinal and renal epithelial cells and cardiomyocytes, with implications useful for consideration in pandemic public hygiene policy and drug development*. [**note: here is a look at a possible protein influencer in the intestine, kidney and cardiomycete. The virus has a clinical impact on these organs in addition to the lungs.]** https://www.biorxiv.org/content/10.1101/2020.10.30.361873v1

DIAGNOSTIC DEVELOPMENT

- Nothing Today

>>

2020-11-01

Yes, it is the day after Halloween and reflection Sunday, but this did not show on my YouTube feed until my newsletter went out. Here is a living room concert from LA Opera of some Halloween themed songs: https://www.youtube.com/watch?v=tF33CQrPTI8 this is a clever recital!!!

The Washington Post points to a Stanford study that looked at COVID-19 outbreaks following large scale rallies held by President Trump. England and other Euro countries are seeing large spikes and moving towards lockdowns. Early distribution of HCQ was done from the Strategic National Stockpile going against the FDA's Emergency Use Authorization. This was not good behavior! There is a good interview with Tony Fauci on all things COVID-19.

The New York Times notes that Americans have no idea how they contracted COVID-19. The Times also covers the Stanford study of MAGA rallies. Discontent is building up in Italy; I would say it is building up everywhere! I want to move to New Zealand!

This LINK is not meant to be a political statement, but it is an interesting graphical showing of SARS-CoV-2 infections since June 1. You can see how the states' position change daily. Pretty cool if you ask me.

MODELING

- Environmental surveillance of surface contamination is an unexplored tool for understanding transmission of SARS-CoV-2 in community settings. We conducted longitudinal swab sampling of high-touch non-porous surfaces in a Massachusetts town during a COVID-19 outbreak from April to June 2020. Twenty-nine of 348 (8.3 %) surface samples were positive for SARS-CoV-2, including crosswalk buttons, trash can handles, and door handles of essential business entrances (grocery store, liquor store, bank, and gas station). *The estimated risk of infection from touching a contaminated surface was low (less than 5 in 10,000), suggesting fomites play a minimal role in SARS-CoV-2 community transmission. The weekly percentage of positive samples (out of n=33 unique surfaces per week) best predicted variation in city-level COVID-19 cases using a 7-day lead time. Environmental surveillance of SARS-CoV-2 RNA on high-touch surfaces could be a useful tool to provide early warning of COVID-19 case trends*. [**note: here is a good study of environmental samples from non-porous surfaces in a Massachusetts town. They believe fomites play a minimal role in transmission.**]
  https://www.medrxiv.org/content/10.1101/2020.10.27.20220905v1

NEWLY REGISTERED CLINICAL TRIALS

- Researchers know that the virus that causes COVID-19 has been found in the saliva (spit) of individuals who exhibit signs of the disease. Investigators would like to test the ability of three mouthwashes to reduce the levels of this virus in participants' mouths. Investigators will ask participants to use a liquid to swish around in the mouth for 30 seconds and spit it into a collection cup. Investigators will also collect spit from participants before and after participants use the mouthwash. Although participants will have no direct benefits from the study, investigators will gain a wealth of information that would benefit patients who are at risk for COVID-19. [**note: here is a mouthwash study from Ohio State. They will be looking at Povidone/iodine; chlorhexidine, and hydrogen peroxide rinses.**] NCT04603794
- Patients requiring hospitalization due to COVID-19 pneumonia (non-severe) will be randomized to standard prophylactic doses or full therapeutic dose of bemiparin (a LMWH) for 10 days. [**note: this is from Spain and another antithrombotic trial.]** NCT04604327
- This is a multi-site, randomized, double-blind, placebo-controlled study assessing the efficacy and safety of ZnAg liquid solution in symptomatic participants with acute COVID-19 that are not hospitalized at the time of enrollment. [**note: this is a Brazilian trial and I have no idea about the rationale for using this combination of zinc and silver.**] NCT04610138
- The investigators reason that Regadenoson treatment will reduce COVID-19-induced lung injury by inhibiting hyperinflammation. Our overarching goal is to demonstrate that Regadenoson treatment increases survival by reducing hyperinflammation and pulmonary function. The investigators will test the hypothesis that Regadenoson elicits clinical improvement and enhances survival compared to placebo control patients with COVID-19. The investigators hypothesize that the survival benefit of Regadenoson will be additive or synergistic with the anti-viral drug, Remdesivir. Remdesivir and Dexamethasone are currently standard of care and would remain so. [**note: this is a Univ of Maryland trial.**] NCT04606069

- Pilot study into low dose naltrexone (LDN) and NAD+ for treatment of patients with post-COVID-19 syndrome. [**note: this trial is from AgelessRx. Again, don't know the rationale.**] NCT04604704
- A randomized, parallel-group treatment, quadruple masked, two-arm study to assess the effectiveness of cod liver oil compared to placebo in the prevention of Covid-19 and airway infections in healthy adults. [**note: I WAS waiting for this one to appear. I remember my mother threatening to give me cod liver oil when I was a kid. Good luck to this Norwegian team!**] NCT04609423
- The investigators propose a prospective, randomized, double-blind, placebo-controlled study, conducted in two phases. The purpose of the study is to evaluate the safety and efficacy of methotrexate in a cholesterol-rich non-protein nanoparticle (MTX -LDE) in adults diagnosed with mild Coronavirus-19(COVID-19) disease. [**note: this one is from Sao Paulo Brazil**] NCT04610567
- This is a Phase 2/3 study to assess the efficacy about therapeutic effect of CT-P59 to the mild to moderate SARS-CoV-2 infected patients and safety during after study drug injection. [**note: this is a South Korean monoclonal antibody developed by Celltrion.**] NCT04602000

CLINICAL TRIAL RESULTS

- Objectives: To study the features of creatine-kinase (CK) in COVID-19 patients with different ages, clinical types and outcomes and quantify the relationship between CK value and clinical type. Methods: All laboratory confirmed COVID-19 patients hospitalized in Xiangyang No.1 People's Hospital were included. Patients' general information, clinical type, all CK values and outcome were collected. Results: The peak median value of CK in cases aged greater than or equal to 71 years old (appeared at T2) was higher than that in cases aged less than or equal to 70 years old. There was statistical difference between the two groups. Similarly, the peak in critical cases (appeared at T2) was higher than moderate and severe types, and significant difference were existed among moderate, severe, and critical types. Moreover, the peak value in death group (appeared at T2) was higher than those in survival group. Significant difference was also found between them. *According to the optimal scale regression model, the CK value and age were associated with the clinical type. Conclusions: Difference of the CK in different ages, clinical types, and outcomes were significant. The results of the optimal scale regression model are helpful to judge the clinical type of COVID-19 patients*. [**note: this is from China and looks at levels of creatine kinase in COVID-19 patients.**] https://www.medrxiv.org/content/10.1101/2020.10.28.20221093v1
- There is no study to systematically analyse the features of hydroxybutyrate dehydrogenase (α-HBDH) in COVID-19 patients during the periods before and after illness progression, before death and course from exposure onset. Methods: We collected all included patients' general information, clinical type, α-HBDH value and outcome, and analyzed α-HBDH values within different initial time and different periods. Results: In the first 30 days after symptom onset, the α-HBDH median value was 156.33 U/L. The first test of α-HBDH since exposure onset appeared on the 8th day, it increased from the 8th day to 18th day and decreased after the 18th day. α-HBDH median value showed a slight change until it started to increase 1 day before transforming to severe type, while it continued to increase during 4 days before and after transforming to critical type. The α-HBDH median value ranged from 191.11 U/L to 455.11U/L before death. Conclusions: α-HBDH value increases in some COVID-19 patients, obviously in

severe type, critical type and death patients, and mainly in 18 days after exposure onset and 10 days after symptom onset. α-HBDH increases 1 day before transforming to severe type, continues to increase in critical type and death patients, increases rapidly 5 days before death. *The increase of α-HBDH suggests that COVID-19 patients have tissues and organs damage, mainly in heart. In brief, α-HBDH is an important indicator to judge the severity and prognosis of COVID-19.* {**note: this is from the same group as the above paper and looks at hydroxybutyrate dehydrogenase.**] https://www.medrxiv.org/content/10.1101/2020.10.28.20221127v1

- Background: To characterize C-reactive protein (CRP) changes features from patients with coronavirus disease 2019 (COVID-19) and to quantify the correlation between CRP value and clinical classification. Methods: This was a bidirectional observational cohort study. All laboratory confirmed COVID-19 patients hospitalized in Xiangyang No.1 People's Hospital were included. Patients' general information, clinical type, CRP value and outcome were collected. Patients were grouped according to the age, clinical type and outcome, and their CRP were compared. The CRP value, age gender, and clinical type were used to build a categorical regression model to investigate the association between CRP and clinical type. Results: The 131 patients aged 50.13 plus-or-minus 17.13 years old. There were 4 mild, 88 moderate, 21 severe and 18 critical cases. *Statistical significance of CRP median exists between different clinical types and ages. There were 10 deaths and 121 cases have been discharged. The CRP in death group dramatically increased continuously until died, while increased firstly and decreased later in the survivor and survivor in critical type. The categorical regression model also showed that CRP and age had significant coefficient. During the first 15 days from symptom onset, the maximum of CRP ranged between 0.47-53.37 mg/L were related to mild combined with moderate type, ranged 53.84-107.08 mg/L were related to severe type, and 107.42-150.00 mg/L were related to the critical type. Conclusions: CRP showed different distribution feature and existed differences in various ages, clinical types and outcomes of COVID-19 patients. The features corresponded with disease progression*. [**note: this time the Chinese researchers look at levels of C-reactive protein.**] https://www.medrxiv.org/content/10.1101/2020.10.26.20220160v1

DRUG DEVELOPMENT

- Nothing Today

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Nothing Today

DIAGNOSTIC DEVELOPMENT

- These have been used for studying the prevalence and spread of infection in different populations, helping establish a diagnosis of COVID-19, and will likely be used to confirm humoral immunity after infection or vaccination. However, nearly all lab-based high-throughput SARS-CoV-2 serological assays require a serum sample from venous blood draw, limiting their applications and scalability. Here, we present a method that enables large scale SARS-CoV-2 serological studies by combining self or office collection of fingerprick blood with an FDA-approved dried blood spot collection device (Neoteryx Mitra®) with a high-throughput electrochemiluminescence-based SARS-CoV-2 total antibody assay (Roche Elecsys®) that is EUA approved for use on serum samples and widely used by clinical laboratories around the world.

We found that the Roche Elecsys® assay has a high dynamic range that allows for accurate detection of SARS-CoV-2 antibodies in serum samples diluted 1:20 as well as contrived dried blood extracts. Extracts of dried blood from Neoteryx Mitra® devices acquired in a community seroprevalence study showed near identical sensitivity and specificity in detection of SARS-CoV-2 antibodies as compared to neat sera using predefined thresholds for each specimen type. Overall, this study affirms the use of Neoteryx Mitra® dried blood collection device with the Roche Elecsys® SARS-CoV-2 total antibody assay for remote or at-home testing as well as large-scale community seroprevalence studies. [**note: remote fingerstick blood collection is a useful approach to collecting blood samples for antibody testing.**]
https://www.medrxiv.org/content/10.1101/2020.10.27.20221028v1