2020-09-21

Welcome to Week 27!!!

This one popped up on my YouTube feed and is spectacular. Frank and Ella two icons of the Big Band Era who had great careers for a long time! Here they are singing the Rogers and Hart classic "The Lady is a Tramp" from the 1960s: https://www.youtube.com/watch?v=xafBWOxqssg This is a very nice performance by Tony Bennett and Lady Gaga: https://www.youtube.com/watch?v=ZPAmDULCVrU

My Yahoo news feed sends this Los Angeles Times article on the CDC guidance on SARS-CoV-2 spread which occurs mainly through the air. This is unsurprising based on all the literature that has come out since the beginning of the pandemic. Good ventilation can reduce the risk of transmission but since the weather is turning colder, opening windows is not so easy a choice.

The Washington Post notes that some universities are managing COVID-19 outbreaks pretty well; others are not. [Checking on Purdue University, the positivity rate from testing remains at 2.6%, pretty much level from the point when the University began testing.] The WaPo also covers the updated CDC guidelines. Britain may face 50K cases per day by mid-October which is not good news. In another of the first-person accounts of dealing with the pandemic, this Florida election official faces some difficult challenges and comes up with creative solutions. He wants all those in the county to be able to vote safely. Let us hope others are doing the same.

The New York Times discusses comments from administration officials on the vaccine development timeline. Some hotels in Manhattan are closing for good. AstraZeneca released the blue print for their vaccine development program based on the Oxford adenovirus vector. According to the article there was a second patient with transverse myelitis. [**Editorial Comment:** I think the FDA Vaccine Advisory Committee is going to have a rough time when they meet at the end of October. Will they feel comfortable that there is enough safety information coming out of the trials that would warrant an Experimental Use Authorization? Dr. Redfield's comment in Congressional testimony last week regarding masks was scoffed out by some. He noted that masks are a better solution than a vaccine. Of course he is correct as anyone who can look at the risk of viral transmission. According to FDA, a COVID-19 vaccine may be approved that is only 50% efficacious at preventing infection. If everyone were to wear masks, the protection against COVID-19 is significantly higher than that based on the literature assessments that so far have come out. **End of Editorial Comment**]

STAT cover how one social media platform is successfully dealing with vaccine misinformation (hint: it is not Facebook). This opinion piece argues for teachers getting priority access to vaccines and treatments. I fully agree with this piece that argues for the White House Coronavirus Task Force being fully transparent (BTW, what is Dr. Birx doing these days? She seems to have dropped from sight.).

The Lancet have this letter from the developers of one of the Russian vaccine candidate about whether there is enough information about it. Here is a UK consensus management pathway providing guidance on pediatric multisystem syndrome associated with COVID-19.

Nature discuss access to COVID-19 vaccines from a world wide perspective. Here is a study of superspreading events in Hong Kong. Money quote, "Public health authorities should focus on rapidly tracing and quarantining contacts, along with implementing restrictions targeting social settings to reduce the risk of SSEs and suppress SARS-CoV-2 transmission." Yes, they got that right!

For those interested, Medscpe links to a site that is tracking retracted COVID-19 papers. The number is up to 33. I don't have time to follow this stuff.

There was only one new preprint on the server this morning a likely result of the weekend. Most medical journals do not come out with new articles on Monday. You can all enjoy the light reading day!!!

MODELING

- Nada

NEWLY REGISTERED CLINICAL TRIALS

- Will check later.

CLINICAL TRIAL RESULTS

- Zilch

DRUG DEVELOPMENT

- Zeio

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- SARS-CoV-2 is thought to disable various features of host immunity and cellular defense. The SARS-CoV-2 nonstructural protein 1 (Nsp1) is known to inhibit host protein translation and could be a target for antiviral therapy against COVID-19. However, how SARS-CoV-2 circumvents this translational blockage for the production of its own proteins is an open question. Here, we report a bipartite mechanism of SARS-CoV-2 Nsp1 which operates by: (1) hijacking the host ribosome via direct interaction of its C-terminal domain (CT) with the 40S ribosomal subunit and (2) specifically lifting this inhibition for SARS-CoV-2 via a direct interaction of its N-terminal domain (NT) with the 5' untranslated region (5′ UTR) of SARS-CoV-2 mRNA. We show that while Nsp1-CT is sufficient for binding to 40S and inhibition of host protein translation, the 5′ UTR of SARS-CoV-2 mRNA removes this inhibition by binding to Nsp1-NT, suggesting that the Nsp1-NTUTR interaction is incompatible with the Nsp1-CT40S interaction. Indeed, lengthening the linker between Nsp1-NT and Nsp1-CT of Nsp1 progressively reduced the ability of SARS-CoV-2 5′ UTR to escape the translational inhibition, supporting that the incompatibility is likely steric in nature. The short SL1 region of the 5′ UTR is required for viral mRNA translation in the presence of Nsp1. *Thus, our data provide a comprehensive view on how Nsp1 switches infected cells from host mRNA translation to SARS-CoV-2 mRNA translation, and that Nsp1 and 5′ UTR may be targeted for anti-COVID-19 therapeutics*. [**note: this is from Harvard and provides further information on the Nsp1 protein of the virus and how it helps hijack the mammalian cellular protein synthesis machinery.**] https://www.biorxiv.org/content/10.1101/2020.09.18.302901v1

DIAGNOSTIC DEVELOPMENT

- Not a thing

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2020-09-22

I was listening to Marc Maron's interview with Alicia Keys on my walk yesterday and thought, why haven't I featured her? We need to take care of this ASAP! Here is Alicia Keys from another one of the fine NPR Tiny Desk concerts with her wonderful song 'Gramercy Park': https://www.youtube.com/watch?v=o5WauEHL43Y Maybe with everyone fleeing New York I can realize my dream of a pied-á-terre that borders the park along with the requisite entry key. It probably won't happen, but loyal readers can contribute to my Gramercy Park housing fund!!! *Make that pledge today*

The Washington Post asks why there continues to be a shortage of N 95 masks. Good question! I missed out on the big rush to corner the Tofu market. We eat a lot of fish which has been in plentiful supply and had homemade crab cakes last night. I haven't bought a brick of Tofu in some years. Now it turns out that what the CDC put on its website last Friday regarding aerosol transmission was in error. Personally, I just follow the simple rule of wearing a mask anytime I am around people, keep to the six foot rule of separation, and don't go into any enclosed spaces where there are large numbers. You really cannot make this kind of stuff up; to bizarre! It gets even worse for this Tulsa public health official who advised against a Presidential rally.

The New York Times discusses what we know about COVID-19 infections in schools. Not much as it turns out as there is not a good collection of data. Since children have not been part of COVID-19 vaccine trials, they might not be immunized until the fall of 2021.

The Atlantic's Ed Yong discusses COVID-19 associated myocarditis. It's complicated as is everything else with this virus.

STAT have a long form article on the road ahead for dealing with COVID-19.

The Lancet have a commentary on what we can expect from the first COVID-19 vaccines. This VA cohort study shows that there is no protective effect of HCQ against COVID-19 in rheumatology patients being given the drug for treatment. Here is a commentary on this paper.

Medscape point to a Reuters story that tocilizumab helps reduce ventilator need for COVID-19 patients. Roche previously had noted a sponsored clinical trial showed no beneficial effect.

Derek Lowe weighs in on the vaccine protocols. Speaking of vaccines, a reader sent me a not yesterday asking about the upcoming FDA Vaccine Advisory Committee meeting that is set for October 22. Unless the Russians or Chinese are planning on presenting, Pfizer are the only sponsor that "might" be in a position to do so based on their protocol. The meeting will be open to the public via the Internet with meeting materials available 48 hours in advance. I hope this doesn't crash the Internet as I expect there will be a lot of people wanting to see what happens.

MODELING

- The herd immunity threshold is the proportion of a population that must be immune to an infectious disease, either by natural infection or vaccination such that, in the absence of additional preventative measures, new cases decline and the effective reproduction number falls below unity. This fundamental epidemiological parameter is still unknown for the recently-emerged COVID-19, and mathematical models have predicted very divergent results. Population

studies using antibody testing to infer total cumulative infections can provide empirical evidence of the level of population immunity in severely affected areas. Here we show that the transmission of SARS-CoV-2 in Manaus, located in the Brazilian Amazon, increased quickly during March and April and declined more slowly from May to September. In June, one month following the epidemic peak, 44% of the population was seropositive for SARS-CoV-2, equating to a cumulative incidence of 52%, after correcting for the false-negative rate of the antibody test. The seroprevalence fell in July and August due to antibody waning. After correcting for this, we estimate a final epidemic size of 66%. Although non-pharmaceutical interventions, plus a change in population behavior, may have helped to limit SARS-CoV-2 transmission in Manaus, the unusually high infection rate suggests that herd immunity played a significant role in determining the size of the epidemic. [**note: herd immunity may have been reached in Manaus Brazil. The estimate of those infected is 66% which is in the upper range of models I've seen. This is the first real world estimate of herd immunity to come out!]**
https://www.medrxiv.org/content/10.1101/2020.09.16.20194787v1

- Background Shielding (extended self-isolation) of people judged, a priori, to be at high-risk from COVID-19 has been used by some countries to protect the individuals and reduce demand on health services. It is unclear how well this strategy works in either regard. Methods A general population study was conducted using linked primary care, prescribing, laboratory, hospital and death records up to end of May 2020. Poisson regression models and population attributable fractions were used to compare COVID-19 outcomes by overall risk category, and individual risk criteria: confirmed infection, hospitalisation, intensive care unit (ICU) admission, population mortality and case-fatality. Results Of the 1.3 million population, 32,533 (2.47%) had been advised to shield, a further 347,374 (26.41%) were classified as moderate risk. Testing for COVID-19 was more common in the shielded (6.75%) and moderate (1.99%) than low (0.72%) risk categories. Referent to low-risk, the shielded group had higher risk of confirmed infection (RR 7.91, 95% 7.01-8.92), case-fatality (RR 5.19, 95% CI 4.12-6.53) and population mortality (RR 48.64, 95% 37.23-63.56). The moderate risk had intermediate risk of confirmed infection (RR 4.11, 95% CI 3.82-4.42) and population mortality (RR 26.10, 95% CI 20.89-32.60), but had comparable case-fatality (RR 5.13, 95% CI 4.24-6.21) to the shielded, and accounted for a higher proportion of deaths (PAF 75.27% vs 13.38%). Age ≥70 years made the largest contribution to deaths (49.53%) and was associated with an 8-fold risk of infection, 7-fold case-fatality and 74-fold mortality. Conclusions Shielding has not been effective at preventing deaths in those with highest risk. To be effective as a population strategy, shielding criteria would need to be widely expanded to include other criteria, such as the elderly. [**note: this is a fascinating study from the Glasgow area of Scotland. They took a retrospective look at how shielding of vulnerable populations worked and the results were not good as it was not effective. The paper goes into some the details and what type of shielding would have been necessary to reduce the fatality numbers in this population.**]
https://www.medrxiv.org/content/10.1101/2020.09.17.20196436v1
- SARS-CoV-2 has spread across the world, causing high mortality and unprecedented restrictions on social and economic activity. Policymakers are assessing how best to navigate through the ongoing epidemic, with models being used to predict the spread of infection and assess the impact of public health measures. Here, we present OpenABM-Covid19: an agent-based simulation of the epidemic including detailed age-stratification and realistic social networks. By

default the model is parameterised to UK demographics and calibrated to the UK epidemic, however, it can easily be re-parameterised for other countries. OpenABM-Covid19 can evaluate non-pharmaceutical interventions, including both manual and digital contact tracing. It can simulate a population of 1 million people in seconds per day allowing parameter sweeps and formal statistical model-based inference. The code is open-source and has been developed by teams both inside and outside academia, with an emphasis on formal testing, documentation, modularity and transparency. A key feature of OpenABM-Covid19 is its Python interface, which has allowed scientists and policymakers to simulate dynamic packages of interventions and help compare options to suppress the COVID-19 epidemic. [**note: Here is a cool model to play with if you are a Python programmer like I am! While oriented toward the UK, the authors note it can be adopted to other regions.**]
https://www.medrxiv.org/content/10.1101/2020.09.16.20195925v1

- Following initial declines, in mid 2020, a resurgence in transmission of novel coronavirus disease (COVID-19) has occurred in the United States and parts of Europe. Despite the wide implementation of non-pharmaceutical interventions, it is still not known how they are impacted by changing contact patterns, age and other demographics. As COVID-19 disease control becomes more localised, understanding the age demographics driving transmission and how these impacts the loosening of interventions such as school reopening is crucial. Considering dynamics for the United States, we analyse aggregated, age-specific mobility trends from more than 10 million individuals and link these mechanistically to age-specific COVID-19 mortality data. In contrast to previous approaches, we link mobility to mortality via age-specific contact patterns and use this rich relationship to reconstruct accurate transmission dynamics. Contrary to anecdotal evidence, we find little support for age-shifts in contact and transmission dynamics over time. *We estimate that, until August, 63.4% [60.9%-65.5%] of SARS-CoV-2 infections in the United States originated from adults aged 20-49, while 1.2% [0.8%-1.8%] originated from children aged 0- 9. In areas with continued, community-wide transmission, our transmission model predicts that re-opening kindergartens and elementary schools could facilitate spread and lead to additional COVID-19 attributable deaths over a 90-day period. These findings indicate that targeting interventions to adults aged 20-49 are an important consideration in halting resurgent epidemics and preventing COVID-19-attributable deaths when kindergartens and elementary schools reopen*. [**note: here is another model from the UK that looks at age related impacts on resurging COVID-19 epidemics.**]
https://www.medrxiv.org/content/10.1101/2020.09.18.20197376v1

NEWLY REGISTERED CLINICAL TRIALS

- Will check tomorrow (contributions to my *Gramercy Park housing fund* might prompt me to do daily updates!).

CLINICAL TRIAL RESULTS

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a rapidly emerging virus causing the ongoing Covid-19 pandemic with no known effective prophylaxis. We investigated whether hydroxychloroquine could prevent SARS CoV-2 in healthcare workers at high-risk of exposure. Methods: We conducted a randomized, double-blind, placebo-controlled clinical trial of healthcare workers with ongoing exposure to persons with Covid-19, including those working

in emergency departments, intensive care units, Covid-19 hospital wards, and first responders. Participants across the United States and in the Canadian province of Manitoba were randomized to hydroxychloroquine 400mg once weekly or twice weekly for 12 weeks. The primary endpoint was confirmed or probable Covid-19-compatible illness. We measured hydroxychloroquine whole blood concentrations. Results: We enrolled 1483 healthcare workers, of which 79% reported performing aerosol-generating procedures. The incidence of Covid-19 (laboratory-confirmed or symptomatic compatible illness) was 0.27 events per person-year with once-weekly and 0.28 events per person-year with twice-weekly hydroxychloroquine compared with 0.38 events per person-year with placebo. For once weekly hydroxychloroquine prophylaxis, the hazard ratio was 0.72 (95%CI 0.44 to 1.16; P=0.18) and for twice weekly was 0.74 (95%CI 0.46 to 1.19; P=0.22) as compared with placebo. Median hydroxychloroquine concentrations in whole blood were 98 ng/mL (IQR, 82-120) with once-weekly and 200 ng/mL (IQR, 159-258) with twice-weekly dosing. Hydroxychloroquine concentrations did not differ between participants who developed Covid-19 (154 ng/mL) versus participants without Covid-19 (133 ng/mL; P=0.08). Conclusions: *Pre-exposure prophylaxis with hydroxychloroquine once or twice weekly did not significantly reduce laboratory-confirmed Covid-19 or Covid-19-compatible illness among healthcare workers.* [**note: I believe this is the first of the HCQ prophylaxis trials in the US to report out. Almost 1500 healthcare workers were enrolled. The active group was broken out into two dose regimens. It doesn't work. The authors note that they did not meet full enrollment for the study and they stopped at the end of May. Here is the money quote from the paper, "Based on the demonstrated absolute risk reduction of 0.11 events per person-years, nine high-risk healthcare workers would need to receive prophylaxis for one year to prevent one Covid-19 case." I trust that except for Peter Navarro, this ends the saga.**]
https://www.medrxiv.org/content/10.1101/2020.09.18.20197327v1

DRUG DEVELOPMENT

- Less than a year after its emergence, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected over 22 million people worldwide with a death toll approaching 1 million. Vaccination remains the best hope to ultimately put this pandemic to an end. Here, using Trimer-Tag technology, we produced both wild-type (WT) and furin site mutant (MT) S-Trimers for COVID-19 vaccine studies. Cryo-EM structures of the WT and MT S-Trimers, determined at 3.2 Angstrom and 2.6 Angstrom respectively, revealed that both antigens adopt a tightly closed conformation and their structures are essentially identical to that of the previously solved full-length WT S protein in detergent. These results validate Trimer-Tag as a platform technology in production of metastable WT S-Trimer as a candidate for COVID-19 subunit vaccine. [**note: another vaccine candidate from China.**]
https://www.biorxiv.org/content/10.1101/2020.09.21.306357v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- The world is in the midst of an ongoing pandemic caused by the novel and highly contagious SARS-CoV-2. There is marked inter-individual variability in the tissues affected as well as the severity of response to SARS-CoV-2. It is unclear why some otherwise healthy individuals experience profound clinical complications to SARS-CoV-2 and others do not. We hypothesize that, in addition to viral load and host antibody repertoire, host genetic variants also impact

vulnerability to infection. Here we apply human induced pluripotent stem cell (hiPSC)-based models and CRISPR-engineering to explore the host genetics of SARS-CoV-2. *We demonstrate that a single nucleotide polymorphism (rs4702), common in the population at large, and located in the 3'UTR of the protease FURIN, impacts alveolar and neuron infection by SARS-CoV-2 in vitro. Thus, we provide a proof-of-principle finding that common genetic variation can impact viral infection, and so potentially contribute to clinical heterogeneity in SARS-CoV-2.* Ongoing genetic studies will help to better identify high-risk individuals, predict clinical complications, and facilitate the discovery of drugs that might treat disease. [**note: more good stuff from Mt. Sinai. Here is a possible example of genetic variability in the population that might be used to identify high risk individuals. I wonder if '23 & me' can identify this.**]
https://www.biorxiv.org/content/10.1101/2020.09.20.300574v1

- The ability to detect recombination in pathogen genomes is crucial to the accuracy of phylogenetic analysis and consequently to forecasting the spread of infectious diseases and to developing therapeutics and public health policies. However, previous methods for detecting recombination and reassortment events cannot handle the computational requirements of analyzing tens of thousands of genomes, a scenario that has now emerged in the effort to track the spread of the SARS-CoV-2 virus. Furthermore, the low divergence of near-identical genomes sequenced in short periods of time presents a statistical challenge not addressed by available methods. In this work we present Bolotie, an efficient method designed to detect recombination and reassortment events between clades of viral genomes. We applied our method to a large collection of SARS-CoV-2 genomes and discovered hundreds of isolates that are likely of a recombinant origin. In cases where raw sequencing data was available, we were able to rule out the possibility that these samples represented co-infections by analyzing the underlying sequence reads. Our findings further show that several recombinants appear to have persisted in the population. [**note: this is from Johns Hopkins and presents 'Bolotie' a new algorithm that can be used to detect recombinant forms and other anomalies in a large set of viral sequences. The analyzed 87,695 genomes and it took 5.5 hours using dual Intel Xenon computer (disclosure: I am an Intel shareholder). Some good graphs and images in this paper.**] https://www.biorxiv.org/content/10.1101/2020.09.21.300913v1
- Coronavirus interaction with viral receptor is a primary genetic determinant of host range and tissue tropism. SARS-CoV-2 utilizes ACE2 as the receptor to enter the host cell in a species-specific manner. We and others have previously shown that ACE2 orthologs from New World monkeys, koala and mouse cannot interact with SARS-CoV-2 to mediate viral entry, and this defect can be restored by humanization of the restrictive residues in New World monkey ACE2. To better understand the genetic determinants of susceptibility of ACE2 orthologs to viral entry, we compared koala and mouse ACE2 sequences with human ortholog, and identified the key residues in koala or mouse ACE2 that restrict its viral receptor activity. Humanization of these critical residues could render the capabilities of koala and mouse ACE2 to bind viral spike protein and facilitate the viral entry. Our work identifies the genetic determinant of ACE2 for SARS-CoV-2 susceptibility, and a single mutation could restore the mouse ACE2 receptor activity, providing a potential avenue for the development of mouse model of SARS-CoV-2. [**note: here is more information on the genetics of ACE2 binding and entry.**]
https://www.biorxiv.org/content/10.1101/2020.09.20.297242v1

- Epitopes that are conserved among SARS-like coronaviruses are attractive targets for design of cross-reactive vaccines and therapeutics. CR3022 is a SARS-CoV neutralizing antibody to a highly conserved epitope on the receptor binding domain (RBD) on the spike protein that can cross-react with SARS-CoV-2, but with lower affinity. Using x-ray crystallography, mutagenesis, and binding experiments, we illustrate that of four amino acid differences in the CR3022 epitope between SARS-CoV-2 and SARS-CoV, a single mutation P384A fully determines the affinity difference. CR3022 does not neutralize SARS-CoV-2, but the increased affinity to SARS-CoV-2 P384A mutant now enables neutralization with a similar potency to SARS-CoV. We further investigated CR3022 interaction with the SARS-CoV spike protein by negative-stain EM and cryo-EM. Three CR3022 Fabs bind per trimer with the RBD observed in different up-conformations due to considerable flexibility of the RBD. In one of these conformations, quaternary interactions are made by CR3022 to the N-terminal domain (NTD) of an adjacent subunit. Overall, this study provides insights into antigenic variation and potential for cross-neutralizing epitopes on SARS-like viruses. [**note: more information on epitopes from a Scripps group.**] https://www.biorxiv.org/content/10.1101/2020.09.21.305441v1
- The COVID-19 pandemic has revealed that infection with SARS-CoV-2 can result in a wide range of clinical outcomes in humans, from asymptomatic or mild disease to severe disease that can require mechanical ventilation. An incomplete understanding of immune correlates of protection represents a major barrier to the design of vaccines and therapeutic approaches to prevent infection or limit disease. This deficit is largely due to the lack of prospectively collected, pre-infection samples from indiviuals that go on to become infected with SARS-CoV-2. Here, we utilized data from a screen of genetically diverse mice from the Collaborative Cross (CC) infected with SARS-CoV to determine whether circulating baseline T cell signatures are associated with a lack of viral control and severe disease upon infection. SARS-CoV infection of CC mice results in a variety of viral load trajectories and disease outcomes. Further, early control of virus in the lung correlates with an increased abundance of activated CD4 and CD8 T cells and regulatory T cells prior to infections across strains. A basal propensity of T cells to express IFNg and IL17 over TNFa also correlated with early viral control. Overall, a dysregulated, pro-inflammatory signature of circulating T cells at baseline was associated with severe disease upon infection. While future studies of human samples prior to infection with SARS-CoV-2 are required, our studies in mice with SARS-CoV serve as proof of concept that circulating T cell signatures at baseline can predict clinical and virologic outcomes upon SARS-CoV infection. Identification of basal immune predictors in humans could allow for identification of individuals at highest risk of severe clinical and virologic outcomes upon infection, who may thus most benefit from available clinical interventions to restrict infection and disease. [**note: here is some good information on T cell signatures and ability to respond to SARS-CoV-2 infection.**] https://www.biorxiv.org/content/10.1101/2020.09.21.306837v1

DIAGNOSTIC DEVELOPMENT

- Nothing new today.

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2020-09-23

Chamber music is on the docket for today. Here is a another in the series from Wigmore Hall in London. The delightful Leonore Piano Trio performs Beethoven's first trio and Brahms's last: https://www.youtube.com/watch?v=MqLAsIk6Fus It is good to see people in the audience again.

This Washington Post op-ed by Bill Haseltine about the designs of the Pfizer and Moderna vaccine trials is not encouraging. The trial designs may be set up to assure success but real-world results might say something different. It appears that FDA will be changing the guidance to vaccine manufacturers seeking an Experimental Use Authorization. Several states are seeing rises in COVID-19 cases. Will there be an autumn surge? This is for the inner Marie Kondo in all of us; what should I do with all the ties, suits and dress shirts that likely won't be worn for the next 12 months? A fight for rural real estate in Woodstock New York ought to free up a Gramercy Park apartment for me!! Here is one that perfectly fits the pied-á-terre for me. But wait, there's more!!! This contrarian view notes that big cities may become more livable. *Contribute to my housing fund (you have been receiving all this great COVID-19 information each day for free)*!!! Okay, I promise no more hard sell. 😀 J&J are starting their phase 3 COVID-19 vaccine trial which will enroll 60,000 patients, double that of other companies. This vaccine only requires a single injection and results are not expected until next year. **Disclosure:** I am a shareholder in J&J. Finland are using COVID-19 sniffing dogs at the airport.

The New York Times has also has an op-ed on COVID-19 vaccine testing by Drs. Topol and Doshi. The Times also discusses the J&J vaccine. New York City begins to recover.

The J&J Phase 3 protocol is HERE.

From the CDC, a report on attempted contact tracing in two North Carolina counties. This is why contact tracing is doomed in the US; people just don't want to participate.

The Daily Show's Trevor Noah interviews Tony Fauci: https://www.youtube.com/watch?v=5rKt54x6Hp0

Science have a good research piece on the immune life history, vaccination and the dynamics of SARS-CoV-2 over the next five years. '*We find that variations in the immune response to primary SARS-CoV-2 infections and a potential vaccine can lead to dramatically different immune landscapes and burdens of critically severe cases, ranging from sustained epidemics to near elimination. Our findings illustrate likely complexities in future Covid-19 dynamics, and highlight the importance of immunological characterization beyond the measurement of active infections for adequately projecting the immune landscape generated by SARS-CoV-2 infections*.' Here is an interesting perspective on COVID-19 in children and young people. '*The near-global closure of schools in response to the pandemic reflected the reasonable expectation from previous respiratory virus outbreaks that children would be a key component of the transmission chain. However, emerging evidence suggests that this is most likely not the case. A minority of children experience a postinfectious inflammatory syndrome, the pathology and long-term outcomes of which are poorly understood. However, relative to their risk of contracting disease, children and adolescents have been disproportionately affected by lockdown measures, and advocates of child health need to ensure that children's rights to health and social care, mental health support, and education are protected throughout subsequent pandemic waves*.'

STAT have an opinion piece on fast, low-cost testing and employment to help avert a second wave of COVID-19. The authors point back to this earlier STAT article on how even imperfect tests can be useful when used in conjunction with a Bayesian construct (pull out the statistics textbooks!).

The Lancet have a nice piece on pooled saliva testing for a COVID-19 surveillance program. Here is yet another article from the Mt. Sinai group on the development and validation of a clinical prediction model for mortality in severe COVID-19 patients.

JAMA have results of *in vitro* efficacy of povidone-iodine nasal antiseptic. SARS-CoV-2 is rapidly inactivated after 15 seconds. This is in clinical trials as both a nasal lavage and gargle. This viewpoint will show you the anatomical features of a correct nasopharyngeal swab (caution: you might not want to look at the diagram 😉). Finally, here is a 60 day serology study of Vanderbilt healthcare workers, 'The window after recovering from SARS-CoV-2 infection when people could donate serum that has sufficiently high antibody levels may be limited. Implications for health care personnel with antibodies assigned to care for infected patients depend on whether decline in these antibodies increases risk of reinfection and disease, which remains unknown, especially given the lack of data on memory B-cell and T-cell responses.'

Medscape summarizes a recent recommendation from the American Academy of Pediatrics that recommends a 14-day sports hiatus for kids after COVID-19.

Kaiser Health News note that the reopening of colleges fueled 3,000 daily new cases of COVID-19.

These German researchers show that surface dried SARS-CoV-2 is rapidly inactivated by UV-C irradiation. Such light wands are readily available but you might want to read this cautionary article before rushing out to get one. There are plenty of fine germicidal products on the market that do not pose the types of health risks that UV-C light sources do (make sure you buy the Clorox-brand as I'm a shareholder and like to see the price appreciation in the stock.)

MODELING

- Background Children are relatively protected from novel coronavirus infection (COVID-19). The reasons for this protection are not well understood but differences in the immune response to Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) have been implicated. If such differences are due to differential exposure to non-SARS-CoV-2 infectious agents, adults who are close contacts of children may partly share in this protection. Such a protective effect would have important implications for the lives of children, not least in terms of schooling. Methods Using a Scotland-wide record-linkage based occupational cohort comprising healthcare workers and members of their households, we examined whether sharing a household with young children (aged 0 to 11) attenuated the risk of hospitalisation with COVID-19, and/or testing positive for COVID-19 infection of any severity (any case of Covid-19). All healthcare workers directly employed by the National health Service (NHS) in Scotland, or contracted to provide general practice services, were included. Outcome and covariate data were obtained via linkage to Scotland-wide microbiology, drug prescribing, hospitalisation and death data. Results 241,266 adults did not share a household with young children; 41,198, 23,783 and 3,850 shared a household with 1, 2 and 3 or more young children respectively. The risk of hospitalisation with COVID-19 was lower in those with one child and lower still in those with two or more children, adjusting for age the hazard ratio (HR) was 0.83 per child (95% CI 0.70-0.99). On additionally adjusting for sex, socioeconomic deprivation, occupation, professional role, staff/non-staff status, the number of adults and adolescents in each household, and comorbidity, the HR was 0.89 per child (95% CI 0.74-1.06). An association of the same magnitude, but more precisely

estimated, was obtained for any case of COVID-19 (fully adjusted model, HR per child 0.89; 95% CI 0.84-0.95). *Conclusion Increased household exposure to young children was associated with an attenuated risk of testing positive for SARS-CoV-2 and appeared to also be associated with an attenuated risk of COVID-19 disease severe enough to require hospitalisation*. [**note: this is really surprising and counter-intuitive. It could be that parents of young children are also younger and less likely to contract COVID-19. The authors do discuss the potential confounders to this study. I think I need to adopt a couple of young children to further attenuating my risk of contracting COVID-19**]
https://www.medrxiv.org/content/10.1101/2020.09.21.20196428v1

- The role of aerosolized SARS-CoV-2 viruses in airborne transmission of COVID-19 is debated. The transmitting aerosol particles are generated through the breathing and vocalization by infectious subjects. Some authors state that this represents the dominant route of spreading, while others dismiss the option. Public health organizations generally categorize it as a secondary transmission pathway. Here we present a simple, easy-to-use spreadsheet algorithm to estimate the infection risk for different indoor environments, constrained by published data on human aerosol emissions, SARS-CoV-2 viral loads, infective dose and other parameters. We evaluate typical indoor settings such as an office, a classroom, a choir practice room and reception/party environments. These are examples, and the reader is invited to use the algorithm for alternative situations and assumptions. Our results suggest that aerosols from highly infective subjects can effectively transmit COVID-19 in indoor environments. This "highly infective" category represents about one fifth of the patients tested positive for SARS-CoV-2. We find that "super infective" subjects, representing the top few percent of positive-tested ones, plus an unknown fraction of less, but still highly infective, high aerosol-emitting subjects, may cause COVID-19 clusters (>10 infections), e.g. in classrooms, during choir singing and at receptions. The highly infective ones also risk causing such events at parties, for example. *In general, active room ventilation and the ubiquitous wearing of face masks (i.e. by all subjects) may reduce the individual infection risk by a factor of five to ten, similar to high-volume HEPA air filtering. The most effective mitigation measure studied is the use of high-quality masks, which can drastically reduce the indoor infection risk through aerosols*. [**note: no, this aerosol study does not come from the CDC, but rather a group of German scientists. They develop an algorithm to estimate infection risk in different indoor environments. I agree that reduction of aerosol production is critical to controlling viral spread.**]
https://www.medrxiv.org/content/10.1101/2020.09.22.20199489v1
- This paper presents a deep learning framework for epidemiology system identification from noisy and sparse observations with quantified uncertainty. The proposed approach employs an ensemble of deep neural networks to infer the time-dependent reproduction number of an infectious disease by formulating a tensor-based multi-step loss function that allows us to efficiently calibrate the model on multiple observed trajectories. The method is applied to a mobility and social behavior-based SEIR model of COVID-19 spread. The model is trained on Google and Unacast mobility data spanning a period of 66 days, and is able to yield accurate future forecasts of COVID-19 spread in 203 US counties within a time-window of 15 days. Strikingly, a sensitivity analysis that assesses the importance of different mobility and social behavior parameters reveals that attendance of close places, including workplaces, residential, and retail and recreational locations, has the largest impact on the basic reproduction number.

The model enables us to rapidly probe and quantify the effects of government interventions, such as lock-down and re-opening strategies. *Taken together, the proposed framework provides a robust workflow for data-driven epidemiology model discovery under uncertainty and produces probabilistic forecasts for the evolution of a pandemic that can judiciously inform policy and decision making*. All codes and data accompanying this manuscript are available at https://github.com/PredictiveIntelligenceLab/DeepCOVID19 [**note: here is a deep learning sutdy of human mobility and social behavior as relates to COVID-19 dynamics in the US. Good that they are sharing the code and data!!! Transparency is great.**] https://www.medrxiv.org/content/10.1101/2020.09.20.20198432v1

- In a survey of household cats and dogs of laboratory-confirmed COVID-19 patients, we found a high seroprevalence of SARS-CoV-2 antibodies, ranging from 21% to 53%, depending on the positivity criteria chosen. Seropositivity was significantly greater among pets from COVID-19+ households compared to those with owners of unknown status. Our results highlight the potential role of pets in the spread of the epidemic. [**YIKES, don't tell me that pets might be a reservoir for SARS-CoV-2!**] https://www.biorxiv.org/content/10.1101/2020.09.22.307751v1
- COVID-19 is a zoonotic disease originated by SARS-CoV-2. Infection of animals with SARS-CoV-2 are being reported during last months, and also an increase of severe lung pathologies in domestic dogs has been detected by veterinarians in Spain. Therefore it is necessary to describe the pathological processes in those animals that show symptoms similar to those described in humans affected by COVID-19. The potential for companion animals contributing to the continued human-to-human disease, infectivity, and community spread is an urgent issue to be considered. Forty animals with pulmonary pathologies were studied by chest X-ray, ultrasound study, and computed tomography. Nasopharyngeal and rectal swab were analyzed to detect canine pathogens, including SARS-CoV-2. Twenty healthy dogs living in SARS-CoV-2 positive households were included. Immunoglobulin detection by different immunoassays was performed. Our findings show that sick dogs presented severe alveolar or interstitial pattern, with pulmonary opacity, parenchymal abnormalities, and bilateral lesions. Forty dogs were negative for SARS-CoV-2 but Mycoplasma spp. was detected in 26 of 33 dogs. Five healthy and one pathological dog presented IgG against SARS-CoV-2. Here we report that despite detecting dogs with IgG α-SARS-CoV-2, we never obtained a positive RT-qPCR, not even in dogs with severe pulmonary disease; suggesting that even in the case of a canine infection transmission would be unlikely. Moreover, dogs living in COVID-19 positive households could have been more exposed to be infected during outbreaks. **[note: this study from Spain may provide solace to dog owners. Little Orphan Annie can rest easy knowing that Sandy is still a trusted and healthy pet! The younger readers of this newsletter probably think that Annie the musical is great but they missed out on the comic strip adventures.**] https://www.biorxiv.org/content/10.1101/2020.09.22.308023v1

NEWLY REGISTERED CLINICAL TRIALS

- Despite not receiving and contributions to my Gramercy Park housing fund I did check the clinical trials database. There were not new trials of therapeutics.

CLINICAL TRIAL RESULTS

- The role of children in the spread of the SARS-CoV2 coronavirus has become a matter of urgent debate as societies in the US and abroad consider how to safely reopen schools. Small studies have suggested higher viral loads in young children. Here we present a multicenter investigation on over five thousand SARS-CoV-2 cases confirmed by real-time reverse transcription (RT) PCR assay. Notably, we found no discernable difference in amount of viral nucleic acid among young children and adults. [**note: here is an interesting finding on nasopharyngeal viral loads in young children and they don't appear to be much different than other age cohorts.**] https://www.medrxiv.org/content/10.1101/2020.09.17.20192245v1
- In COVID-19, hypertension and cardiovascular diseases have emerged as major risk factors for critical disease progression. Concurrently, the impact of the main anti-hypertensive therapies, angiotensin-converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB), on COVID-19 severity is controversially discussed. By combining clinical data, single-cell sequencing data of airway samples and in vitro experiments, we assessed the cellular and pathophysiological changes in COVID-19 driven by cardiovascular disease and its treatment options. *Anti-hypertensive ACEi or ARB therapy, was not associated with an altered expression of SARS-CoV-2 entry receptor ACE2 in nasopharyngeal epithelial cells and thus presumably does not change susceptibility for SARS-CoV-2 infection. However, we observed a more critical progress in COVID-19 patients with hypertension associated with a distinct inflammatory predisposition of immune cells. While ACEi treatment was associated with dampened COVID-19-related hyperinflammation and intrinsic anti-viral responses, under ARB treatment enhanced epithelial-immune cell interactions were observed. Macrophages and neutrophils of COVID-19 patients with hypertension and cardiovascular comorbidities, in particular under ARB treatment, exhibited higher expression of CCL3, CCL4, and its receptor CCR1, which associated with critical COVID-19 progression*. Overall, these results provide a potential explanation for the adverse COVID-19 course in patients with cardiovascular disease, i.e. an augmented immune response in critical cells for the disease course, and might suggest a beneficial effect of clinical ACEi treatment in hypertensive COVID-patients. [**note: from Germany, a study of delayed viral clearance and airway hyperinlammation in hypertensive COVID-19 patients. The interesting finding is the adverse role ARBs may play as this is somewhat different from what other researchers have noted.**] https://www.medrxiv.org/content/10.1101/2020.09.22.20199471v1

DRUG DEVELOPMENT

- Designing covalent inhibitors is a task of increasing importance in drug discovery. Efficiently designing irreversible inhibitors, though, remains challenging. Here, we present covalentizer, a computational pipeline for creating irreversible inhibitors based on complex structures of targets with known reversible binders. For each ligand, we create a custom-made focused library of covalent analogs. We use covalent docking, to dock these tailored covalent libraries and to find those that can bind covalently to a nearby cysteine while keeping some of the main interactions of the original molecule. We found ~11,000 cysteines in close proximity to a ligand across 8,386 protein-ligand complexes in the PDB. Of these, the protocol identified 1,553 structures with covalent predictions. In prospective evaluation against a panel of kinases, five out of nine predicted covalent inhibitors showed IC50 between 155 nM - 4.2 µM. Application of the protocol to an existing SARS-CoV-1 Mpro reversible inhibitor led to a new acrylamide inhibitor series with low micromolar IC50 against SARS-CoV-2 Mpro. The docking prediction was

validated by 11 co-crystal structures. This is a promising lead series for COVID-19 antivirals. Together these examples hint at the vast number of covalent inhibitors accessible through our protocol. [**note: this is another computer approach to drug design. Some interesting structural inhibitors of the Mpro come out of the work. You will need to download the paper to see what the compounds look like.**]
https://www.biorxiv.org/content/10.1101/2020.09.21.299776v1

- Facing the worldwide disease progression of COVID-19 caused by the SARS-CoV-2 virus, the situation is highly critical and there is an unmet need for effective vaccination, reliable diagnosis and therapeutic intervention. Neutralizing binding molecules such as antibodies or derivatives thereof have become important tools for acute treatment of COVID-19. Additionally, such binders provide the unique possibility to monitor the emergence and presence of a neutralizing immune response in infected or vaccinated individuals. Here we describe a set of 11 unique nanobodies (Nbs), originated from an immunized alpaca which bind with high affinities to the glycosylated SARS-CoV-2 Spike receptor domain (RBD). Using a multiplex in vitro binding assay we showed that eight of the selected Nbs effectively block the interaction between RBD, S1-domain and homotrimeric Spike protein with the angiotensin converting enzyme 2 (ACE2) as the viral docking site on human cells. According to competitive binding analysis and detailed epitope mapping, we grouped all Nbs blocking the RBD:ACE2 interaction in three distinct Nb-Sets and demonstrated their neutralizing effect with IC50 values in the low nanomolar range in a cell-based SARS-CoV-2 neutralization assay. Tested Nb combinations from different sets showed substantially lower IC50 values in both functional assays indicating a profound synergistic effect of Nbs simultaneously targeting different epitopes within the RBD. Finally, we applied the most potent Nb combinations in a competitive multiplex binding assay which we termed NeutrobodyPlex and detected a neutralizing immune response in plasma samples of infected individuals. We envisage that our Nbs have a high potential for prophylactic as well as therapeutic options and provide a novel approach to screen for a neutralizing immune response in infected or vaccinated individuals thus helping to monitor the immune status or to guide vaccine design. [**note: from Germany, more interesting nanobody work. I would like to see some of this get into the clinic sooner rather than later.**]
https://www.biorxiv.org/content/10.1101/2020.09.22.308338v2

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- COVID-19, caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), represents a global crisis. Key to SARS-CoV-2 therapeutic development is unraveling the mechanisms driving high infectivity, broad tissue tropism and severe pathology. Our 2.85 Å cryo-EM structure of SARS-CoV-2 spike (S) glycoprotein reveals that the receptor binding domains (RBDs) tightly bind the essential free fatty acid (FFA) linoleic acid (LA) in three composite binding pockets. The pocket also appears to be present in the highly pathogenic coronaviruses SARS-CoV and MERS-CoV. LA binding stabilizes a locked S conformation giving rise to reduced ACE2 interaction in vitro. In human cells, LA supplementation synergizes with the COVID-19 drug remdesivir, suppressing SARS-CoV-2 replication. Our structure directly links LA and S, setting the stage for intervention strategies targeting LA binding by SARS-CoV-2. [**note: more information on the binding between the virus and ACE2 and how linoleic acid may effect resistance to binding.**]
https://science.sciencemag.org/content/early/2020/09/18/science.abd3255

- Coronavirus disease 2019 (COVID-19) can lead to severe pneumonia and hyperinflammation. So far, insufficient or excessive T cell responses were described in patients. We applied novel approaches to analyze T cell reactivity and showed that T anergy is already present in non-ventilated COVID-19 patients, very pronounced in ventilated patients, strongly associated with virus persistence and reversible with clinical recovery. T cell activation was measured by downstream effects on responder cells like basophils, plasmacytoid dendritic cells, monocytes and neutrophils in whole blood and proved to be much more meaningful than classical readouts with PBMCs. Monocytes responded stronger in males than females and IL-2 partially reversed T cell anergy. Downstream markers of T cell anergy were also found in fresh blood samples of critically ill patients with severe T cell anergy. Based on our data we were able to develop a score to predict fatal outcomes and to identify patients that may benefit from strategies to overcome T cell anergy. [**note: these German researchers point to the importance of a robust T cell response in COVID-19 patients. Interesting that IL-2 may have partially helped out here.**] https://www.medrxiv.org/content/10.1101/2020.09.21.20198671v1
- In recognizing the host cellular receptor and mediating fusion of virus and cell membranes, the spike (S) glycoprotein of coronaviruses is the most critical viral protein for cross-species transmission and infection. Here we determined the cryo-EM structures of the spikes from bat (RaTG13) and pangolin (PCoV_GX) coronaviruses, which are closely related to SARS-CoV-2. All three receptor-binding domains (RBDs) of these two spike trimers are in the "down" conformation, indicating they are more prone to adopt this receptor-binding inactive state. However, we found that the PCoV_GX, but not the RaTG13, spike is comparable to the SARS-CoV-2 spike in binding the human ACE2 receptor and supporting pseudovirus cell entry. Through structure and sequence comparisons, we identified critical residues in the RBD that underlie the different activities of the RaTG13 and PCoV_GX/SARS-CoV-2 spikes and propose that N-linked glycans serve as conformational control elements of the RBD. These results collectively indicate that strong RBD-ACE2 binding and efficient RBD conformational sampling are required for the evolution of SARS-CoV-2 to gain highly efficient infection. [**note: from China, more evolutionary information on the Spike glycoprotein based on bat and pangolin coronaviruses.}** https://www.biorxiv.org/content/10.1101/2020.09.21.307439v1

DIAGNOSTIC DEVELOPMENT

- Nothing today.

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2020-09-24

We will stay with Wigmore Hall for today and maybe tomorrow. Here is the wonderful Angela Hewitt playing an all Bach recital (cue up Radar O'Reilly's famous statement, "ah Bach.") : https://www.youtube.com/watch?v=-PlN0k-xOQc This is a somewhat long recital but it is BACH! Let us take a moment and celebrate the life and artistry of Juliette Greco who just passed away. Ms. Greco led an extraordinary life as a singer and actress. Two movie roles that were memorable even though the films were pretty much disasters were in the late 1950s films 'The Sun also Rises' and 'The Roots of Heaven' They are often shown on cable movie channels and one can find them on streaming sites. Here is Ms. Greco singing the title song in Otto Preminger's 'Bonjour Tristesse':

https://www.youtube.com/watch?v=kjNkrlLiJQg That film's star, Jean Seberg, also lived a fascinating life! Enough for today's culture lesson, let's move on to what's new with COVID-19.

A reader sent me a blog post that linked to a Financial Times article that the UK will be embarking on human challenge trials early next year. The article is behind a paywall at the FT so I don't know all the particulars. Reuters have confirmed this story. There was a notation that the US was preparing a strain of SARS-CoV-2 that might be used in such trials. I was skeptical but Google (still free at this moment from anti-trust litigation) confirms it in this Washington Post story. I am still doubtful that this will save much time in vaccine development. Challenge trials will only involve a small group and likely not be age or ethnically diverse. The full set of potential safety issues cannot be acquired, and larger phase 3 trials will still be required. From my perspective, research into antibody profiles after vaccination and viral susceptibility are a far more logical approach if one wants to correctly figure out efficacy response in a vaccine.

The Washington Post has an article on the genomic analysis of SARS-CoV-2 mutations. I would note that a number of groups in other countries have done similar work and I've provided links as those papers have come out. Things did not turn out well for Missouri's governor who did not want to mandate masks in the state. I wish him and his wife a speedy recovery. In another cautionary tale, parents in parts of Wisconsin are sending ill children back to school. Fortunately, most of the early data shows there are minimal outbreaks of COVID-19 in many schools.

The New York Times has more on the politics of the FDA vaccine guidance. This may not end well. Israel is seeing a huge spike in cases and is now extending the lockdown. Here is a nice photo journalism piece on the arts in New York City and the impact of COVID-19.

STAT have a nice update on the vaccine race. Perhaps slow and steady will lead to the best COVID-19 vaccine!

The Lancet have a good comparison study of five immunoassays along with a commentary.

JAMA have a perspective on the 'long-haulers.' Here is a perspective on the need for CDC independence.

Kaiser Health News discusses the role of Data Safety Monitoring Boards (DSMB) in the ongoing vaccine trials.

MODELING

- SARS-CoV-2 infectious virions are viable on various surfaces (e.g., plastic, metals, cardboard) for several hours. This presents a transmission cycle for the human infection that can be broken by developing new inactivation approaches. We employed an efficient cold atmospheric plasma (CAP) with argon feed gas to inactivate SARS-CoV-2 on various surfaces including plastic, metal, cardboard, basketball composite leather, football leather, and baseball leather. These results demonstrate the great potential of CAP as a safe and effective means to prevent virus transmission and infections. [**note: cold plasma is the way to go if you want to clean your surfaces. There are some cool pictures in the paper but somehow, I don't see this making it into the home use arena.**]
  https://www.medrxiv.org/content/10.1101/2020.09.17.20192872v1

- Background: COVID-19 has had a disproportionate impact on ethnic minority populations, both in the UK and internationally. To date, much of the evidence has been derived from studies within single healthcare settings, mainly those hospitalised with COVID-19. Working on behalf of NHS England, the aim of this study was to identify ethnic differences in the risk of COVID-19 infection, hospitalisation and mortality using a large general population cohort in England. Methods: We conducted an observational cohort study using linked primary care records of 17.5 million adults between 1 February 2020 and 3 August 2020. Exposure was self-reported ethnicity collapsed into the 5 and 16 ethnicity categories of the English Census. Multivariable Cox proportional hazards regression was used to identify ethnic differences in the risk of being tested and testing positive for SARS-CoV-2 infection, COVID-19 related intensive care unit (ICU) admission, and COVID-19 mortality, adjusted for socio-demographic factors, clinical co-morbidities, geographic region, care home residency, and household size. Results: A total of 17,510,002 adults were included in the study; 63% white (n=11,030,673), 6% south Asian (n=1,034,337), 2% black (n=344,889), 2% other (n=324,730), 1% mixed (n=172,551), and 26% unknown (n=4,602,822). After adjusting for measured explanatory factors, south Asian, black, and mixed groups were marginally more likely to be tested (south Asian HR 1.08, 95%CI 1.07-1.09; black HR 1.08; 95%CI 1.06-1.09, mixed HR 1.03, 95%CI 1.01-1.05), and substantially more likely to test positive for SARS-CoV-2 compared with white adults (south Asian HR 2.02. 95% CI 1.97-2.07; black HR 1.68, 95%CI 1.61-1.76; mixed HR 1.46, 95%CI 1.36-1.56). The risk of being admitted to ICU for COVID-19 was substantially increased in all ethnic minority groups compared with white adults (south Asian HR 2.22, 95%CI 1.96-2.52; black HR 3.07, 95%CI 2.61-3.61; mixed HR 2.86, 95%CI 2.19-3.75, other HR 2.86, 95%CI 2.31-3.63). Risk of COVID-19 mortality was increased by 25-56% in ethnic minority groups compared with white adults (south Asian HR 1.27, 95%CI 1.17-1.38; black HR 1.55, 95%CI 1.38-1.75; mixed HR 1.40, 95%CI 1.12-1.76; other HR 1.25, 95%CI 1.05-1.49). We observed heterogeneity of associations after disaggregation into detailed ethnic groupings; Indian and African groups were at higher risk of all outcomes; Pakistani, Bangladeshi and Caribbean groups were less or equally likely to be tested for SARS-CoV-2, but at higher risk of all other outcomes, Chinese groups were less likely to be tested for and test positive for SARS-CoV-2, more likely to be admitted to ICU, and equally likely to die from COVID-19. Conclusions: We found evidence of substantial ethnic inequalities in the risk of testing positive for SARS-CoV-2, ICU admission, and mortality, which persisted after accounting for explanatory factors, including household size. It is likely that some of this excess risk is related to factors not captured in clinical records such as occupation, experiences of structural discrimination, or inequitable access to health and social services. Prioritizing linkage between health, social care, and employment data and engaging with ethnic minority communities to better understand their lived experiences is essential for generating evidence to prevent further widening of inequalities in a timely and actionable manner. [**note: this is a large UK study (17 million patients) of ethnic differences in COVID-19 infections and associated outcomes.**] https://www.medrxiv.org/content/10.1101/2020.09.22.20198754v1
- The COVID-19 outbreak has highlighted our vulnerability to novel infections. Faced with this threat and no effective treatment, most countries adopted some form of enforced social distancing (lockdown) to reduce transmission - in most cases successfully reducing the reproductive number,R, below one. However, given the large pool of susceptible individuals that remain, complete relaxation of controls is likely to generate a substantial second wave.

Vaccination remains the only foreseeable means of both containing the infection and returning to normal interactions and behaviour. *Here, we consider the optimal targeting of vaccination with the aim of minimising future deaths or quality adjusted life year (QALY) losses. We show that, for a range of assumptions on the action and efficacy of the vaccine, targeting older age groups first is optimal and can avoid a second wave if the vaccine prevents transmission as well as disease*. [**note: here is a model for optimizing SARS-CoV-2 vaccine deployment.**]
https://www.medrxiv.org/content/10.1101/2020.09.22.20194183v1

- Two cats from different COVID-19-infected households in the UK were found to be infected with SARS-CoV-2 from humans, demonstrated by immunofluorescence, in situ hybridisation, reverse transcriptase quantitative PCR and viral genome sequencing. Lung tissue collected post-mortem from cat 1 displayed pathological and histological findings consistent with viral pneumonia and tested positive for SARS-CoV-2 antigens and RNA. SARS-CoV-2 RNA was detected in an oropharyngeal swab collected from cat 2 that presented with rhinitis and conjunctivitis. High throughput sequencing of the virus from cat 2 revealed that the feline viral genome contained five single nucleotide polymorphisms (SNPs) compared to the nearest UK human SARS-CoV-2 sequence, and this human virus contained eight SNPs compared to the original Wuhan-Hu-1 reference. An analysis of the viral genome of cat 2 together with nine other feline-derived SARS-CoV-2 sequences from around the world revealed no shared cat-specific mutations. These findings indicate that human-to-cat transmission of SARS-CoV-2 occurred during the COVID-19 pandemic in the UK, with the infected cats developing mild or severe respiratory disease. Given the versatility of the new coronavirus, it will be important to monitor for human-to-cat, cat-to-cat and cat-to-human transmission. [**note: more on transfer of SARS-CoV-2 from humans to cats. We don't know if it can move in the other direction.**]
https://www.biorxiv.org/content/10.1101/2020.09.23.309948v1

NEWLY REGISTERED CLINICAL TRIALS

- I checked yesterday.

CLINICAL TRIAL RESULTS

- In a randomized control trial on convalescent plasma therapy (CPT) in severe COVID-19, we characterized the nature, in terms of abundance of forty eight cytokines, and dimensions, in terms of their interrelationships, of the hyper-immune activation-associated cytokine storm in patients suffering from acute respiratory distress syndrome. We found plasma MCP3 level to be a key correlate for mitigation of hypoxia, irrespective of therapeutic regimen. We also identified an anti-inflammatory role of CPT independent of its neutralizing antibody content, and a linear regression analysis revealed that neutralizing antibodies as well as the anti-inflammatory effect of CPT both contribute to marked immediate reductions in hypoxia, as compared to patients on standard therapy. [**note: here is an Indian trial using convalescent plasma terapy.**]
https://www.medrxiv.org/content/10.1101/2020.09.21.20199109v1
- Background: Famotidine has been posited as a potential treatment for COVID-19. We compared the incidence of COVID-19 outcomes (i.e., death; and death or intensive services use) among hospitalized famotidine users vs. proton pump inhibitors (PPIs) users, hydroxychloroquine users or famotidine non-users separately. Methods: We constructed a retrospective cohort study using data from COVID-19 Premier Hospital electronic health records. Study population were

COVID-19 hospitalized patients aged 18 years or older. Famotidine, PPI and hydroxychloroquine exposure groups were defined as patients dispensed any medication containing one of the three drugs on the day of admission. The famotidine non-user group was derived from the same source population with no history of exposure to any drug with famotidine as an active ingredient prior to or on the day of admission. Time-at-risk was defined based on the intention-to-treat principle starting 1 day after admission to 30 days after admission. For each study comparison group, we fit a propensity score (PS) model through large-scale regularized logistic regression. The outcome was modeled using a survival model. Results: We identified 2193 users of PPI, 5950 users of the hydroxychloroquine, 1816 users of famotidine and 26,820 non-famotidine users. After PS stratification, the hazard ratios for death were as follows: famotidine vs no famotidine HR 1.03 (0.89-1.18); vs PPIs: HR 1.14 (0.94-1.39); vs hydroxychloroquine:1.03 (0.85-1.24). Similar results were observed for the risk of death or intensive services use. Conclusion: *We found no evidence of a reduced risk of COVID-19 outcomes among hospitalized COVID-19 patients who used famotidine compared to those who did not or compared to PPI or hydroxychloroquine users*. [**note: here is an observational study on the utility of famotidine as a treatment for COVID-19 from some Jansen Pharma folks. It does not appear to offer any clinical benefit. I still have not seen the big Northwell RCT of famotidine but am not holding out hope that it is a game changer.**]
https://www.medrxiv.org/content/10.1101/2020.09.23.20199463v1

DRUG DEVELOPMENT

- The SARS-CoV-2 pandemic has challenged researchers at a global scale. The scientific community's massive response has resulted in a flood of experiments, analyses, hypotheses, and publications, especially in the field drug repurposing. However, many of the proposed therapeutic compounds obtained from SARS-CoV-2 specific assays are not in agreement and thus demonstrate the need for a singular source of COVID-19 related information from which a rational selection of drug repurposing candidates can be made. In this paper, we present the COVID-19 PHARMACOME, a comprehensive drug-target-mechanism graph generated from a compilation of several disease maps and experimental data focused on SARS-CoV-2 / COVID-19 pathophysiology. By applying a systematic approach, we were able to predict the effect of drug pairs on SARS-CoV-2 infection. Experimental validation of our results demonstrate that our graph can be used to not only explore the involved mechanistic pathways, but also to identify novel combinations of drug repurposing candidates. [**note: another interesting approach to drug discovery.**] https://www.biorxiv.org/content/10.1101/2020.09.23.308239v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- We sequenced the genomes of 5,085 SARS-CoV-2 strains causing two COVID-19 disease waves in metropolitan Houston, Texas, an ethnically diverse region with seven million residents. The genomes were from viruses recovered in the earliest recognized phase of the pandemic in Houston, and an ongoing massive second wave of infections. The virus was originally introduced into Houston many times independently. Virtually all strains in the second wave have a Gly614 amino acid replacement in the spike protein, a polymorphism that has been linked to increased transmission and infectivity. Patients infected with the Gly614 variant strains had significantly higher virus loads in the nasopharynx on initial diagnosis. We found little evidence of a

significant relationship between virus genotypes and altered virulence, stressing the linkage between disease severity, underlying medical conditions, and host genetics. Some regions of the spike protein - the primary target of global vaccine efforts - are replete with amino acid replacements, perhaps indicating the action of selection. We exploited the genomic data to generate defined single amino acid replacements in the receptor binding domain of spike protein that, importantly, produced decreased recognition by the neutralizing monoclonal antibody CR30022. Our study is the first analysis of the molecular architecture of SARS-CoV-2 in two infection waves in a major metropolitan region. The findings will help us to understand the origin, composition, and trajectory of future infection waves, and the potential effect of the host immune response and therapeutic maneuvers on SARS-CoV-2 evolution. [**note: this is the genomic paper referred to in the Washington Post story above. As I noted there have been other such studies.**] https://www.medrxiv.org/content/10.1101/2020.09.22.20199125v1

- The SARS-CoV-2 lineage carrying the amino acid change D614G has become the dominant variant in the global COVID-19 pandemic. The rapid spread of the G614 mutant suggests that it may have a transmission advantage over the D614 wildtype. Using our previous epidemiological framework to analyze COVID-19 surveillance and sequence data, we estimated that the G614 mutant is 31% (28-34%) more transmissible than the D614 wildtype. As such, interventions that were previously effective in containing or mitigating the D614 wildtype (e.g. in China, Vietnam, Thailand, etc.) might be less effective against the G614 mutant. Our framework can be readily integrated into current COVID-19 surveillance to monitor the emergence and fitness of mutant strains, such that pandemic surveillance, disease control and development of treatment and vaccines can be adjusted dynamically. [**note: here is a paper from Hong Kong, also looking at the infection dynamics of the D614G strain.**]
https://www.medrxiv.org/content/10.1101/2020.09.22.20199810v1
- Pre-existing immune responses to seasonal endemic coronaviruses could have profound consequences for antibody responses to SARS-CoV-2, either induced in natural infection or through vaccination. Such consequences are well established in the influenza and flavivirus fields. A first step to establish whether pre-existing responses can impact SARS-CoV-2 infection is to understand the nature and extent of cross-reactivity in humans to coronaviruses. We compared serum antibody and memory B cell responses to coronavirus spike (S) proteins from pre-pandemic and SARS-CoV-2 convalescent donors using a series of binding and functional assays. We found weak evidence of pre-existing SARS-CoV-2 cross-reactive serum antibodies in pre-pandemic donors. However, we found stronger evidence of pre-existing cross-reactive memory B cells that were activated on SARS-CoV-2 infection. Monoclonal antibodies (mAbs) isolated from the donors showed varying degrees of cross-reactivity with betacoronaviruses, including SARS and endemic coronaviruses. None of the cross-reactive mAbs were neutralizing except for one that targeted the S2 subunit of the S protein. The results suggest that pre-existing immunity to endemic coronaviruses should be considered in evaluating antibody responses to SARS-CoV-2. [**note: from Scripps, more on the cross reactive immune responses to the spike protein from SARS-CoV02 and endemic coronaviruses. This is an interesting area and I've seen some conjectures that this effect may be important in those who only get mild COVID-19. I'm not sure this is right but await further research.**]
https://www.biorxiv.org/content/10.1101/2020.09.22.308965v1

DIAGNOSTIC DEVELOPMENT

- Nothing exceptionally new.

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2020-09-25

Here is a group that plays and sings traditional jazz standards. It popped up on my YouTube feed and I took a quick listen. It is the Avalon Jazz Band with Tatiana Eva Marie and I had not heard them before. The group is inspired by the jazz played in Paris during the 1930s and 40s. Here is a video set that displays the infectious charm of the group: https://www.youtube.com/watch?v=A2oVx_Bgux4 Note: can I still use the adjective 'infectious' during a pandemic?

The Washington Post has a good long-form piece on how a COVID-19 outbreak in an Iowa meatpacking plant was deciphered. There are some good graphics and videos attached to this article. College enrollment is down at some schools this fall. Some European universities are having COVID-19 infection problems just as their US counterparts. Here is a feel good story from Italy; a meeting across balconies leads to love. This is totally unacceptable behavior on the part of farmers! It is now five for five as the lone holdout major football conference elects to play fall football. United Airlines steps up their game and offers COVID-19 tests to passengers who want to fly on their San Francisco to Hawaii route. This WaPo interactive is disturbing and scary!

The New York Times reports on COVID-19 associated hair loss. I have not noticed this. Novavax have entered Phase 3 trials with their COVID-19 vaccine.

STAT report that pharmacies are confronting a large demand for flu vaccine. I can attest to this as I am still waiting for my CVS to get the high dose vaccine back in stock. In not so good news, kids' heart rates are rising as he pandemic drags on.

The Lancet has a paper on the use of inhaled corticosteroids with patients suffering from chronic obstructive pulmonary disease (COPD). This UK study notes that results do not support a major role for regular ICS use in protecting against COVID-19-related death among people with asthma or COPD. Observed increased risks of COVID-19-related death can be plausibly explained by unmeasured confounding due to disease severity. Here is an associated commentary on the study. Lancet editor, Richard Horton argues that the term 'pandemic' is too narrow for COVID-19, an intriguing comment. Here is a review of playwright David Hare's account with COVID-19 that is now being staged with Ralph Fiennes. Here is a one patient case study of the treatment of severe COVID-19 with human soluble recombinant ACE2 (it acts as a decoy to bind SARS-CoV-2). The patient also had methicillin resistant Staph aureus pneumonia. Treatment with the rACE2 led to a drop in viremia showing this has promise. There are clinical trials of this approach underway but this is the first clinical data I have seen.

Medscape notes that FDA has given the first Emergency Use Authorization for a point of care COVID-19 antibody test. In Congressional testimony, CDC expects most Americans to be vaccinated for COVID-19 by next July.

Kaiser Health News shares a story on the intra-hospital debate on how SARS-CoV-2 virus is spread.

The Annals of Internal Medicine has a useful review of *current knowledge* about the transmission of SARS-CoV-2.

MODELING

- Nothing New

NEWLY REGISTERED CLINICAL TRIALS

- A two arm open label multi-centered randomized interventional trial is proposed to assess aspects of safety and efficacy of Nuvastatic™ (Serial No: C5OSEW5050ESA) . Two parallel groups of (1:1) ratio comparing Nuvastatic™ versus standard care will be conducted on patients on oxygen saturation (SaO2) of 94% or less while they are breathing ambient air or a ratio of the partial pressure of oxygen (Pao2) to the fraction of inspired oxygen (Fio2) (PaO2:FiO2) at or below 300 mg Hg. [**note: this is a trial from India on a botanical.**] NCT04542447
- VXA-CoV2-1 is a non-replicating Ad5 vector adjuvanted oral tableted vaccine being developed to prevent COVID-19, the disease resulting from Severe Acute Respiratory Syndrome coronavirus (SARS-CoV-2) infection. The study is designed to evaluate the safety and immunogenicity of VXA-CoV2-1 vaccine with repeat dosing at multiple dose levels. Safety and immunogenicity will be evaluated for up to 12 months after the second dose of VXA-CoV2-1. [**note: this is the Phase 1 Vaxart oral COVID-19 vaccine trial.**] NCT04563702

CLINICAL TRIAL RESULTS

- Unfortunately, nothing new

DRUG DEVELOPMENT

- The current COVID-19 pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has an enormous impact on human health and economy. In search for therapeutic options, researchers have proposed resveratrol, a food supplement with known antiviral, anti-inflammatory and anti-oxidant properties as an advantageous antiviral therapy for SARS-CoV-2 infection. Here, we provide evidence that both resveratrol and its metabolically more stable structural analog, pterostilbene, exhibits potent antiviral properties against SARS-CoV-2 in vitro. Resveratrol and pterostilbene showed antiviral activity in African green monkey kidney cells and in human primary bronchial epithelial cells cultured in an air-liquid interface system. Mechanistic analyses demonstrated that both compounds actively interfere with the post-entry steps of virus replication cycle and their antiviral activity is long-lasting. Collectively, our data indicate that resveratrol and pterostilbene are promising antiviral compounds to treat SARS-CoV-2 infection and advocate evaluation of these compounds in clinical trials. [**note: *in vitro* work from Holland showing resveratrol and pterostilbene to be viral inhibitors. There is a Swedish trial of resveratrol.**]
  https://www.biorxiv.org/content/10.1101/2020.09.24.285940v1
- SARS-CoV-2 is the underlying cause for the COVID-19 pandemic. Like most enveloped RNA viruses, SARS-CoV-2 uses a homotrimeric surface antigen to gain entry into host cells. Here we describe S-Trimer, a native-like trimeric subunit vaccine candidate for COVID-19 based on Trimer-Tag technology. Immunization of S-Trimer with either AS03 (oil-in-water emulsion) or CpG 1018 (TLR9 agonist) plus alum adjuvants induced high-levels of neutralizing antibodies and Th1-biased cellular immune responses in animal models. Moreover, rhesus macaques

immunized with adjuvanted S-Trimer were protected from SARS-CoV-2 challenge compared to vehicle controls, based on clinical observations and reduction of viral loads in lungs. Trimer-Tag may be an important new platform technology for scalable production and rapid development of safe and effective subunit vaccines against current and future emerging RNA viruses. [**note: more vaccine work from Chinese company Clover Biopharmaceuticals.**] https://www.biorxiv.org/content/10.1101/2020.09.24.311027v1

- Niclosamide (NIC) has demonstrated promising in vitro antiviral efficacy against SARS-CoV-2, the causative agent of the COVID-19 pandemic. Though NIC is already FDA-approved, the oral formulation produces systemic drug levels that are too low to inhibit SARS-CoV-2. As an alternative, direct delivery of NIC to the respiratory tract as an aerosol could target the primary site of for SARS-CoV-2 acquisition and spread. We have developed a niclosamide powder suitable for delivery via dry powder inhaler, nebulizer, and nasal spray through the incorporation of human lysozyme (hLYS) as a carrier molecule. This novel formulation exhibits potent in vitro and in vivo activity against MERS-CoV and SARS-CoV-2 and protects against methicillin-resistance staphylococcus aureus pneumonia and inflammatory lung damage. The suitability of the formulation for all stages of the disease and low-cost development approach will ensure wide-spread utilization. [**note: this is a new formulation for nicloamide. There are currently two clinical trial of this compound but in different formulations. Interesting that it is protective for methicillin-resistant staph aureus pneumonia.**] https://www.biorxiv.org/content/10.1101/2020.09.24.310490v1
- Coronavirus Disease 2019 (COVID-19) represents a new global threat demanding a multidisciplinary effort to fight its etiological agent, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In this regard, immunoinformatics may aid to predict prominent immunogenic regions from critical SARS-CoV-2 structural proteins, such as the spike (S) glycoprotein, for their use in prophylactic or therapeutic interventions against this rapidly emerging coronavirus. Accordingly, in this study, an integrated immunoinformatics approach was applied to identify cytotoxic T cell (CTC), T helper cell (THC), and Linear B cell (BC) epitopes from the S glycoprotein in an attempt to design a high-quality multi-epitope vaccine. The best CTC, THC, and BC epitopes showed high viral antigenicity, lack of allergenic or toxic residues, and suitable HLA-viral peptide interactions. Remarkably, SARS-CoV-2 receptor-binding domain (RBD) and its receptor-binding motif (RBM) harbour several potential epitopes. The structure prediction, refinement, and validation data indicate that the multi-epitope vaccine has an appropriate conformation and stability. Three conformational epitopes and an efficient binding between Toll-like receptor 4 (TLR4) and the vaccine model were observed. Importantly, the population coverage analysis showed that the multi-epitope vaccine could be used globally. Notably, computer-based simulations suggest that the vaccine model has a robust potential to evoke and maximize both immune effector responses and immunological memory to SARS-CoV-2. Further research is needed to accomplish with the mandatory international guidelines for human vaccine formulations. [**note: congrats to this Venezuelan researcher for doing good work and making his country's first time entry into the newsletter. This is an interesting vaccine approach.**] https://www.biorxiv.org/content/10.1101/2020.09.24.312355v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Severe acute respiratory syndrome coronavirus 2 was quickly identified as the cause of COVID 19 disease soon after its earliest reports. The knowledge of the contemporary evolution of this nova coronavirus is urgently needed not only for a retrospective on how, when, and why COVID 19 has emerged and spread, but also for creating remedies through efforts of science, technology, medicine, and public policy. Global sequencing of thousands of genomes has revealed many common genetic variants, which are the key to unraveling the early evolutionary history of Severe acute respiratory syndrome coronavirus 2 and tracking its global spread over time. However, our knowledge of fundamental events in the evolution and spread of this coronavirus remains grossly incomplete and highly uncertain. Here, we present the heretofore cryptic mutational history, phylogeny, and dynamics of Severe acute respiratory syndrome coronavirus 2 from an analysis of tens of thousands of high-quality genomes. The reconstructed mutational progression is highly concordant with the timing of coronavirus sampling dates. It predicts the progenitor genome whose earliest offspring without any non-synonymous mutations were still spreading worldwide months after the report of COVID 19. Over time, mutations gave rise to seven major lineages that spread episodically, some of which arose in Europe and North America after the genesis of the ancestral lineages in China. Mutational barcoding establishes that North American coronaviruses harbor very different genome signatures than coronaviruses prevalent in Europe and Asia that have converged over time. These spatiotemporal patterns continue to evolve as the pandemic progresses and can be viewed live online. [**note: this is a cool paper from Temple Univ showing the genomic evolution of SARS-CoV-2. There are some good graphs in the paper worth looking at.**] https://www.biorxiv.org/content/10.1101/2020.09.24.311845v1
- *COVID-19 CG is an open resource for tracking SARS-CoV-2 single-nucleotide variations (SNVs) and lineages while filtering by location, date, gene, and mutation of interest. COVID-19 CG provides significant time, labor, and cost-saving utility to diverse projects on SARS-CoV-2 transmission, evolution, emergence, immune interactions, diagnostics, therapeutics, vaccines, and intervention tracking.* Here, we describe case studies in which users can interrogate (1) SNVs in the SARS-CoV-2 Spike receptor binding domain (RBD) across different geographic regions to inform the design and testing of therapeutics, (2) SNVs that may impact the sensitivity of commonly used diagnostic primers, and (3) the recent emergence of a dominant lineage harboring an S477N RBD mutation in Australia. To accelerate COVID-19 research and public health efforts, COVID-19 CG will be continually upgraded with new features for users to quickly and reliably pinpoint mutations as the virus evolves throughout the pandemic and in response to therapeutic and public health interventions. [**note: here is an open resource for tracking mutations in SARS-CoV-2.**] https://www.biorxiv.org/content/10.1101/2020.09.23.310565v1
- The Nucleocapsid Protein (N Protein) of severe acute respiratory syndrome Coronavirus 2 (SARS-CoV2) is located in the viral core. Immunoglobulin G (IgG) targeting N protein is detectable in the serum of infected patients. The effect of high titers of IgG against N-protein on clinical outcomes of SARS-CoV2 disease has not been described. We studied 400 RT-PCR confirmed SARS-CoV2 patients to determine independent factors associated with poor outcomes, including MICU admission, prolonged MICU stay and hospital admissions, and in-hospital mortality. We also measured serum IgG against the N protein and correlated its concentrations with clinical outcomes. We found that several factors, including Charlson comorbidity Index (CCI), high levels

of IL6, and presentation with dyspnea were associated with poor clinical outcomes. It was shown that higher CCI and higher IL6 levels were independently associated with in-hospital mortality. Anti-N protein IgG was detected in the serum of 55 (55%) patients at the time of admission. A high concentration of antibodies, defined as signal to cut off ratio (S/Co)> 1.5 (75 percentile of all measurements), was found in 25 (25%) patients. The multivariable logistic regression models showed that between being an African American, higher CCI, lymphocyte counts, and S/Co ratio> 1.5, only S/Co ratio were independently associated with MICU admission and longer length of stay in hospital. This study recommends that titers of IgG targeting N-protein of SARS-CoV2 at admission is a prognostic factor for the clinical course of disease and should be measured in all patients with SARS-CoV2 infection. [**note: this is an interesting finding regarding antibodies against the nucleocapsid protein. The paper focuses on antibody dependent enhancement where the virus uses antibodies to gain access to host immune cells. This worsens the infections and this particular antibody may be a marker for worse outcomes.**] https://www.medrxiv.org/content/10.1101/2020.09.23.20197251v1

DIAGNOSTIC DEVELOPMENT

- Nothing new.

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2020-09-26

It is a dubious achievement, but today's newsletter marks the ½ year point since this project started.

I have some loyal readers in New York City and of course I still have my eyes set on a flat in Gramercy Park. Well, Diana Krall has a new album out and one of the tracks is 'Autumn in New York'. Here is the music video of that track with great filming by Davis McCutcheon and direction by Mark Seliger. I find this a very optimistic song/video. Enjoy it: https://www.youtube.com/watch?v=v5FVmJKPSrY It appears that this was filmed during the pandemic as the streets are pretty much empty.

In a good sign for the upcoming election, The Washington Post notes that Millenials are stepping up to replace older poll workers who dropped out because of COVID-19 concerns. Even more good news, death rates for children remain very low eight months into the pandemic. Now for the bad news☹ . Downtown Washington has turned into pretty much of a ghost city. I suspect the same thing is happening elsewhere. I don't think this is reflected in the current economic outlook statistics. Here is an op-ed on the difficulties of vaccine distribution.

The New York Times writes that outdoor dining may become permanent. COVID-19 cases in some Orthodox Jewish communities are on the rise. A fair number of Australians cannot return home because of travel restrictions into the country. Here is more on the big Chinese vaccine experiment. Large scale employment of not fully tested vaccines sometimes ends badly. It is perilous to be a public health worker these days!

Politico queries a number of experts about how the pandemic ends (hint: not with a bang but with a whimper).

The Lancet has a large-scale US COVID-19 antibody study. Looking at sera from dialysis patients in July they found less than 10% having antibodies to SARS-CoV-2. Extrapolations are always dicey but this does hint that we are some distance from herd immunity. Here is a commentary on the study.

MODELING

- We estimate the impact of mask mandates and other non-pharmaceutical interventions (NPI) on COVID-19 case growth in Canada, including regulations on businesses and gatherings, school closures, travel and self-isolation, and long-term care homes. We partially account for behavioral responses using Google mobility data. Our identification approach exploits variation in the timing of indoor face mask mandates staggered over two months in the 34 public health regions in Ontario, Canada's most populous province. *We find that, in the first few weeks after implementation, mask mandates are associated with a reduction of 25 percent in the weekly number of new COVID-19 cases. Additional analysis with province-level data provides corroborating evidence. Counterfactual policy simulations suggest that mandating indoor masks nationwide in early July could have reduced the weekly number of new cases in Canada by 25 to 40 percent in mid-August, which translates into 700 to 1,100 fewer cases per week*. [**note: model based on information from Ontario in Canada on the impact of mask wearing.**]
https://www.medrxiv.org/content/10.1101/2020.09.24.20201178v1
- Qatar experienced a large severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) epidemic that disproportionately affected the craft and manual workers (CMWs) who constitute 60% of the population. This study aimed to investigate level of immunity in communities within this population as well as infection exposure required to achieve herd immunity. Methods: Anti-SARS-CoV-2 seropositivity was assessed in ten CMW communities between June 21 and September 9, 2020. PCR positivity, infection positivity (antibody and/or PCR positive), and infection severity rate were also estimated. Associations with anti-SARS-CoV-2 positivity were investigated using regression analyses. Results: Study included 4,970 CMWs who were mostly men (95.0%) and <40 years of age (71.5%). Seropositivity ranged from 54.9% (95% CI: 50.2-59.4%) to 83.8% (95% CI: 79.1-87.7%) in the different CMW communities. Pooled mean seropositivity across all communities was 66.1% (95% CI: 61.5-70.6%). PCR positivity ranged from 0.0% to 10.5% (95% CI: 7.4-14.8%) in the different CMW communities. Pooled mean PCR positivity was 3.9% (95% CI: 1.6-6.9%). Median cycle threshold (Ct) value was 34.0 (range: 15.8-37.4). The majority (79.5%) of PCR-positive individuals had Ct value >30 indicative of earlier rather than recent infection. Infection positivity (antibody and/or PCR positive) ranged from 62.5% (95% CI: 58.3-66.7%) to 83.8% (95% CI: 79.1-87.7%) in the different CMW communities. Pooled mean infection positivity was 69.5% (95% CI: 62.8-75.9%). Only five infections were ever severe and one was ever critical, an infection severity rate of 0.2% (95% CI: 0.1-0.4%). Conclusions: *Based on an extended range of epidemiological measures, active infection is rare in these communities with limited if any sustainable infection transmission for clusters to occur. At least some CMW communities in Qatar have reached or nearly reached herd immunity for SARS-CoV-2 infection at a proportion of ever infection of **65-70%**.* [**note: evidence for herd immunity in Qatar. They see a high level of infection for herd immunity.**]
https://www.medrxiv.org/content/10.1101/2020.09.24.20200543v1

NEWLY REGISTERED CLINICAL TRIALS

- I checked yesterday!

CLINICAL TRIAL RESULTS

- The subset of patients who develop critical illness in Covid-19 have extensive inflammation affecting the lungs[PMID: 32526193] and are strikingly different from other patients: immunosuppressive therapy benefits critically-ill patients, but may harm some non-critical cases.[PMID: 32678530] Since susceptibility to life-threatening infections and immune-mediated diseases are both strongly heritable traits, we reasoned that host genetic variation may identify mechanistic targets for therapeutic development in Covid-19.[PMID: 24855243] GenOMICC (Genetics Of Mortality In Critical Care, genomicc.org) is a global collaborative study to understand the genetic basis of critical illness. Here we report the results of a genome-wide association study (GWAS) in 2244 critically-ill Covid-19 patients from 208 UK intensive care units (ICUs), representing >95% of all ICU beds. Ancestry-matched controls were drawn from the UK Biobank population study and results were confirmed in GWAS comparisons with two other population control groups: the 100,000 genomes project and Generation Scotland. We identify and replicate three novel genome-wide significant associations, at chr19p13.3 (rs2109069, $p = 3.98 \times 10^{-12}$), within the gene encoding dipeptidyl peptidase 9 (DPP9), at chr12q24.13 (rs10735079, $p = 1.65 \times 10^{-8}$) in a gene cluster encoding antiviral restriction enzyme activators (OAS1, OAS2, OAS3), and at chr21q22.1 (rs2236757, $p = 4.99 \times 10^{-8}$) in the interferon receptor gene IFNAR2. Consistent with our focus on extreme disease in younger patients with less comorbidity, we detect a stronger signal at the known 3p21.31 locus than previous studies (rs73064425, $p = 4.77 \times 10^{-30}$). [**note: this is a study of UK patients and what types of genetic linkages there is to severe COVID-19.**] https://www.medrxiv.org/content/10.1101/2020.09.24.20200048v2
- Recovery from COVID-19 is associated with production of anti-SARS-CoV-2 antibodies, but it is uncertain whether these confer immunity. We describe viral RNA shedding duration in hospitalized patients and identify patients with recurrent shedding. *We sequenced viruses from two distinct episodes of symptomatic COVID-19 separated by 144 days in a single patient, to conclusively describe reinfection with a new strain harboring the spike variant D614G. With antibody and B cell analytics, we show correlates of adaptive immunity, including a differential response to D614G. Finally, we discuss implications for vaccine programs and begin to define benchmarks for protection against reinfection from SARS-CoV-2*. [**note: here is a paper from Seattle that looks at viral shedding and one patient in particular who experienced to distinct episodes of COVID-19. The second one had the D61G strain. This is a worthwhile paper to read.**] https://www.medrxiv.org/content/10.1101/2020.09.22.20192443v1

DRUG DEVELOPMENT

- BACKGROUND The ongoing coronavirus disease (COVID)-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) might be controlled by an efficacious vaccine. Multiple vaccines are in development, but no efficacious vaccine is currently available. METHODS We designed a multi-center phase 1/2a randomized, double-blinded, placebo-controlled clinical study to assesses the safety, reactogenicity and immunogenicity of

Ad26.COV2.S, a non-replicating adenovirus 26 based vector expressing the stabilized pre-fusion spike (S) protein of SARS-CoV-2. Ad26.COV2.S was administered at a dose level of 5x1010 or 1x1011 viral particles (vp) per vaccination, either as a single dose or as a two-dose schedule spaced by 56 days in healthy adults (18-55 years old; cohort 1a & 1b; n= 402 and healthy elderly >65 years old; cohort 3; n=394). Vaccine elicited S specific antibody levels were measured by ELISA and neutralizing titers were measured in a wild-type virus neutralization assay (wtVNA). CD4+ T-helper (Th)1 and Th2, and CD8+ immune responses were assessed by intracellular cytokine staining (ICS). RESULTS We here report interim analyses after the first dose of blinded safety data from cohorts 1a, 1b and 3 and group unblinded immunogenicity data from cohort 1a and 3. In cohorts 1 and 3 solicited local adverse events were observed in 58% and 27% of participants, respectively. Solicited systemic adverse events were reported in 64% and 36% of participants, respectively. Fevers occurred in both cohorts 1 and 3 in 19% (5% grade 3) and 4% (0% grade 3), respectively, were mostly mild or moderate, and resolved within 1 to 2 days after vaccination. The most frequent local adverse event (AE) was injection site pain and the most frequent solicited AEs were fatigue, headache and myalgia. After only a single dose, seroconversion rate in wtVNA (50% inhibitory concentration - IC50) at day 29 after immunization in cohort 1a already reached 92% with GMTs of 214 (95% CI: 177; 259) and 92% with GMTs of 243 (95% CI: 200; 295) for the 5x1010 and 1x1011vp dose levels, respectively. A similar immunogenicity profile was observed in the first 15 participants in cohort 3, where 100% seroconversion (6/6) (GMTs of 196 [95%CI: 69; 560]) and 83% seroconversion (5/6) (GMTs of 127 [95% CI: <58; 327]) were observed for the 5x1010 or 1x1011 vp dose level, respectively. Seroconversion for S antibodies as measured by ELISA (ELISA Units/mL) was observed in 99% of cohort 1a participants (GMTs of 528 [95% CI: 442; 630) and 695 (95% CI: 596; 810]), for the 5x1010 or 1x1011 vp dose level, respectively, and in 100% (6/6 for both dose levels) of cohort 3 with GMTs of 507 (95% CI: 181; 1418) and 248 (95% CI: 122; 506), respectively. On day 14 post immunization, Th1 cytokine producing S-specific CD4+ T cell responses were measured in 80% and 83% of a subset of participants in cohort 1a and 3, respectively, with no or very low Th2 responses, indicative of a Th1-skewed phenotype in both cohorts. CD8+ T cell responses were also robust in both cohort 1a and 3, for both dose levels. CONCLUSIONS The safety profile and immunogenicity after only a single dose are supportive for further clinical development of Ad26.COV2.S at a dose level of 5x1010 vp, as a potentially protective vaccine against COVID-19. Trial registration number: NCT04436276 [**note: here is the clinical data for the Phase 1/2a J&J COVID-19 vaccine.**] https://www.medrxiv.org/content/10.1101/2020.09.23.20199604v1

- Here, using a recombinant reporter virus-based compound screening approach, we identified several small-molecule inhibitors that potently block the replication of the newly emerged severe acute respiratory syndrome virus 2 (SARS-CoV-2). Two compounds, nitazoxanide and JIB-04 inhibited SARS-CoV-2 replication in Vero E6 cells with an EC50 of 4.90 µM and 0.69 µM, respectively, with specificity indices of greater than 150. Both inhibitors had in vitro antiviral activity in multiple cell types against some DNA and RNA viruses, including porcine transmissible gastroenteritis virus. In an in vivo porcine model of coronavirus infection, administration of JIB-04 reduced virus infection and associated tissue pathology, which resulted in improved body weight gain and survival. These results highlight the potential utility of nitazoxanide and JIB-04 as antiviral agents against SARS-CoV-2 and other viral pathogens. [**note: there are four trials going on with nitazoxanide. The other drug is an experimental one originally developed at**

Univ of Texas medical school in Dallas. I don't see any trials of this drug for any condition in the NIH database.] https://www.biorxiv.org/content/10.1101/2020.09.24.312165v1

- The emergence of COVID-19 has led to a pandemic that has caused millions of cases of disease, variable morbidity and hundreds of thousands of deaths. Currently, only remdesivir and dexamethasone have demonstrated limited efficacy, only slightly reducing disease burden, thus novel approaches for clinical management of COVID-19 are needed. We identified a panel of human monoclonal antibody clones from a yeast display library with specificity to the SARS-CoV-2 spike protein receptor binding domain that neutralized the virus in vitro. Administration of the lead antibody clone to Syrian hamsters challenged with SARS-CoV-2 significantly reduced viral load and histopathology score in the lungs. Moreover, the antibody interrupted monocyte infiltration into the lungs, which may have contributed to the reduction of disease severity by limiting immunopathological exacerbation. The use of this antibody could provide an important therapy for treatment of COVID-19 patients. [**note: here is another mAb developed by the company AvantGen.**] https://www.biorxiv.org/content/10.1101/2020.09.25.313601v1
- Respiratory viruses such as coronaviruses represent major ongoing global threats, causing epidemics and pandemics with huge economic burden. Rapid spread of virus through populations poses an enormous challenge for outbreak control. Like all respiratory viruses, the most recent novel human coronavirus SARS-CoV-2, initiates infection in the upper respiratory tract (URT). Infected individuals are often asymptomatic, yet highly infectious and readily transmit virus. A therapy that restricts initial replication in the URT has the potential to prevent progression of severe lower respiratory tract disease as well as limiting person-to-person transmission. We show that prophylactic intra-nasal administration of the TLR2/6 agonist INNA-051 in a SARS-CoV-2 ferret infection model effectively reduces levels of viral RNA in the nose and throat. The results of our study support clinical development of a therapy based on prophylactic TLR2/6 innate immune activation in the URT to reduce SARS-CoV-2 transmission and provide protection against COVID-19. [**note: here is an intranasal TLR2 agonist that reduces upper respiratory viral shedding in an animal model. You have to read the paper to find out that INNA-051 belongs to a series of closely-related, pegylated synthetic analogues of the diacylated lipopeptide, S-[2,3-bis(palmitoyl oxy)propyl] cysteine (Pam2Cys) (INNA compound series), with selective TLR2/TLR6 agonist activity. They also don't define TLR and I had to go to Wikipedia for this one.**] https://www.biorxiv.org/content/10.1101/2020.09.25.309914v1
- A key step to the SARS-CoV-2 infection is the attachment of its Spike receptor-binding domain (S RBD) to the host receptor ACE2. Considerable research have been devoted to the development of neutralizing antibodies, including llama-derived single-chain nanobodies, to target the receptor-binding motif (RBM) and to block ACE2-RBD binding. Simple and effective strategies to increase potency are desirable for such studies when antibodies are only modestly effective. Here, we identify and characterize a high-affinity synthetic nanobody (sybody, SR31) as a fusion partner to improve the potency of RBM-antibodies. Crystallographic studies reveal that SR31 binds to RBD at a conserved and 'greasy' site distal to RBM. Although SR31 distorts RBD at the interface, it does not perturb the RBM conformation, hence displaying no neutralizing activities itself. However, fusing SR31 to two modestly neutralizing sybodies dramatically increases their affinity for RBD and neutralization activity against SARS-CoV-2 pseudovirus. Our work presents a tool protein and an efficient strategy to improve nanobody potency. [**note: from China, a way**

to improve nanobody activity against SARS-CoV-2]
https://www.biorxiv.org/content/10.1101/2020.09.24.312595v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Three lethal lower respiratory tract coronavirus epidemics have occurred over the past 20 years. This coincided with major developments in genome-wide gene and protein expression analysis, resulting in a wealth of datasets in the public domain. Seven such in vitro studies were selected for comparative bioinformatic analysis through the VirOmics Playground, a user-friendly visualisation and exploration platform we recently developed. Despite the heterogeneous nature of the data sets, several commonalities could be observed across studies and species. Differences, on the other hand, reflected not only variations between species, but also other experimental variables, such as cell lines used for the experiments, infection protocols and potential discrepancies between transcriptome and proteome data. The results presented here are available online and can be replicated through the VirOmics Playground. [**note: here is a nifty tool that can be used to visualize genomic effects and differences between MERS, SARS, and COVID-19. I finds common patterns in gene and protein expression and can be used for a number of different purposes.**]
https://www.biorxiv.org/content/10.1101/2020.09.25.313510v1
- Identifying drugs that regulate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and its symptoms has been a pressing area of investigation during the coronavirus disease 2019 (COVID-19) pandemic. Nonsteroidal anti-inflammatory drugs (NSAIDs), which are frequently used for the relief of pain and inflammation, could modulate both SARS-CoV-2 infection and the host response to the virus. NSAIDs inhibit the enzymes cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), which mediate the production of prostaglandins (PGs). PGE_2, one of the most abundant PGs, has diverse biological roles in homeostasis and inflammatory responses. Previous studies have shown that NSAID treatment or inhibition of PGE_2 receptor signaling leads to upregulation of angiotensin-converting enzyme 2 (ACE2), the cell entry receptor for SARS-CoV-2, thus raising concerns that NSAIDs could increase susceptibility to infection. COX/PGE_2 signaling has also been shown to regulate the replication of many viruses, but it is not yet known whether it plays a role in SARS-CoV-2 replication. The purpose of this study was to dissect the effect of NSAIDs on COVID-19 in terms of SARS-CoV-2 entry and replication. We found that SARS-CoV-2 infection induced COX-2 upregulation in diverse human cell culture and mouse systems. However, suppression of COX-2/PGE_2 signaling by two commonly used NSAIDs, ibuprofen and meloxicam, had no effect on ACE2 expression, viral entry, or viral replication. Our findings suggest that COX-2 signaling driven by SARS-CoV-2 may instead play a role in regulating the lung inflammation and injury observed in COVID-19 patients. [**note: not sure what category to put this paper in as it fits several different categories. Cyclooxgenase-2 is induced by SARS-CoV-2 infection but doesn't affect viral entry or replication. They looked at a couple of NSAIDS that showed no effect on key factors related to viral activity.**] https://www.biorxiv.org/content/10.1101/2020.09.24.312769v1
- Coronaviruses are adept at evading and/or antagonizing double-stranded RNA-induced host antiviral pathways, including interferon signaling, OAS-RNase L and PKR while robust cytokine responses characterize severe coronavirus disease. Knowledge of how newly emerged SARS-CoV-2 interacts with these pathways is minimal. SARS-CoV-2 readily infects patient-derived

nasal epithelial cells and induced pluripotent stem cell-derived alveolar type 2 cells (iAT2) and cardiomyocytes (iCM). Robust activation of interferons or RNase L is not observed, while PKR activation is evident in iAT2 and iCM. In SARS-CoV-2 infected Calu-3 and A549ACE2 lung derived cell lines, activation of all pathways is observed, similar to a mutant MERS-CoV lacking innate immune antagonists. Moreover, increased replication in RNASEL knockout A549ACE2 cells, implicates RNase L in restricting SARS-CoV-2. *Finally, while SARS-CoV-2 is less adept at antagonizing these host defense pathways compared to other coronaviruses, the innate immune response is still generally weak. These host-virus interactions may contribute to the unique pathogenesis of SARS-CoV-2*. [**note: more on SARS-CoV-2 and the immune response from Univ of Pennsylvania.]** https://www.biorxiv.org/content/10.1101/2020.09.24.312553v1

- Children and youth infected with SARS-CoV-2 have milder disease than do adults and, even among those with the recently described multi-system inflammatory syndrome (MIS-C), mortality is rare. The reasons for the differences in clinical manifestations are unknown, but suggest that age-dependent factors may modulate the anti-viral immune response. We compared cytokine, humoral, and cellular immune responses in pediatric (children and youth, age < 24 years) (n=65) and adult (n=60) patients with COVID-19 at a metropolitan hospital system in New York City. The pediatric patients had a shorter length of stay, decreased requirement for mechanical ventilation and lower mortality compared to adults. The serum concentrations of IL-17A and IFN-γ, but not TNF-α or IL-6, were inversely related to age. Adults mounted a more robust T cell response to the viral spike protein compared to pediatric patients as evidenced by increased expression of CD25+ on CD4+ T cells and the frequency of IFN-γ+CD4+ T cells. Moreover, serum neutralizing antibody titers and antibody-dependent cellular phagocytosis were higher in adults compared to pediatric COVID-19 patients. The neutralizing antibody titer correlated positively with age and negatively with IL-17A and IFN-γ serum concentrations. There were no differences in anti-spike protein antibody titers to other human coronaviruses. Together these findings demonstrate that the poor outcome in hospitalized adults with COVID-19 compared to children may not be attributable to a failure to generate adaptive immune responses. [**note: this is an interesting finding in that it points to why most children have mild, if that, cases of COVID-19. Older people who have adverse COVID-19 outcomes may not be able to generate an adaptive immune response.**] https://stm.sciencemag.org/content/early/2020/09/21/scitranslmed.abd5487

DIAGNOSTIC DEVELOPMENT

- Significant barriers to the diagnosis of latent and acute SARS-CoV-2 infection continue to hamper population-based screening efforts required to contain the COVID-19 pandemic in the absence of effective antiviral therapeutics or vaccines. We report an aptamer-based SARS-CoV-2 salivary antigen assay employing only low-cost reagents ($3.20/test) and an off-the-shelf glucometer. The test was engineered around a glucometer as it is quantitative, easy to use, and the most prevalent piece of diagnostic equipment globally making the test highly scalable with an infrastructure that is already in place. *Furthermore, many glucometers connect to smartphones providing an opportunity to integrate with contract tracing apps, medical providers, and electronic medical records. In clinical testing, the developed assay detected SARS-CoV-2 infection in patient saliva across a range of viral loads - as benchmarked by RT-qPCR - within one hour, with 100% sensitivity (positive percent agreement) and distinguished infected*

specimens from off-target antigens in uninfected controls with 100% specificity (negative percent agreement). We propose that this approach can provide an inexpensive, rapid, and accurate diagnostic for distributed screening of SARS-CoV-2 infection at scale. [**note: kudos to these UC San Diego researchers for developing an innovative approach to POC salivary antigen testing using an off the shelf glucometer!!!!]**
https://www.medrxiv.org/content/10.1101/2020.09.24.20200394v1

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2020-09-27

For this reflection Sunday I offer a recent live outdoor concert from Berlin by the Staatskapelle Orchestra conducted by Daniel Barenboim. It's an all-Beethoven program with a pair of violin romances with Anne-Sophie Mutter and the Symphony #9. I would advise watching this sooner rather than later as the first YouTube posting was taken down by the apparent copyright owner. This is just great playing: https://www.youtube.com/watch?v=XTCBHRauWRg It is interesting to see how the chorus is socially distanced.

NOTE; There will be no newsletter tomorrow as I will be observing Yom Kippur.

The New York Times has a tale about a small Vermont town whose population has skyrocketed from COVID-19 refuges. Here is one of the courageous healthcare workers lost to COVID-19.

The Washington Post has a story on a small restaurant owner who is closing up shop because of COVID-19. The hard hit airline industry may be laying off 35,000 employees this week. There is a slow return to in class teaching at colleges and universities in the DC region. A shopping area in Friendship Heights (about 2 miles from our house) is seeing lots of closures as a result of COVID-19.

It's a modest list of articles today with a couple of interesting model papers.

MODELING

- As in many other settings, peak excess mortality preceded the officially reported `first wave' peak of the COVID-19 epidemic in Manaus, Brazil, reflecting delayed case recognition and limited initial access to diagnostic testing. To avoid early information bias, we used detailed age and gender stratified death certificate and hospitalisation data to evaluate the epidemic's trajectory and infer the cause of its decline using a stochastic model. Our results are consistent with heterogenous transmission reducing over time due to the development of herd immunity. Relative to a baseline model that assumed homogenous mixing across Manaus, a model that permitted a small, self-isolated population fraction raised the estimated herd-immunity threshold from 28% to 30% and reduced the final attack rate from 86% to 65%. In the latter scenario, a substantial proportion of vulnerable, older individuals remained susceptible to infection. Given uncertainties regarding the distancing behaviours of population subgroups with different social and economic characteristics, and the duration of sterilising or transmission-modifying immunity in exposed individuals, we conclude that the potential for epidemic outbreaks remains, but that future waves of infection are likely to be much less pronounced than that already experienced. [**note: this Australian/Brazil group models the outbreak in Manaus. Their value for herd immunity is at the lower end of the scale in terms of the models**

I've seen. I took a look at the paper and don't understand why there should be so many excess infections over the herd immunity value. Here is one of the earlier papers that I referenced that had herd immunity just above 40%.]
https://www.medrxiv.org/content/10.1101/2020.09.25.20201939v1

NEWLY REGISTERED CLINICAL TRIALS

- There looked to be less than five trials added to the database so I will wait a couple more days before going through and seeing what the new ones are.

CLINICAL TRIAL RESULTS

- The multifaceted disease manifestation of COVID-19 requires longitudinal characterization of symptoms, to aid with screening and disease management. Methods: Phone interviews and follow-ups were completed with 112 mild COVID-19 RT-PCR-positive adult patients, over a 6 week period. Results: More than one symptom at disease onset was experienced by ~70 of the patients. Over one third of patients experienced fever, dry cough, headache, or muscle ache as the first symptom. If fatigue was reported, it was usually the first symptom to appear. Smell and taste changes had occurred 3.9 ± 5.4 and 4.6 ± 5.7 days (mean ± SD) since disease onset and emerged as first symptoms in 15% and 18% of patients, respectively. Fever was the shortest lasting symptom (5.8 ± 8.6 days (mean ± SD), and smell and taste changes were the most long-lasting symptoms (24.3 ± 22.9 days and 19.4 ± 19.1 (mean ± SD), respectively), with longer smell recovery correlated with smell change severity. In one third of patients who reported cough, smell and taste changes, these symptoms persisted after negative RT-PCR tests. Conclusions: Each symptom can occur as first or later, though some are more likely to appear as firsts, and typically more than one symptom occurs at disease onset. The severity of olfactory change is associated with its recovery time. Lack of chemosensory recuperation in recovered patients is common. These findings can aid patients through their illness and provide expected recovery patterns. [**note: a longitudinal study of taste and smell changes and other COVID-19 symptoms from Israel.**] https://www.medrxiv.org/content/10.1101/2020.09.25.20201343v1
- Objectives: To evaluate antihypertensive medications and COVID-19 diagnosis and mortality, accounting for healthcare seeking behaviour. Design: A population-based case control study with additional cohort analysis. Setting: Primary care patients from the UK Clinical Practice Research Datalink (CPRD). Participants: 16 866 patients with COVID-19 events in the CPRD from 29th January to June 25th 2020 and 70 137 matched controls. Main outcome measures: We explored associations between COVID-19 diagnosis and prescriptions for angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers (B), calcium-channel blockers (C), thiazide diuretics (D) and other antihypertensive drugs (O). We evaluated all-cause mortality among COVID-19 cases. Analyses were adjusted for covariates and consultation frequency. Results: In covariate adjusted analyses, ACEIs were associated with lower odds of COVID-19 diagnosis (0.82, 95% confidence interval 0.77 to 0.88) as were ARBs, 0.87 (0.80 to 0.95) with little attenuation from adjustment for consultation frequency. In fully adjusted analyses, C and D were also associated with lower odds of COVID-19. Increased odds of COVID-19 for B (1.19, 1.12 to 1.26), were attenuated after adjustment for consultation frequency (1.01, 0.95 to 1.08). In adjusted analyses, patients treated with ACEIs or ARBs had similar mortality to patients treated with classes B, C, D or O (1.00, 0.83 to 1.20) or patients

receiving no antihypertensive therapy (0.99, 0.83 to 1.18). Conclusions: *Associations were sensitive to adjustment for confounding and healthcare seeking, but there was no evidence that antihypertensive therapy is associated with increased risk of COVID-19 diagnosis or mortality; most classes of antihypertensive therapy showed negative associations with COVID-19 diagnosis.* [**note: a large study of the effect of antihypertensive therapy on COVID-19 diagnosis and mortality. There appears to be none.**] https://www.medrxiv.org/content/10.1101/2020.09.25.20201731v1

- Pediatric COVID-19 following SARS-CoV-2 infection is associated with fewer hospitalizations and often milder disease than in adults. A subset of children, however, present with Multisystem Inflammatory Syndrome in Children (MIS-C) that can lead to vascular complications and shock, but rarely death. The immune features of MIS-C compared to pediatric COVID-19 or adult disease remain poorly understood. We analyzed peripheral blood immune responses in hospitalized SARS-CoV-2 infected pediatric patients (pediatric COVID-19) and patients with MIS-C. MIS-C patients had patterns of T cell-biased lymphopenia and T cell activation similar to severely ill adults, and all patients with MIS-C had SARS-CoV-2 spike-specific antibodies at admission. A distinct feature of MIS-C patients was robust activation of vascular patrolling CX3CR1+ CD8 T cells that correlated with use of vasoactive medication*. Finally, whereas pediatric COVID-19 patients with acute respiratory distress syndrome (ARDS) had sustained immune activation, MIS-C patients displayed clinical improvement over time, concomitant with decreasing immune activation. Thus, non-MIS-C versus MIS-C SARS-CoV-2 associated illnesses are characterized by divergent immune signatures that are temporally distinct and implicate CD8 T cells in clinical presentation and trajectory of MIS-C.* [**note: here is a immunological study of multisystem inflammatory syndrome in children compared to COVID-19 in children and adults.**] https://www.medrxiv.org/content/10.1101/2020.09.25.20201863v1

DRUG DEVELOPMENT

- Nothing today

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Nothing today

DIAGNOSTIC DEVELOPMENT

- Serological testing is emerging as a powerful tool to progress our understanding of COVID-19 exposure, transmission and immune response. Large-scale testing is limited by the need for in-person blood collection by staff trained in venepuncture. Capillary blood self-sampling and postage to laboratories for analysis could provide a reliable alternative. Two-hundred and nine matched venous and capillary blood samples were obtained from thirty nine participants and analysed using a COVID-19 IgG ELISA to detect antibodies against SARS-CoV-2. Thirty seven out of thirty eight participants were able to self-collect an adequate sample of capillary blood (≥50 µl). Using plasma from venous blood collected in lithium heparin as the reference standard, matched capillary blood samples, collected in lithium heparin-treated tubes and on filter paper as dried blood spots, achieved a Cohen's kappa coefficient of >0.88 (near-perfect agreement). Storage of capillary blood at room temperature for up to 7 days post sampling did not affect concordance. Our results indicate that capillary blood self-sampling is a reliable and feasible

alternative to venepuncture for serological assessment in COVID-19. [**note: from England, a small pilot test of self sampling serological testing. It works out reasonably well.**] https://www.medrxiv.org/content/10.1101/2020.09.25.20183459v1

- Objectives: The optimal diagnostic specimen to detect SARS-CoV-2 by PCR in the upper respiratory tract is unclear. Mouthwash fluid has been reported as an alternative to nasopharyngeal and oropharyngeal swabs. We compared mouthwash fluid with a combined oro-nasopharyngeal swab regarding test performance. Methods: We tested asymptomatic persons with a previous diagnosis of COVID-19 and their household contacts. First, a mouthwash (gargling for at least 5 sec) with sterile water was performed. Then, with a single flocked swab the back of the throat and subsequently the nasopharynx were sampled. Samples were inactivated and analysed on a Roche cobas 6800 system with the Roche SARS-CoV-2 test. Results: Of 76 persons, 39 (51%) tested positive for SARS-CoV-2 by oro-nasopharyngeal swab. Mouthwash detected 13 (17%) of these infections but did not detect any additional infection. Samples that were positive in both tests, had lower cycle threshold (Ct)-values for oro-nasopharyngeal samples, indicating a higher virus concentration, compared to samples only positive in oro-nasopharyngeal swabs. Conclusions: Mouthwash is not as sensitive as combined oro-nasopharyngeal swab in detecting upper respiratory tract infection. [**note: here is a German study that shows mouthwash sample collection is not as good as nasopharyngeal collection.**] https://www.medrxiv.org/content/10.1101/2020.09.25.20201541v1