2020-03-29

We are entering our third week of closures here in Maryland and last night we helped one of our local restaurants by ordering in with delivery from one of the Internet food delivery apps. This is nice way to help keep your local restaurants running in this time of closure.

To help take your mind of SARS-CoV-2, here is a YouTube performance of Wagner's Tannhauser overture as transcribed by Franz Liszt. Melodic and devilishly difficult to play well: https://www.youtube.com/watch?v=W46BKM0mg-g

More partially good news on the diagnostic front from Abbott Labs but do see the caveats I have added.

Here is a link to yesterday's OHDSI's wrap up call where their observational model for studying hydroxychloroquine is posted and discussed. Daniel Prieto-Alhambra takes over around the 22:45 mark **of the wrap-up call** to discuss the work of the estimation team, with a focus on the study of hydroxychloroquine, which is certainly drawing a great deal of attention right now. This study compares hydroxychloroquine to comparator drugs with a significant dataset, again highlighting the quality of real-world evidence being produced.

All the OHDSI work is at their website and a lot of the discussions are recorded for streaming on YouTube. https://forums.ohdsi.org/c/general

NEWLY REGISTERED CLINIAL TRIALS

- I didn't see any today

CLINICAL TRIAL RESULTS

- A group of New York researchers conducted an observational study on the impact of BCG vaccination and health outcomes. We found that countries without universal policies of BCG vaccination (Italy, Nederland, USA) have been more severely affected compared to countries with universal and long-standing BCG policies. Countries that have a late start of universal BCG policy (Iran, 1984) had high mortality, consistent with the idea that BCG protects the vaccinated elderly population. We also found that BCG vaccination also reduced the number of reported COVID-19 cases in a country. The combination of reduced morbidity and mortality makes BCG vaccination a potential new tool in the fight against COVID-19. More work needs to be done on this down to the patient level.
  https://www.medrxiv.org/content/10.1101/2020.03.24.20042937v1

DRUG DEVELOPMENT

- Here's a paper from joint US/Belgium group that analyzes the spike protein and single domain antibodies can potentially neutralize the class of CoV viruses. We desperately need some MAbs in the clinic. https://www.biorxiv.org/content/10.1101/2020.03.26.010165v1
- A Beijing group designed a novel lipopeptide fusion inhibitor with highly potent activity to inhibit SARS-CoV-2 fusion and cellular entry. This will need further work to figure out how to optimally

design it for human administration.
https://www.biorxiv.org/content/10.1101/2020.03.26.009233v1

- More good work from China. This is one of the first papers I've seen on structure based drug design. In an effort to rapidly discover lead compounds targeting Mpro (the main protease), two compounds (11a and 11b) were designed and synthesized, both of which exhibited excellent inhibitory activity with an IC50 value of 0.05 μM and 0.04 μM respectively. Significantly, both compounds exhibited potent anti-SARS-CoV-2 infection activity in a cell-based assay with an EC50 value of 0.42 μM and 0.33 μM, respectively. The X-ray crystal structures of SARS-CoV-2 Mpro in complex with 11a and 11b were determined at 1.5 Å resolution, respectively. The crystal structures showed that 11a and 11b are irreversible, the aldehyde groups of which are bound covalently to Cys145 of Mpro. Both compounds are promising drug leads with clinical potential that merits further studies.
https://www.biorxiv.org/content/10.1101/2020.03.25.996348v1
- Here is an Indian group that uses deep learning to come up with some novel chemical structures that inhibit Mpro. When screened against a natural products library, two of the small molecules shoed high similarity to a plant natural product, aurantiamide.
https://chemrxiv.org/articles/De_Novo_Design_of_New_Chemical_Entities_NCEs_for_SARS-CoV-2_Using_Artificial_Intelligence/11998347

DIAGNOSTIC DEVELOPMENT

- Abbott Labs got an emergency use approval for a quick gene test that can be run on their ID Now system: https://www.abbott.com/corpnewsroom/product-and-innovation/detect-covid-19-in-as-little-as-5-minutes.html this is commonly used in physician offices. Before we all get excited the press release notes that there are 18K ID Now units in the US according to Bloomberg. Abbott plans on producing 50K tests per day which works out less than 3 tests per machine per day. Of course, there is the logistics issue of getting tests out to the offices that need them. Those in MD or urgent care offices will still have to address the PPE issue if suspected SARS-CoV-2 patients come in for testing. Even so, this is a good sign that the diagnostics industry is gearing things up.

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2020-03-30

Welcome to a new week. Thus far the hospital case load here in Maryland has been manageable but reported cases of SARS-CoV-2 continue to increase. Some good work out of China looking at serological testing.

For the musical selection, here is a cute, short, video of how opera during a pandemic might be staged. The two singers are voice professors from Augustana College and even the notable Dr. Fauci has a role:
https://www.youtube.com/watch?v=7S5WnAIogxQ

The OHDSI study-a-thon wrapped up last night with a two-hour teleconference. The project involved 340 collaborators from 30 nations; an impressive effort. I listened to half of it and was impressed by all the progress made. The link to the call is here:

https://www.youtube.com/watch?v=VDsZiSzfgqM&feature=youtu.be and if you want to scan to specific parts the index times for presentations are:

Literature Review – Jennifer Lane (22:00)
Data Network In Action – Kristin Kostka (26:10)
Phenotype Development – Anna Ostropolets (31:38)
Clinical Characterization of COVID-19 – Ed Burn (42:10)
The Journey Through Patient-Level Prediction – Peter Rijnbeek (50:12)
Prediction #1: Amongst Patients Presenting with COVID-19, Influenza, or Associated Symptoms, Who Are Most Likely to be Admitted to the Hospital in the Next 30 Days? – Jenna Reps (56:55)
Prediction #2: Amongst Patients at GP Presenting with Virus or Associated Symptoms with/without Pneumonia Who Are Sent Home, Who Are Most Likely to Require Hospitalization in the Next 30 Days? – Ross Williams (1:08:42)
Prediction #3: Amongst Patients Hospitalized with Pneumonia, Who Are Most Likely To Require Intensive Services or Die? – Aniek Markus (1:15:25)
Estimation #1: Hydroxychloroquine – Daniel Prieto-Alhambra (1:23:32)
Estimation #2: Safety of HIV/HepC Protease Inhibitors – Albert Prats (1:31:24)
Estimation #3: Association of Angiotensin Converting Enzyme (ACE) Inhibitors and Angiotensin II Receptor Blockers (ARB) on COVID Incidence and Complications – Daniel Morales (1:36:58)
#OpenData4COVID19 – Seng Chan You (1:45:32)
The Journey Ahead – Patrick Ryan (1:50:28)
Questions & Answers – Daniel Prieto-Alhambra, Peter Rijnbeek and Patrick Ryan (2:08:15)

MODELING

- I've tried to minimize the number of references to modeling papers but an interesting comparison of examining traffic data in two South Korea cities proved to be useful in looking at control of the spread. The outbreak spread rapidly within a church community in the city of Daegu, spreading to other parts of the country. 56% of cases in the country were related to the church. South Korea's intensive testing using novel contact tracing techniques allowed rapid identification and isolation cases and reduction of onward transmission. Investigators describe potential roles of social distancing in mitigating the spread of COVID-19 in South Korea by using metro traffic data to compare epidemics in two major cities. (https://www.medrxiv.org/content/10.1101/2020.03.27.20045815v1)
- Here is an interesting use of "big data" to model the impact of climate on the infection rate of SARS-CoV-2: "To our knowledge, this is the first empirical study to comprehensively examine the association between the incidence of Covid-19 and a range of meteorological factors spanning across the world. Our finding of an inverse relationship between temperature (and humidity) and the incidence of Covid-19 may suggest a cold and dry environment more favourable condition for virus survival, as was proposed for other coronavirus such as SARS-CoV and MERS-CoV.2–5An inverse association with wind speed may indicate a shorter suspending time in the air due to dilution and removal of Covid-19.3 An inverse association with a higher UV index would suggest viral destruction at higher temperature,3 but the association did not hold with the concurrent or 7-day UV index."
  https://www.medrxiv.org/content/10.1101/2020.03.27.20045658v1

- From an Oxford group in the UK: Here we use simple stochastic simulations to evaluate different approaches taken to tackle the crisis, along with the efficiency they will hold and the number of casualties they may incur. It is clear that the less strict the social distancing the more time it will take for life to return to normal, and the more lives will be at risk. This is shown through simulations formed by an open sourced code, which allows evaluation of the outcomes from different intervention scenarios or conditions.
  https://www.medrxiv.org/content/10.1101/2020.03.29.20046870v1

NEWLY REGISTERED CLINICAL TRIALS

- none

CLINICAL TRIAL RESULTS

- none, though I hope chloroquine/hydroxychloroquine data begins to come out of the New York City effort

DRUG DEVELOPMENT

- While most of the work has been centered on looking for efficacious therapies, here is a Chinese paper that examines potential drug safety issues via pharmacogentics for several drugs currently in clinical trials. Pharmacogenes, including CYP3A4, ABCB1, SLCO1B1, ALB, CYP3A5, were involved in the process of more than multi DCTs. 224 potential drug-drug interactions (DDIs) of DCTs were predicted, while 112 of them have been reported. Racial discrepancy of common nonsynonymous mutations was found in pharmacogenes including: VDR, ITPA, G6PD, CYP3A4 and ABCB1 which related to DCTs including ribavirin, α-interferon, chloroquine and lopinavir. Moreover, ACE2, the target of 2019-nCoV, was only found in parts of lung cells, which makes drugs like chloroquine that prevent virus binding to ACE2 more specific than other targeted drugs such as camostat mesylate.
  https://www.medrxiv.org/content/10.1101/2020.03.23.20041350v1
- Here is another computational study, this time from Brazil, looking at SARS-CoV-2 receptor antagonists from an approved drug library. This work has shown that, in comparative terms, *Simeprevir*, *Paritaprevir*, *Remdesivir* and *Baricitinib* are currently among the most promising in remission of symptoms from the disease. *Hydroxy-chloroquine*, *Chloroquine* and *Azithromicin* were not showed effective, as monotherapies, against COVID-19 or *lung cell* receptors. [**NOTE**: I am confused by parts of this paper and it seems to contradict some of the other modeling papers I have read. I included it for the purpose of providing an alternative look at how docking modeling can be applied]
  https://chemrxiv.org/articles/Comparative_Computational_Study_of_SARS-CoV-2_Receptors_Antagonists_from_Already_Approved_Drugs/12044538

DIAGNOSTIC DEVELOPMENT

- A Chinese group evaluates two approaches to a serological test for diagnosing SARS-CoV-2; it may be relevant regarding which approach is taken towards developing a commercially viable test. Here, we developed a chemiluminescence-immunoassay method based on the recombinant nucleocapsid antigen and the magnetic beads for diagnosis of SARS-CoV-2 infections and surveillance of antibody changing pattern. Serums from 29 healthy individuals, 51 tuberculosis patients, and 79 SARS-CoV-2 confirmed patients were employed to evaluate the performance of this approach. Compared to the IgM testing, the IgG testing was more reliable in which it identified 65 SARS-CoV-2 infections from the 79 confirmed patients and only two false-positive cases from the 80 control group with a sensitivity and specificity reaching 82.28% and 97.5%, respectively. However, only a slight difference (not statistically significant) in the detected cases of SARS-CoV-2 infections was observed between the IgM and IgG testing manner in patients at a different time of onset of disease. A performance comparison between an ELISA kit using the same nucleocapsid antigen and our chemiluminescence method was undertaken. The same false-positive cases were seen in both methods from the paired control group, while ELISA kit can only detect half of the SARS-CoV-2 infections from paired SARS-CoV-2 confirmed patients group than that of the chemiluminescence method, indicating a higher performance for the chemiluminescence-immunoassay approach.
  https://www.medrxiv.org/content/10.1101/2020.03.27.20045153v1
- Another paper from China compares antibody testing to gene testing. Among 38 patients, the total seropositive rate for IgM and IgG was 50.0% and 92.1%, respectively. Two patients remained seronegative throughout the course of illness. In the early phase of illness, the RNA test for sputum specimens possessed the highest detectability(92.3%), followed by the the RNA test for throat swabs (69.2%), and the antibodies assays presented lower positive rates(IgM, 23.0%, IgG, 53.8%). While, the sensitivity of antibodies assays overtook that of RNA test since day 8 after onset (IgM, 50.0%; IgG, 87.5%). Of note, the positive rate of throat swabs was only 13.0% for cases in later phase(≥15 d.a.o), and the sensitivities of IgM and IgG rose to 52.2% and 91.3%, respectively. Combined use of antibodies assay and qRT-PCR at the same time was able to improve the sensitivities of pathogenic-diagnosis, especially for the throat swabs group at the later stage of illness. Moreover, most of these cases with undetectable viral RNA in throat swabs specimens at the early stage of illness were able to be IgM/IgG seropositive after 7 days. Conclusions: The antibodies detection against SARS-CoV-2 offers vital clinical information for physicians, and could be used as an effective supplementary indicator for suspected cases of negative viral nucleic acid detection or in conjunction with nucleic acid detection in the diagnosis of suspected cases.
  https://www.medrxiv.org/content/10.1101/2020.03.26.20042044v1
- Another paper from China looking at a rapid serological test and comparing it to the gene based test. A total of 179 patients were enrolled. Serum were collected for IgG-IgM combined antibody test and corresponding nasal and pharyngeal swab specimens were collected for SARS-CoV-2 RT-PCR. According to SARS-CoV-2 RT-PCR results, patients under study were categorized as PCR positive group in 90 patients and PCR negative group in 89 patients. Results 1. Of the 90 PCR positive samples, 77 were tested positive by SARS-CoV-2 IgG-IgM test kit, yielding a sensitivity of 85.6%. Meanwhile, of the 89 PCR negative sample, 8 samples were detected positive, resulting in a specificity of 91%. Positive predictive value, negative predictive value and

accuracy of this test kit was 95.1%, 82.7%, and 88.3%, respectively. Kappa efficiency between IgG/IgM test kit and RT-PCR were 0.75. 2. Accuracy in mild/common and severe/critical subgroup were 73.9% and 97.7%, respectively. Accuracy in clinical confirmed, suspected cases and other disease subgroups were 70%, 60%, and 100%, respectively. 3. Patients were further divided into 0-7, 8-15 and >= 16 groups according to the time from illness onset to sample collection. Sensitivity, specificity and accuracy in these three groups were 18.8%, 77.8% and 40%; 100%, 50% and 87.5%; 100%, 64.3%, and 93.9, respectively. Conclusion The sensitivity and specificity of this ease-of-use IgG/IgM combined test kit were adequate, plus short turnaround time, no specific requirements for additional equipment or skilled technicians, all of these collectively contributed to its competence for mass testing. At the current stage, it cannot take the place of SARA-CoV-2 nucleic acid RT-PCR, but can be served as a complementary option for RT-PCR. The combination of RT-PCR and IgG-IgM combined test kit could provide further insight into SARS-CoV-2 infection diagnosis.
https://www.medrxiv.org/content/10.1101/2020.03.26.20044883v1

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2020-03-31

I've added a new section to cover modeling. I have only scanned these papers but have added them to give you a sense of what is going on and how this may affect policy decisions. If you just want to look at the slides from the OHDSI study-a-thon rather than watching the video of the final call, they are now posted: https://www.ohdsi.org/covid-19-updates/

I've linked to one of the early hydroxychloroquine trials in China where they do see an effect compared to the control. Note that they excluded critically ill patients from this trial. There is still no approved serological test in the US, at least according to the FDA's list of emergency use applications. I was also intrigued by the Chinese finding that a serological test was slightly better than the RT-PCR test. I'll need to go back and look at some previous papers as I wonder how many false negatives arise from RT-PCR testing.

MODELING

- From Germany: We come to the following conclusions: 1. Complete lockdown works. About 10 days after lockdown, the infection dynamics dies down. This assumes that lockdown is complete, which can be guaranteed in the simulation, but not in reality. Still, it gives strong support to the argument that it is never too late for complete lockdown. 2. As a rule of thumb, we would suggest complete lockdown no later than once 10% of hospital capacities available for COVID-19 are in use, and possibly much earlier. This is based on the following insights: a. Even after lockdown, the infection dynamics continues at home, leading to another tripling of the cases before the dynamics is slowed. b. There will be many critical cases coming from people who were infected before lockdown. Because of the exponential growth dynamics, their number will be large. c. Researchers with more detailed disease progression models should improve upon these statements. 3. Our simulations say that complete removal of infections at child care, primary schools, workplaces and during leisure activities will not be enough to sufficiently slow

down the infection dynamics. It would have been better, but still not sufficient, if initiated earlier. 4. Infections in public transport play an important role. In the simulations shown later, removing infections in the public transport system reduces the infection speed and the height of the peak by approximately 20%. Evidently, this depends on the infection parameters, which are not well known. -- This does not point to reducing public transport capacities as a reaction to the reduced demand, but rather use it for lower densities of passengers and thus reduced infection rates. 5. In our simulations, removal of infections at child care, primary schools, workplaces, leisure activities, and in public transport may barely have been sufficient to control the infection dynamics if implemented early on. Now according to our simulations it is too late for this, and (even) harsher measures will have to be initiated until possibly a return to such a restrictive, but still somewhat functional regime will again be possible. Evidently, all of these results have to be taken with care. They are based on preliminary infection parameters taken from the literature, used inside a model that has more transport/movement details than all others that we are aware of but still not enough to describe all aspects of reality, and suffer from having to write computer code under time pressure. Optimally, they should be confirmed independently. Short of that, given current knowledge we believe that they provide justification for "complete lockdown" at the latest when about 10% of available hospital capacities for COVID-19 are in use (and possibly earlier; we are no experts of hospital capabilities). What was not investigated in detail in our simulations was contact tracing, i.e. tracking down the infection chains and moving all people along infection chains into quarantine. The case of Singapore has so far shown that this may be successful. https://www.medrxiv.org/content/10.1101/2020.03.27.20045302v1

- From Spain: We fit data to quarantined populations in order to account for the uncertainties in case reporting and study the scenario projections for the 17 individual regions (CCAA). Results indicate that with data for March 23, the epidemics follows an evolution similar to the isolation of 1.5 percent of the population and if there were no effects of intervention actions it might reach a maximum over 1.4M infected around April 27. The effect on the epidemics of the ongoing partial confinement measures is yet unknown, but increasing the isolation around ten times more could drastically reduce the peak to over 100K cases by early April, while each day of delay in taking this hard containment scenario represents an 90 percent increase of the infected population at the peak. Dynamics at the sub aggregated levels of CCAA show epidemics at the different levels of progression with the most worrying situation in Madrid an Catalonia. Increasing alpha values up to 10 times, in addition to a drastic reduction in clinical cases, would also more than halve the number of deaths.
  https://www.medrxiv.org/content/10.1101/2020.03.27.20045005v1
- From Switzerland: Here we devise a simple model to predict the effectiveness of different mitigation strategies. The model consists of a set of simple differential equations considering the population size, reported and unreported infections, reported and unreported recoveries and the number of Covid-19-inflicted deaths. For simplification, we assume that Covid-19 survivors are immune (e.g. mutations are not considered) and that the virus can only be passed on by persons with undetected infections. While the latter assumption is a simplification (it is neglected that e.g. hospital staff may be infected by detected patients with symptoms), it was introduced here to keep the model as simple as possible. Moreover, the current version of the model does not account for age-dependent differences in the death rates, but considers higher mortality rates due to temporary shortage of intensive care units. Some of the model

parameters have been fitted to the reported cases outside of China1 from January 22 to March 12 of the 2020 Covid-19 pandemic. The other parameters were chosen in a plausible range to the best of our knowledge. We compared infection rates, the total number of people getting infected and the number of deaths in six different scenarios. Social distancing or increased testing can contain or drastically reduce the infections and the predicted number of deaths when compared to a situation without mitigation. We find that mass-testing alone and subsequent isolation of detected cases can be an effective mitigation strategy, alone and in combination with social distancing. However, unless one assumes that the virus can be globally defeated by reducing the number of infected persons to zero, testing must be upheld, albeit at reduced intensity, to prevent subsequent waves of infection. The model suggests that testing strategies can be equally effective as social distancing, though at much lower economical costs. We discuss how our mathematical model may help to devise an optimal mix of mitigation strategies against the Covid-19 pandemic. The website corona-lab.ch provides an interactive simulation tool based on the presented model.
https://www.medrxiv.org/content/10.1101/2020.03.27.20045237v1

- This is a complicated paper from UCLA researchers (the math is above my age-based comprehension level) showing that estimation of population-based case fatality rates during epidemics may be misleading. The key parameters that affect the dynamics of the different mortality estimates are the incubation period and the length of time individuals were infected before confirmation of infection. We stress that none of these ratios are accurately represented by the often misinterpreted case fatality ratio (CFR), the number of deaths to date divided by the total number of infected cases to date. Using available data on the recent SARS-CoV-2 outbreaks and simple assumptions, we estimate and compare the different dynamic mortality ratios and highlight their differences. Informed by our modeling, we propose a more systematic method to determine mortality ratios during epidemic outbreaks and discuss sensitivity to confounding effects and errors in the data.
https://www.medrxiv.org/content/10.1101/2020.03.26.20044693v1
- From England a relatively easy to understand model about the repercussions of a lockdown strategy to tackle the COVID-19 pandemic and to spark discussion and thought. Here we use simple stochastic simulations to evaluate different approaches taken to tackle the crisis, along with the efficiency they will hold and the number of casualties they may incur. It is clear that the less strict the social distancing the more time it will take for life to return to normal, and the more lives will be at risk. This is shown through simulations formed by an open sourced code, which allows evaluation of the outcomes from different intervention scenarios or conditions.
https://www.medrxiv.org/content/10.1101/2020.03.29.20046870v1

NEWLY REGISTERED CLINICAL TRIALS

- I posted a link the other day about the possibility of BCG vaccine being protective. Here's a new Dutch trial that will look at this. They will look at whether health care workers can be protected through vaccination by looking at absenteeism among those who have direct patient contact. NCT04328441 also an Australian trial: NCT04327206

- Maybe this falls into the 'any port in a storm' category. An Egyptian trial will look at the efficacy of natural honey treatment. Natural honey has been well known for its high health properties in diabetes, nutrition, dyslipidemia, skin lesions and it got FDA approval for topical wound treatment in 2007 as the most potent antimicrobial agent. Honey has been previously considered as an alternative for acyclovir in the treatment of herpes simplex virus 1 (HSV-1) and it also demonstrated for its significant antiviral effect against varicella zoster virus (VZV). Many studies have demonstrated the broad spectrum antimicrobial effect of honey as an antibacterial, anti fungal, antiviral and antimycobacterial. The National Institute for Health and Care Excellence (NICE) and the Public Health England (PHE) guidelines recommended honey as a first line of treatment for acute cough caused by upper respiratory tract infection which is currently a cornerstone symptom in COVID-19 infectious disease. Moreover, natural honey should no longer be used as "alternative" and deserves to gain more attention by scientists and researchers. The aim of this trial is to study the efficacy of natural honey in treatment of patients infected with COVID-19 in comparison with current standard care. NCT04323345

CLINICAL TRIAL RESULTS

- Observational analysis of data on children indicating that they are unlikely to have been the primary source of household SARS-CoV-2 infections. FINDINGS: Drawing on studies from China, Singapore, South Korea, Japan, and Iran a broad range of clinical symptoms were observed in children. These ranged from asymptomatic to severe disease. Of the 31 household transmission clusters that were identified, 9.7% (3/31) were identified as having a paediatric index case. This is in contrast other zoonotic infections (namely H5N1 influenza virus) where 54% (30/56) of transmission clusters identified children as the index case. INTERPRETATION: Whilst SARS-CoV-2 can cause mild disease in children, the data available to date suggests that children have not played a substantive role in the intra-household transmission of SARS-CoV-2. https://www.medrxiv.org/content/10.1101/2020.03.26.20044826v1
- Here is a randomized trial from Wuhan with hydroxychloroquine that suggests benefit. From February 4 to February 28, 2020, 62 patients suffering from COVID-19 were diagnosed and admitted to Renmin Hospital of Wuhan University. All participants were randomized in a parallel-group trial, 31 patients were assigned to receive an additional 5-day HCQ (400 mg/d) treatment, Time to clinical recovery (TTCR), clinical characteristics, and radiological results were assessed at baseline and 5 days after treatment to evaluate the effect of HCQ. Key findings: For the 62 COVID-19 patients, 46.8% (29 of 62) were male and 53.2% (33 of 62) were female, the mean age was 44.7 (15.3) years. No difference in the age and sex distribution between the control group and the HCQ group. But for TTCR, the body temperature recovery time and the cough remission time were significantly shortened in the HCQ treatment group. Besides, a larger proportion of patients with improved pneumonia in the HCQ treatment group (80.6%, 25 of 32) compared with the control group (54.8%, 17 of 32). Notably, all 4 patients progressed to severe illness that occurred in the control group. However, there were 2 patients with mild adverse reactions in the HCQ treatment group. Significance: Among patients with COVID-19, the use of HCQ could significantly shorten TTCR and promote the absorption of pneumonia. [**NOTE: they excluded patients with severe and critical illness]**
  https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v1

- Small observational study from China on patients who fully recovered. This single-center, retrospective, and observational study included 55 patients with COVID-19 who were transferred to Shenyang Sixth People's Hospital between January 20 and March 15, 2020. Demographic information, symptoms, laboratory indicators, treatment processes, and clinical outcomes were collected. Administered drugs and intervention times were compared in 47 and eight patients with mild and severe symptoms, respectively. Findings: All 55 patients recovered. Fifty-three patients (96.36%) received antiviral therapy, including 45 in the mild group (median treatment: 14 days; 17 received umifenovir) and all eight severe-group patients (median treatment: 17.5 days; four received lopinavir/ritonavir). Twenty-nine patients (52.72%) were administered antibiotics, including 21 in the mild group (median treatment: 13.5 days; 15 received moxifloxacin) and all eight in the severe group (median treatment: 9 days; two received linezolid). Moreover, seven patients (12.72%) were treated with glucocorticoids and nine (16.36%) with immunomodulators. Interpretation: Given the 100% recovery rate, early administration of antiviral drugs can be considered. Umifenovir may benefit patients with mild symptoms, while lopinavir/ritonavir may benefit those with severe symptoms. Prophylactic administration of common antibiotics may reduce the risk of co-infection. The use of glucocorticoids is usually not necessary.
https://www.medrxiv.org/content/10.1101/2020.03.28.20045955v1

DRUG DEVELOPMENT

- A group from IBM looks at the main protease of SARS-CoV-2 with respect to ligand binding. Some of the compounds that came up have very poor bioavailability (curcurmin from turmeric) but could serve as platforms for drug design [**note: probably not useful in a pandemic response**]. The HIV protease inhibitor, nelfinavir, had good binding properties.
https://chemrxiv.org/articles/In_Silico_Exploration_of_Molecular_Mechanism_and_Potency_Ranking_of_Clinically_Oriented_Drugs_for_Inhibiting_SARS-CoV-2_s_Main_Protease/12045549

DIAGNOSTIC DEVELOPMENT

- An interesting paper from China shows that an antibody test outperforms a RT-PCR test!! Data were compared between IgM-IgG antibody test and real-time RT-PCR detection for COVID-19 patients. Results: Of 133 patients with SARS-CoV-2 infection, there were 44 moderate cases, 52 severe cases, and 37 critical cases with no significant difference of gender and age among three subgroups. Overall, the positive ratio in IgM antibody test was higher than in RT-PCR detection. In RT-PCR detection, the positive ratio was 65.91%, 71.15%, and 67.57% in moderate, severe, and critical cases, respectively. Whereas, the positive ratio of IgM/IgG antibody detection in patients was 79.55%/93.18%, 82.69%/100%, and 72.97%/97.30% in moderate, severe, and critical cases, respectively. Moreover, the concentrations of antibodies were also measured in three subgroups. Conclusion: The IgM-IgG antibodies-based test exhibited a comparative superiority to the NAT for COVID-19 diagnosis, which provides an effective complement to the false negative results from NAT for SARS-CoV-2 infection diagnosis.
https://www.medrxiv.org/content/10.1101/2020.03.28.20045765v1

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2020-04-01

Lots of pre-prints today; I guess there was a lot of work being done over the weekend. I've been posting some music links that have inspired me. One of the pieces that I find most spiritual is the Chaconne from Bach's second partita for unaccompanied violin. Here is a nice rendition by the Bulgarian/American violinist, Bella Hristova, filmed at the Curtis Institute: https://www.youtube.com/watch?v=XkfsGCIiHb4

I'm a big fan of podcasts and listen to them when I'm out walking, in my car, or working out. I may have already mentioned that Noah Feldman, a law professor at Harvard, has a very good one called 'Deep Background' https://pushkin.fm/deep-background (all of his podcasts are at the link). Yesterday, he had a conversation with Nobel Laureate in Economics Paul Romer and the discussion moved quickly to massive testing of the US population beyond what is being done right now. Romer, as we all do, wants to get people back to work and massive testing to find those who have not had SARS-CoV-2 or had it and have recovered would help solve this problem. There are obvious issues such as drastically ramping up test kits and keeping track of those who test negative, but in this day of big data and even bigger projects, this strikes me as the key one to undertake. Romer argued the point well and it's worth a half hour to listen to it.

There is a nice paper in the New England Journal of Medicine on renin-angiotensin-aldosterone system inhibitors in patients with SARS-CoV-2 https://www.nejm.org/doi/full/10.1056/NEJMsr2005760 (free text). On the basis of the available evidence, we think that, despite the theoretical concerns and uncertainty regarding the effect of RAAS inhibitors on ACE2 and the way in which these drugs might affect the propensity for or severity of Covid-19, RAAS inhibitors should be continued in patients in otherwise stable condition who are at risk for, are being evaluated for, or have Covid-19.

I've been corresponding with some economists on a number of issues. I got an email yesterday morning from one of them telling me a blood test was just approved by the FDA. Hot damn I thought. Sure enough there were a lot of press reports coming out including from Reuters, Axios and others. I looked up the company BODYSPHERE which I had never heard of. There was a website with four COVID-19 products in addition to the diagnostic test and this was an unsecured website which seemed odd (there were other things wrong with the website as well). There was also no FDA announcement, no announcement in the two national papers I regularly read (NY Times and Washington Post) nor was there any mention in the press briefing where Drs. Fauci and Birx talked about the need for a serology test. **This looks like a hoax of the highest value.** The press if forgetting the classic aphorism, "trust but verify."

MODELING

- There has been conjecture that with increasing temperatures through spring and into summer, SARS-CoV-2 cases would drop. This Saudi paper indicates this may not be so [**note: it's**

observational and based on only one country]
https://www.medrxiv.org/content/10.1101/2020.03.29.20046706v1

- A German team looks at daily reproduction numbers of SARS-CoV-2 based on death cases and suggests a more rapid initial spread in Italy and the US. Thus, our analysis provides evidence that basic epidemiological parameters differ between countries to an extent compromising epidemiological predictions of the pandemic. It also suggests that suppression of spread in Italy and the US may be more difficult to achieve.
https://www.medrxiv.org/content/10.1101/2020.03.28.20046094v1

NEWLY REGISTERED CLINICAL TRIALS

- Here is a newly registered trial from Vanda Pharmaceuticals looking at the efficacy of tradipitant, a neurokinin 1 antagonist. It works by blocking substance P, a small signaling molecule. The compound was first developed by Eli Lilly. 85 mg orally given twice daily to treat inflammatory lung injury associated with severe or critical COVID-19 infection. NCT04326426

CLINICAL TRIAL RESULTS

- No new pre-prints

DRUG DEVELOPMENT

- The Coalition for Epidemic Preparedness Innovations have a very nice piece in the New England Journal of Medicine about developing vaccines at pandemic speed. It does a good job of identifying bottlenecks in development and issues in scale up.
https://www.nejm.org/doi/full/10.1056/NEJMp2005630 and it is not behind their paywall.
- Here is a computer analysis of the structure of SARS-CoV-2 and the prediction of human interactome. We calculated the structural properties of >2500 coronaviruses and computed >100000 human protein interactions with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Using the CROSS method, we found that the SARS-CoV-2 region encompassing nucleotides 23000 and 24000 is highly conserved at the structural level, while the region 1000 nucleotides up-stream varies significantly. The two sequences code for a domain of the spike S protein that binds to the host receptor angiotensin-converting enzyme 2 (ACE2) that mediates human infection and in the homologue from Middle East respiratory syndrome coronavirus (MERS-CoV) interacts with sialic acids. We predicted structured regions at the 5 prime and 3 prime ends where our calculations indicate strong propensity to bind proteins. Using the catRAPID method, we computed 3500 protein interactions with the 5 prime end and identified Cyclin T1 CCNT1, ATP-dependent RNA helicase DDX1, Zinc Finger Protein ZNF175 and other 20 high-confidence candidate partners. We propose these proteins, also implicated in HIV replication, to be further investigated for a better understanding of host-virus interaction mechanisms. https://www.biorxiv.org/content/10.1101/2020.03.28.013789v1

- Azithromycin and ciprofloxacin have a chloroquine-like effect on respiratory epithelial cells, from researchers at the University of New Mexico. There is interest in the use of chloroquine/hydroxychloroquine (CQ/HCQ) and azithromycin (AZT) in COVID-19 therapy. Employing cystic fibrosis respiratory epithelial cells, here we show that drugs AZT and ciprofloxacin (CPX) act as acidotropic lipophilic weak bases and confer in vitro effects on intracellular organelles similar to the effects of CQ. These seemingly disparate FDA-approved antimicrobials display a common property of modulating pH of endosomes and trans-Golgi network. We believe this may in part help understand the potentially beneficial effects of CQ/HCQ and AZT in COVID-19, and that the present considerations of HCQ and AZT for clinical trials should be extended to CPX.
  https://www.biorxiv.org/content/10.1101/2020.03.29.008631v1
- From the University of Michigan, computational design of peptides to block binding of the SARS-CoV-2 spike protein to human ACE2. Though peptides may not be useful as drug therapy because of delivery issues, studies such as this can better model small molecule interactions with the viral binding site.
- Some more good work from China, lectin-like intestinal defensin inhibits SARS-CoV-2 binding to ACE2. Angiotensin-converting enzyme-2 (ACE2) is a receptor of 2019-nCoV spike 1 protein (S1) and mediates viral entry into host cells. Despite the abundance of ACE2 in small intestine, few digestive symptoms are observed in patients infected by 2019-nCoV. Herein, we investigated the interactions between ACE2 and human defensins (HDs) specifically secreted by intestinal Paneth cells. The lectin-like HD5, rather than HD6, bound ACE2 with a high affinity of 39.3 nM and weakened the subsequent recruitment of 2019-nCoV S1. The cloak of HD5 on the ligand-binding domain of ACE2 was confirmed by molecular dynamic simulation. A remarkable dose-dependent preventive effect of HD5 on 2019-nCoV S1 binding to intestinal epithelial cells was further evidenced by in vitro experiments. Our findings unmasked the innate defense function of lectin-like intestinal defensin against 2019-nCoV, which may provide new insights into the prevention and treatment of 2019-nCoV infection.
  https://www.biorxiv.org/content/10.1101/2020.03.29.013490v1
- From Italian scientists in Milan, an in vitro evaluation of hydroxychloroquine on Vero cells. In this study, we evidence that the anti-SARS-CoV2 activity of a clinically achievable hydroxychloroquine concentration is maximized only when administered before and after the infection of Vero E6 cells. This strongly suggests that only a combined prophylactic and therapeutic use of hydroxychloroquine may be effective in limiting viral replication in patients.
  https://www.biorxiv.org/content/10.1101/2020.03.29.014407v1
- Here is a Chinese report of preparation of fully human single-domain antibodies against SARS-CoV-2. We describe here the development of a phage-displayed single-domain antibody library by grafting naive CDRs into framework regions of an identified human germline IGHV allele. This enabled the isolation of high-affinity single-domain antibodies of fully human origin. The panning using SARS-CoV-2 RBD and S1 as antigens resulted in the identification of antibodies targeting five types of neutralizing or non-neutralizing epitopes on SARS-CoV-2 RBD. These fully human single-domain antibodies bound specifically to SARS-CoV-2 RBD with subnanomolar to low nanomolar affinities. Some of them were found to potently neutralize pseudotyped and live virus, and therefore may represent promising candidates for prophylaxis and therapy of COVID-19. This study also reports unique immunogenic profile of SARS-CoV-2 RBD compared to that of

SARS-CoV and MERS-CoV, which may have important implications for the development of effective vaccines against SARS-CoV-2.
https://www.biorxiv.org/content/10.1101/2020.03.30.015990v1

- From Canada, another paper that predicts interactions of SARS-CoV-2 with the human interactome. Modeling studies such as this can help identify the most promising targets for drug design. we leverage two state-of-the-art, sequence-based PPI predictors (PIPE4 & SPRINT) capable of generating the comprehensive SARS-CoV-2 vs. human interactome, comprising approximately 285,000 pairwise predictions. Of these, we identify the high-scoring subset of human proteins predicted to interact with each of the 14 SARS-CoV-2 proteins by both methods, comprising 279 high-confidence putative interactions involving 225 human proteins. Notably, the Spike-ACE2 interaction was the highest ranked for both the PIPE4 and SPRINT predictors, corroborating existing evidence for this PPI. Furthermore, the PIPE-Sites algorithm was used to predict the putative subsequence that might mediate each interaction and thereby inform the design of inhibitory polypeptides intended to disrupt the corresponding host-pathogen interactions. https://www.biorxiv.org/content/10.1101/2020.03.29.014381v1
- Here's a paper from FDA scientists on the sequence analysis of the SARS-CoV-2 genome and features important for vaccine design. We performed comprehensive in silico analyses of several features of SARS-CoV-2 genomic sequence (e.g., codon usage, codon pair usage, dinucleotide/junction dinucleotide usage, RNA structure around the frameshift region) in comparison with other members of the coronaviridae family of viruses, the overall human genome, and the transcriptome of specific human tissues such as lung, which are primarily targeted by the virus. Our analysis identified the spike (S) and nucleocapsid (N) proteins as promising targets for deoptimization and suggests a roadmap for SARS-CoV-2 vaccine development, which can be generalizable to other viruses. [**note: I haven't seen details on the J&J/BARDA vaccine but I think that is the path they took**]
https://www.biorxiv.org/content/10.1101/2020.03.30.016832v1

- From Univ of Texas Southwestern Medical School, here is a list of identified FDA-approved drugs targeted against Mpro (main protease). The top hits bound to the central site of Mpro substrate-binding pocket include antiviral drugs such as Darunavir, Nelfinavir and Saquinavir, some of which are already being tested in Covid-19 patients. Interestingly, one of the most promising hits in our screen is the hypercholesterolemia drug Rosuvastatin. In addition, the top hits bound to the terminal site of Mpro substrate-binding pocket include the anti-asthma drug Montelukast and the anti-histaminic Fexofenadine among others. [**note: I volunteer to be a CT of one as I've been taking fexofenadine for the past three weeks as it's seasonal tree pollen time here in the DC area. Unfortunately, I still have an allergic cough and only a test would rule out SARS-CoV2** *I needed to inject some humor into this daily report*]
https://chemrxiv.org/articles/Identification_of_FDA_Approved_Drugs_Targeting_COVID-19_Virus_by_Structure-Based_Drug_Repositioning_Version_2_/12049647

- I haven't seen anything like this one, a group of researchers from Nashville do some screening of food bioactive compounds to predict potential inhibitors of Mpro and RdRp. The results showed that Phycocyanobilin, Riboflavin, Cyanidin, Daidzein, Genistein are potent inhibitor bioactive

compounds to Mpro and RdRp in comparison to antiviral drugs. Though, further in vitro and/or in vivo research is required to validate the docking results. https://chemrxiv.org/articles/In_silico_Screening_of_Food_Bioactive_Compounds_to_Predict_Potential_Inhibitors_of_COVID-19_Main_protease_Mpro_and_RNA-dependent_RNA_polymerase_RdRp_/12051927

- Another study of potential inhibitors of Mpro Virtual screening has identified a number of antiviral drugs, top ten of which on the basis of their bending energy score are further examined through molecular docking with Mpro. Docking studies revealed that drug Lopinavir-Ritonavir, Tipranavir and Raltegravir among others binds in the active site of the protease with similar or higher affinity than the crystal bound inhibitor α-ketoamide. https://chemrxiv.org/articles/In_Silico_Identification_and_Docking-Based_Drug_Repurposing_Against_the_Main_Protease_of_SARS-CoV-2_Causative_Agent_of_COVID-19/12049590

DIAGNOSTIC DEVELOPMENT

- From the University of Texas, a one-enzyme RT-qPCR assay for SARS-CoV-2, and procedures for reagent production. Given the scale of the ongoing COVID-19 pandemic, the need for reliable, scalable testing, and the likelihood of reagent shortages, especially in resource-poor settings, we have developed a RT-qPCR assay that relies on an alternative to conventional viral reverse transcriptases, a thermostable reverse transcriptase / DNA polymerase (RTX)1. Here we show that RTX performs comparably to the other assays sanctioned by the CDC and validated in kit format. We demonstrate two modes of RTX use - (i) dye-based RT-qPCR assays that require only RTX polymerase, and (ii) TaqMan RT-qPCR assays that use a combination of RTX and Taq DNA polymerases (as the RTX exonuclease does not degrade a TaqMan probe). We also provide straightforward recipes for the purification of this alternative reagent. We anticipate that in low resource or point-of-need settings researchers could obtain the available constructs from Addgene or our lab and begin to develop their own assays, within whatever regulatory framework exists for them. https://www.biorxiv.org/content/10.1101/2020.03.29.013342v1

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2020-04-02

Today's musical selection is indie rocker Grace Potter who pays a visit to Darryl Hall's house (this was a wonderful show that ran for five years where Hall invited singers of all genres to come to his home studio and play). The song is Low Road, one that I've always enjoyed: https://youtu.be/jt5rKGsMKyM

Finally, some good news on the diagnostic front as FDA approved the first serological test for SARS-CoV-2. Now some bad news, states are still not getting enough tests, particularly the new Abbott rapid test: https://www.washingtonpost.com/health/2020/04/01/scramble-rapid-coronavirus-tests-everybody-wants/ I watched a bit of the White House Task Force briefing last night and they still don't get it. Dr. Birx was asked about testing and she said they are enlisting universities to start running ELISA assays to help out. Until we can do testing on a massive scale and more than the million tests a week that some

are asking for things will remain unsettled. A widely deployed serological test will be extremely helpful in identifying the background infection level and getting people back to work. *End of Rant!!!*

The other problem is that there is not a coherent plan for conducting clinical trials in a pandemic. Single site trials won't cut it. This is where multicenter trials with a single central IRB and DSMB should be mandatory. Data acquisition and analysis should all be automatic, and results aggregated in real time. Pharma companies do this well (I remember having Pfizer come into PhRMA for a presentation of how they ran trials world-wide with such a platform and this was back in 2002!!!!) Good drugs should be kept in the study and those that don't work, kicked out. I'm going to try to write something up on this and have contacted FDA to see what they might be doing. *End of 2nd Rant!!!*

There has been a lot of discussion about the presence of SARS-CoV-2 on environmental surfaces and in the air. Some researchers in Singapore measured this in the worst case scenario, hospital rooms of infected patients. Measurements: Extent of environmental surface contamination in AIIRs of 30 COVID-19 patients by PCR on environmental swabs. The particle size distribution of SARS-CoV-2 in the air was measured using NIOSH air samplers. Results: 245 surface samples were collected from 30 rooms of COVID-19 patients, and air sampling was conducted in 3 rooms. 56.7% of the rooms had at least one environmental surface contaminated, with 18.5% of the toilet seats and toilet flush button being contaminated. High touch surface contamination was shown in ten (66.7%) out of 15 patients in the first week of illness, and three (20%) beyond the first week of illness (p = 0.010). Air sampling of two COVID-19 patients (both day 5 of symptoms) detected SARS-CoV-2 PCR-positive particles of sizes >4 μm and 1-4 μm. In a single subject at day 9 of symptoms, no SARS-CoV-2 PCR-positive particles were detected. Limitations: Viral culture results were not available to assess the viability of the virus contaminating the air and surface. Conclusion: Environmental contamination was detected in rooms with COVID-19 patients in early stages of illness, but was significantly less after day 7 of disease. Under AIIR conditions, SARS-CoV-2 respiratory particles can be detected at sizes 1-4 μm and >4 μm in diameter in the air which warrants further studies. https://www.medrxiv.org/content/10.1101/2020.03.29.20046557v1

MODELING

- Swiss model predicting growth and containment using AI and big data. The predictions estimate that between 22 February and 11 April 2020, there will be 720 deaths from 83300 COVID-19 cases, and 73300 will have recovered; our preliminary variability in these estimates is about 21% over the aforementioned period. In the absence of governmental intervention, 42.7% of the Swiss population would have been infected by 25 April 2020 compared to our prediction of a 1% infection over this time period, saving thousands of lives. It is argued that future scenarios regarding relaxation of the lockdown should be carefully simulated, as by 19 April 2020, there will still remain a substantial number of infected individuals, who could retrigger a second spread of COVID-19. https://www.medrxiv.org/content/10.1101/2020.03.30.20047472v1
- Here's an Italian paper analyzing the outbreak there. They predict that the new infection rate should begin decreasing the first week in April. We statistically investigate the COVID-19 epidemics, which is particularly invasive in Italy. We show that the high apparent mortality (or Case Fatality Ratio, CFR) observed in Italy, as compared with other countries, is likely biased by a strong underestimation of infected cases. To give a more realistic estimate of the mortality of Covid-19, we use the most recent estimates of the IFR (Infection Fatality Ratio) of epidemic, based on CFR for Germany, and furthermore analyse data obtained from the ship Diamond

Princess, a good representation of a laboratory case-study from an isolated system in which all the people have been tested. From such analyses we try to derive more realistic estimates of the real extension of the infection, as well as more accurate indicators of how fast the infection propagates. We then try to point out, from the various explanations proposed, the dominant factors causing such an abnormal seriousness of the disease in Italy. Finally, we use the deceased data, the only ones estimated to be reliable enough, to predict the total number of infected people and the interval of time when the infection in Italy could stop.
https://www.medrxiv.org/content/10.1101/2020.03.28.20046243v1

- This British paper explores a variety of models that can help lead to policy decisions. By combining an epidemiological model of COVID-19 for the United Kingdom with simple sub-models for these societal processes, this study aims to shed light on the conceivable trajectories that the pandemic might follow over the next 1.5 years. We show strong improvements in outcomes if governments review NPI more frequently whereas, in comparison, the stability of compliance has surprisingly small effects on cumulative mortality. Assuming that mortality does considerably increase once a country's hospital capacity is breached, we show that the inherent randomness of societal processes can lead to a wide range of possible outcomes, both in terms of disease dynamics and mortality, even when the principles according to which policy and population operate are identical.. Our model is easily modified to take other aspects of the socio-pandemic interaction into account.
https://www.medrxiv.org/content/10.1101/2020.03.30.20047597v1
- This Spanish paper is intriguing as it tries to deal with the large number of unreported cases. Building that into the model, mortality rates significantly drop [**note: we need more testing**] I show that, after few days from the beginning of the outbreak, the apparent death rate can be extrapolated to infinite time through regularized regression such as rescaled ridge regression. The variation from country to country of these extrapolated death rates appears to depend almost only (r^2=0.91) on the ratio between performed tests and detected cases even when the instantaneous apparent lethality rates are as different as 9% in Italy and 0.4% in Germany. Extrapolating to the limit of infinite number of tests, I obtain a death rate of 0.012+/- 0.012, in agreement with other estimates. The inverse relationship between the extrapolated death rate and the intensity tests allows estimating that more than 50% of cases were undetected in most countries, with more than 90% undetected cases in countries severely hit by the epidemics such as Italy. Finally, I propose to adopt the ratio between the cumulative number of recovered and deceased persons as an indicator that can anticipate the halting of the epidemics.
https://www.medrxiv.org/content/10.1101/2020.03.27.20045062v1

NEWLY REGISTERED CLINICAL TRIALS

- A Belgium trial using the GM-CSF, sargramostim, has been registered. Phase IV study to evaluate the effectiveness of additional inhaled sargramostim (GM-CSF) versus standard of care on blood oxygenation in patients with COVID-19 coronavirus infection and acute hypoxic respiratory failure. NCT04326920

- Here is a German trial looking at removing cytokines via extracorporeal adsorption. Our primary goal is to investigate the efficacy of treatment with a CytoSorb® adsorber in patients with severe

COVID-19 disease requiring venous ECMO over 72 hours after initiation of ECMO. The primary endpoint is the reduction of plasma interleukin-6 levels 72 hours after initiation of ECMO support. As secondary endpoints we investigate 30-day survival, vasopressor and volume requirements, lactate in terms of lactate and platelet function. As safety variables, we further investigate the levels of the applied antibiotics (usually ampicillin and sulbactam). NCT04324528

- Here is an Irish study that proposes to look at the impact of various ACE inhibitors and their impact on infection by SARS-CoV-2. Early reports from China and Italy suggest that many of those who die from COVID-19 have a coexisting history of hypertension. Consequently, there have been questions raised as to whether these 2 types of blood pressure medication might increase the risk of death among patients with COVID-19. However, it is well known that the prevalence of hypertension increases linearly with age. Therefore, it is possible that the high prevalence of hypertension and ACEi/ARB use among persons who die from COVID-19 is simply confounded by age (older people are at risk of both a history of hypertension and dying from COVID-19). Whether these commonly prescribed blood pressure medications increase the risk of COVID-19 or not remains unanswered. Statements from professional cardiology societies on both sides of the Atlantic have called for urgent research into this question. Our study aims to randomize patients with primary (essential) hypertension who are already taking ACEi/ARB to either switch to an alternative BP medication or continue with the ACEi/ARB that they have already been prescribed. Adults with compelling indications for ACEi/ARB will not be enrolled. NCT04330300

CLINICAL TRIAL RESULTS

- Derek Lowe has a very nice blog post comparing hydroxychloroquine trials. I was not aware of the PK information and how long it hangs around: A 200mg oral dose hits its Cmax in the 3-hour range, but boy, does it tail off slowly after that: plasma half-life is 123 days (!) with a large volume of distribution (extensive uptake in tissue). https://blogs.sciencemag.org/pipeline/archives/2020/03/31/comparing-chloroquine-trials
- Here is a Chinese study of the impact of low molecular weight heparin (LMWH). Patients in the study were divided into a heparin and a control group based on whether low molecular weight heparin (LMWH) was used. D-dimer, C-reactive protein (CRP), peripheral blood lymphocyte percentage, interleukin-6, and other indices in 42 patients with novel coronavirus pneumonia were retrospectively analyzed to compare and evaluate the progress of patients before and after LMWH treatment. Results Compared to the control group, D-dimer levels in the heparin group significantly increased before treatment, and there was no significant difference after treatment. There was no significant difference in the change of CRP levels between the two groups of patients before and after LMWH treatment, and levels for both groups were significantly lower after, compared to before, treatment. Compared to the control group, patients in the heparin group had a higher percentage of lymphocytes after treatment and lower levels of interleukin-6; these differences were statistically significant. Conclusions Under conventional antiviral treatment regimens, LMWH can improve hypercoagulability, inhibit IL-6 release, and counteract IL-6 biological activity in patients. LMWH has potential antiviral effects and can help delay or block inflammatory cytokine storms. It can also increase the lymphocytes

(LYM%)of patients and has the potential for treatment of COVID-19. [**note: though it is a small study, it suggests LMWH will be clinically useful in treating patients that have progressed to pneumonia**] https://www.medrxiv.org/content/10.1101/2020.03.28.20046144v1

DRUG DEVELOPMENT

- A group at Emory have discovered a novel new antiviral that targets the RNA polymerase. Unlike remesdivir, EIDD-2801 can be given orally. The mode of action appears to be different from the Gilead drug. It's been licensed out to Ridgeback, a small company. The is no human tox data for this drug and whether they can shorten development time is unknown. https://cen.acs.org/biological-chemistry/infectious-disease/Emory-discovered-antiviral-poised-COVID/98/i12?utm_source=Newsletter&utm_medium=Newsletter&utm_campaign=CEN
- Here is a molecular docking study of some phytochemicals that have displayed some antiviral activity in other studies. The compounds Scopodulic acid and Dammarenolic acid showed the best-fit value of activity against SARS-CoV-2 spike glycoprotein 6vsb and main protease Mpro 6lu7 targets, respectively. Our data suggest silibinin a repurposing candidate drug may have multitarget activity against SARS-CoV-2. So further in vitro and in vivo evaluations are recommended. https://www.biorxiv.org/content/10.1101/2020.03.31.017657v1
- This is the first Algerian paper I've seen. They use molecular docking to examine compounds from the medicinal plant Nigella Sativa. Nigellidine and α- Hederin appeared to have the best potential to act as COVID-19 treatment and were equivalent or better in binding simulation to hydroxychloroquine and favipiravir. https://chemrxiv.org/articles/Identification_of_Compounds_from_Nigella_Sativa_as_New_Potential_Inhibitors_of_2019_Novel_Coronasvirus_Covid-19_Molecular_Docking_Study_/12055716

DIAGNOSTIC DEVELOPMENT

- No April Fools joke!!! FDA just issued an EUA for a serological test!!!!!!! The company is Cellex Inc down in Research Triangle, NC. Here is the link to the letter that describes the test in more detail: https://www.fda.gov/media/136622/download It's restricted CLIA certified laboratories. Run time is 20 minutes and requires a venus puncture sample.
- Yale group on the sensitivity of different RT-PCR assays. we generated RNA transcripts to create standards and distributed them to other laboratories for internal validation. We then used these RNA transcript standards, full-length SARS-CoV-2 RNA, and RNA-spiked mock samples to determine analytical efficiency and sensitivity of nine primer-probe sets. We show that all primer-probe sets can be used to detect SARS-CoV-2, but there are clear differences in the ability to differentiate between true negatives and positives with low amounts of virus. Adding to this, many primer-probe sets, including the "N2" and "N3" sets issued by the US Centers for Disease Control and Prevention, have background amplification with SARS-CoV-2-negative nasopharyngeal swabs, which may lead to inconclusive results. Our findings characterize the limitations of commonly used primer-probe sets and can assist other laboratories in selecting appropriate assays for the detection of SARS-CoV-2. https://www.medrxiv.org/content/10.1101/2020.03.30.20048108v1

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2020-04-03

Today's music selection is one of the great country songs that goes back to the Appalachian hill country. Though it started off as a church hymn, the words were reworked and A.P. Carter reworked the words so that it was funereal in nature. Despite the somber nature, it can be uplifting to listen to. Here is a video of the second all-star recording by the Nitty Gritty Dirt Band: https://www.youtube.com/watch?v=7bRJLkNqNXI The first version was featured in Ken Burns's Country Music documentary that was aired on PBS last fall and featured one of the original vocalists, Mother Maybelle Carter.

The OHDSI group that I've referenced in previous emails continues to do great work. Here is an observational trial that they just got up and running: https://beat19.org/ this type of out of the box thinking can make a contribution. More community studies are needed to look at Rx/OTC medication use and what their impact might be on viral infection and illness progression.

The Wuhan researcher continue to turn up interesting findings. Here, we investigated the infection of SARS-CoV-2 in cats by detecting specific serum antibodies. A cohort of serum samples were collected from cats in Wuhan, including 102 sampled after COVID-19 outbreak, and 39 prior to the outbreak. 15 of 102 (14.7%) cat sera collected after the outbreak were positive for the receptor binding domain (RBD) of SARS-CoV-2 by indirect enzyme linked immunosorbent assay (ELISA). Among the positive samples, 11 had SARS-CoV-2 neutralizing antibodies with a titer ranging from 1/20 to 1/1080. No serological cross-reactivity was detected between the SARS-CoV-2 and type I or II feline infectious peritonitis virus (FIPV). Our data demonstrates that SARS-CoV-2 has infected cat population in Wuhan during the outbreak. [**note: no report of feline mortality**] https://www.biorxiv.org/content/10.1101/2020.04.01.021196v1

I have clarified the serological test situation.

MODELING

- The preprint site is down right now. I'm not sure how worthwhile it is to provide more abstracts of modeling papers. I'll see what the landscape looks like tomorrow.

NEWLY REGISTERED CLINICAL TRIALS

- Here is an English trial looking at medicines that might prevent cardiac injury for those who progress to serious symptoms. Drugs in the study are: aspirin, clopidogrel, rivaroxaban, atorvastatin and omeprazole. NCT04333407
- Wow, first Iranian trial I've come across! It's a two arm trial: 1) levamisole and budesonide/formoterol inhaler; 2) hydroxychloroquine and lopinavir/ritonavir NCT04331470
- A Mexican trial will look at the cytokine modulator, ruxolitinib, to halt progression to acute pneumonia NCT04334044
- An Israeli trial is looking at Piclidenoson, an adenosine receptor agonist upon hospital administration. NCT04333472

CLINICAL TRIAL RESULTS

- Here is an interesting Swedish study looking at the protein expression profile of ACE2 in human tissues. Here, we aim to verify a reliable expression profile of ACE2 in all major human tissues and cell types. Based on stringently validated immunohistochemical analysis and high-throughput mRNA sequencing from several datasets, we found that ACE2 expression is mainly localized to microvilli of the intestinal tract and renal proximal tubules, gallbladder epithelium, testicular Sertoli cells and Leydig cells, glandular cells of seminal vesicle and cardiomyocytes. The expression in several other previously reported locations, including alveolar type II (AT2) cells, could not be confirmed. Furthermore, ACE2 expression was absent in the AT2 lung carcinoma cell line A549, often used as a model for viral replication studies. Our analysis suggests that the expression of ACE2 in the human respiratory system appears to be limited, and the expression of the receptor in lung or respiratory epithelia on the protein level is yet to be confirmed. **This raises questions regarding the role of ACE2 for infection of human lungs and highlights the need to further explore the route of transmission during SARS-CoV-2 infection.** https://www.biorxiv.org/content/10.1101/2020.03.31.016048v1
- This Swiss study may explain why the sense of smell is damaged upon SARS-CoV-2 infection. In the respiratory tract, these targets are ciliated cells. Interestingly, various reports indicate an association between SARS-CoV-2 infection and anosmia, suggesting an alteration not restricted to the respiratory tissue, but that might also include the olfactory sensory epithelium. We explored this possibility by generating RNA-seq libraries from human neuroepithelium, in which we found significant expression of ACE2 and TMPRSS2. To determine whether specific cell types of this chemosensory tissue may coexpress both of the virus entry genes, we analyzed a scRNA-seq dataset. We determined that sustentacular cells, which are in direct contact with the external world and maintain the integrity of olfactory sensory neurons, represents a prime candidate for SARS-CoV-2 infection via the nose, and possibly for SARS-CoV-2-induced anosmia. https://www.biorxiv.org/content/10.1101/2020.03.31.013268v1 [**note: I've wondered whether seasonal allergic symptoms resulting in the production of large amounts of nasal mucous might be protective. I still have my sense of smell and huge amounts of nasal drainage from tree pollen. My observational study of one.**]
- Here is one of the first Italian observational trials I've seen. Interesting finding. a more severe course of COVID-19 is associated with older age, comorbidities, and male sex. Hence, we searched for possible genetic components of the peculiar severity of COVID-19 among Italians, by looking at expression levels and variants in *ACE2* and *TMPRSS2* genes, which are crucial for viral infection. **Methods**: Exome and SNP array data from a large Italian cohort representative of the country's population were used to compare the burden of rare variants and the frequency of polymorphisms with European and East Asian populations. Moreover, we looked into gene expression databases to check for sex-unbalanced expression. **Results**: While we found no significant evidence that *ACE2* is associated with disease severity/sex bias in the Italian population, *TMPRSS2* levels and genetic variants proved to be possible candidate disease modulators, contributing to the observed epidemiological data among Italian patients. **Conclusions**: Our analysis suggests a role for *TMPRSS2* variants and expression levels in modulating COVID-19 severity, a hypothesis that fosters a rapid experimental validation on large

cohorts of patients with different clinical manifestations.
https://www.medrxiv.org/content/10.1101/2020.03.30.20047878v1

DRUG DEVELOPMENT

- A group from Lyon has advantageously used human reconstituted airway epithelial models of nasal or bronchial origin to characterize viral infection kinetics, tissue-level remodeling of the cellular ultrastructure and transcriptional immune signatures induced by SARS-CoV-2. Our results underline the relevance of this model for the preclinical evaluation of antiviral candidates. Foremost, we provide evidence on the antiviral efficacy of remdesivir and the therapeutic potential of the remdesivir-diltiazem combination as a rapidly available option to respond to the current unmet medical need imposed by COVID-19.
https://www.biorxiv.org/content/10.1101/2020.03.31.017889v1
- Here is a Chinese study that uses proteomics to reveal potential virulence factors influencing SARS-CoV-2 pathogenesis. We exploited an integrated proteomics approach to systematically investigate intra-viral and virus-host interactomes for the identification of unrealized SARS-CoV-2 host targets and participation of cellular proteins in the response to viral infection using peripheral blood mononuclear cells (PBMCs) isolated from COVID-19 patients. Using this approach, we elucidated 251 host proteins targeted by SARS-CoV-2 and more than 200 host proteins that are significantly perturbed in COVID-19 derived PBMCs. From the interactome, we further identified that non-structural protein nsp9 and nsp10 interact with NKRF, a NF-kB repressor, and may precipitate the strong IL-8/IL-6 mediated chemotaxis of neutrophils and overexuberant host inflammatory response observed in COVID-19 patients. Our integrative study not only presents a systematic examination of SARS-CoV-2-induced perturbation of host targets and cellular networks to reflect disease etiology, but also reveals insights into the mechanisms by which SARS-CoV-2 triggers cytokine storms and represents a powerful resource in the quest for therapeutic intervention.
https://www.biorxiv.org/content/10.1101/2020.03.31.019216v1

DIAGNOSTIC DEVELOPMENT

- I'm not an expert in device regulations. In the re-write of the guidance document for diagnostics, FDA allows tests to be distributed with self-validation by the company with qualifications that it has not been reviewed by the FDA and the company is not pursuing a EUA. In other words, **these tests are self-validated by the company**. They must have a disclaimer that results from antibody testing should not be used as the sole basis to diagnose SARS-CoV-2 infection or to inform infection status. Positive results may be due to past or present infection with non-SARS-CoV-2 strains. Here's the link to the FDA site https://www.fda.gov/medical-devices/emergency-situations-medical-devices/faqs-diagnostic-testing-sars-cov-2#5e861f4e0e33a lots of companies, mostly Asian are listed. Bottom line – there is still only one test that has been reviewed by the FDA.

Dr. Birx was asked about this the other day at a White House briefing and said this is not a priority right now. Amazing!! Why hasn't the FDA and CDC worked together with interested parties to come up with universal validation criteria. This is another failure of imagination.

For those who want a primer on antibody testing, Derek Lowe has a concise blog post: https://blogs.sciencemag.org/pipeline/archives/2020/04/02/antibody-tests-for-the-coronavirus

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2020-04-04

The musical choice for today is the beautiful tenor/baritone duet from Bizet's Pearl Fishers: https://www.youtube.com/watch?v=yfvjWD4GGck The setting is unusual and would be frowned upon right now. This is my favorite duet and one that I've sung several times with baritone colleagues.

Oracle has built and donated to the US government a Therapueutic Learning System that allows physicians and patients to record the effectiveness of promising COVID-19 drug therapies. These drugs, like Hydroxychloroquine, Remdesivir, and Kaletra, have been safely used to treat other diseases but are not yet definitively proven to be effective against COVID-19. Physicians are now routinely prescribing these drugs to treat COVID-19 patients. The Oracle Therapeutic Learning System lets the physician record the patient's daily progress. By collecting this real-world patient data throughout the United States now, and throughout the world soon thereafter, we will quickly discover which of the new drugs are most effective against COVID-19, their optimal dosages, and how early in the disease progression the drugs need to be administered. In this way, each patient will participate in the fight against this deadly virus.

MODELING

- Nothing new.

NEWLY REGISTERED CLINICAL TRIALS

- Not sure what to make of this one; Iranian trial to look at the iron chelator, deferoxamine in patients with SARS-CoV-2 pneumonia. NCT04333550

CLINICAL TRIAL RESULTS

- Here is a Bayesian reanalysis of the Marseilles hydroxychloroquine/azithromycin CT from Danish researchers. Needless to say it is not positive. Here we apply Bayesian statistics to assess the robustness of the original papers claims by testing four variants of the data: 1) The original data;

2) Data including patients who deteriorated; 3) Data including patients who deteriorated with exclusion of untested patients in the comparison group; 4) Data that includes patients who deteriorated with the assumption that untested patients were negative. To ask if HCQ monotherapy is effective, we performed an A/B test for a model which assumes a positive effect, compared to a model of no effect. We find that the statistical evidence is highly sensitive to these data variants. Statistical evidence for the positive effect model ranged from strong for the original data (BF ~11), to moderate when including patients who deteriorated (BF ~4.35), to anecdotal when excluding untested patients (BF ~2), and to anecdotal negative evidence if untested patients were assumed positive (BF ~0.6). To assess whether HCQ is more effective when combined with AZ, we performed the same tests, and found only anecdotal evidence for the positive effect model for the original data (BF ~2.8), and moderate evidence for all other variants of the data (BF ~5.6). Our analyses only explore the effects of different assumptions about excluded and untested patients. These assumptions are not adequately reported, nor are they justified in the original paper, and we find that varying them causes substantive changes to the evidential support for the main claims of the original paper. This statistical uncertainty is exacerbated by the fact that the treatments were not randomised, and subject to several confounding variables including the patients' consent to treatment, different care centres, and clinical decision-making. Furthermore, while the viral load measurements were noisy, showing multiple reversals between test outcomes, there is greater certainty around other clinical outcomes such as the 4 patients who seriously deteriorated. The fact that all of these belonged to the HCQ monotherapy group should be assigned greater weight when evaluating the potential clinical efficacy of HCQ. Randomised controlled trials are currently underway, and will be critical in resolving this uncertainty as to whether HCQ and AZ are effective as a treatment for COVID-19. https://www.medrxiv.org/content/10.1101/2020.03.31.20048777v1

- I think this is the first IL-6 blocker study report I've seen; Italian researchers but small patient population. We report preliminary data from 21 patients with COVID-19 who developed pneumonia/acute respiratory distress syndrome (ARDS) and participated in a compassionate-use program at Papa Giovanni XXIII hospital in Bergamo, Italy. All 21 patients received intravenous siltuximab, a chimeric mAb that binds to and blocks the effect of IL-6, at a dose ranging between 700 to 1,200 mg (median 900 mg). The median age of patients treated was 64 years, and all patients were followed for a median of eight days. Serum CRP levels reduced in all 16 patients with available data following treatment. An improvement in the clinical condition was observed in 33% (7/21) of patients, 43% (9/21) of patients stabilized as evidenced by no clinically relevant change in their condition, and 24% (5/21) experienced a worsening in their condition. Of those patients who experienced a worsening in their condition, one patient died, and one patient experienced a cerebrovascular event. This analysis is presented to inform the medical community of the potential role of siltuximab in treating patients with ARDS secondary to SARS-CoV-2 infection, and a cohort study with patients treated with standard therapy in our hospital is ongoing, and will report the 30-day mortality rates upon completion. https://www.medrxiv.org/content/10.1101/2020.04.01.20048561v1
- Speaking of IL-6, here is a meta-analysis of trials (I only look at one database), looking at raised IL-6 levels. We systematically searched MEDLINE and EMBASE for studies investigating the immunological response in COVID-19 or its treatment with tocilizumab; additional grey literature searches were undertaken. Meta-analysis was undertaken using random effects

models. Results: Eight published studies, three pre-prints, and five registered trials were eligible. Meta-analysis of mean IL-6 concentrations demonstrated 2.9-fold higher levels in patients with complicated COVID-19 compared with patients with non-complicated disease (six studies; n=1302; 95%CI, 1.17-7.19; I2=100%). A single non-randomized, single-arm study assessed tocilizumab in patients with severe COVID-19, demonstrating decreased oxygen requirements, resolution of radiographic abnormalities, and clinical improvement. No adverse events or deaths were observed. Conclusions: In patients with COVID-19, IL-6 levels are significantly elevated and associated with adverse clinical outcomes. While inhibition of IL-6 with tocilizumab appears to be efficacious and safe in preliminary investigation, the results of several ongoing clinical trials should be awaited to better define the role of tocilizumab in COVID-19 prior to routine clinical application. https://www.medrxiv.org/content/10.1101/2020.03.30.20048058v1

- Another IL-6 paper, this time from Germany. Patients requiring mechanical ventilation 13/40 (32.5%) did not differ in age, comorbidities, radiological findings, respiratory rate or qSofa score. However, elevated interleukin-6 (IL-6) was strongly associated with the need for mechanical ventilation ($p=1.2.10^{-5}$). In addition, the maximal IL-6 level (cutoff 80 pg/ml) for each patient during disease predicted respiratory failure with high accuracy ($p=1.7.10^{-8}$, AUC=0.98). The risk of respiratory failure for patients with IL-6 levels of ≥ 80 pg/ml was 22 times higher compared to patients with lower IL-6 levels. In the current situation with overwhelmed intensive care units and overcrowded emergency rooms, correct triage of patients in need of intensive care is crucial. Our study shows that IL-6 is an effective marker that might be able to predict upcoming respiratory failure with high accuracy and help physicians correctly allocate patients at an early stage. https://www.medrxiv.org/content/10.1101/2020.04.01.20047381v1
- From NYC, caution concerning QT interval in patients treated with hydroxychloroquine/azithromycin. We report the change in the QT interval in 84 adult patients with SARS-CoV-2 infection treated with Hydroxychloroquine/Azithromycin combination. QTc prolonged maximally from baseline between days 3 and 4. in 30% of patients QTc increased by greater than 40ms. In 11% of patients QTc increased to >500 ms, representing high risk group for arrhythmia. The development of acute renal failure but not baseline QTc was a strong predictor of extreme QTc prolongation.
https://www.medrxiv.org/content/10.1101/2020.04.02.20047050v1
- Here is a paper from Wuhan that supports the use of ARBs and ACE inhibitors. We aimed to evaluate the correlation of ARBs/ACEIs usage with the pathogenesis of COVID-19 in a retrospective, single-center study. 126 COVID-19 patients with preexisting hypertension at Hubei Provincial Hospital of Traditional Chinese Medicine (HPHTCM) in Wuhan from January 5 to February 22, 2020 were retrospectively allocated to ARBs/ACEIs group (n=43) and non-ARBs/ACEIs group (n=83) according to their antihypertensive medication. 125 age- and sex-matched COVID-19 patients without hypertension were randomly selected as non-hypertension controls. In addition, the medication history of 1942 hypertension patients that were admitted to HPHTCM from November 1 to December 31, 2019 before COVID-19 outbreak were also reviewed for external comparison. Epidemiological, demographic, clinical and laboratory data were collected, analyzed and compared between these groups. The frequency of ARBs/ACEIs usage in hypertension patients with or without COVID-19 were comparable. Among COVID-19 patients with hypertension, those received either ARBs/ACEIs or non-ARBs/ACEIs had comparable blood pressure. However, ARBs/ACEIs group had significantly lower concentrations

of CRP (p=0.049) and procalcitonin (PCT, p=0.008). Furthermore, much lower proportion of critical patients (9.3% vs 22.9%; p=0.061), and a lower death rate (4.7% vs 13.3%; p=0.216) were observed in ARBs/ACEIs group than non-ARBs/ACEIs group, although these differences failed to reach statistical significance. Our findings thus support the use of ARBs/ACEIs in COVID-19 patients with preexisting hypertension.
https://www.medrxiv.org/content/10.1101/2020.03.31.20038935v1

DRUG DEVELOPMENT

- Here is an interesting paper from China on systematic *in silico* drug discovery screening. Under current adverse situation, we employ virtual screening tools in searching for drugs and nature products which have been already deposited in the DrugBank in attempt to accelerate the drug discovery process. This study provides an initial evaluation of current drug candidates from various reports using our systemic in silico drug screening based on structures of viral proteins and human ACE2 receptor. Besides, we built an interactive online platform (https://shennongproject.com:11443/#/home) for browsing these results with the visual display of small molecule docked on its potential target protein, without installing any specialized structural software. With continuous maintenance and incorporation of data from laboratory works, it may serve not only as the assessment tool for the new drug discovery but also an educational website to meet general interest from the public. From the paper: "A few drugs, including Saquinavir, Beclabuvir, Bictegravir and Dolutegravir are not currently under investigation for treatment of COVID-19 to our knowledge. However, the antiviral mechanisms of these drugs, together with their performance in our screening, make them the drugs we recommended should be tested in treatment of COVID-19."
https://chemrxiv.org/articles/Systemic_in_Silico_Screening_in_Drug_Discovery_for_Coronavirus_Disease_COVID-19_with_an_Online_Interactive_Web_Server/12058143
- Another molecular docking model, this time from Egypt. The results stimulate the evaluation of these drugs as anti COVID-19 especially aliskiren which showed the highest score of binding with the binding site of N3. This will be added to its renin inhibition and advantage of renin inhibition and possibility of the reduced expression of ACE2[12]. Dipyridamole and mopidamol showed a potential to be more M^{pro} inhibitor than ligand N3 and darunavir. Also, dipyridamole has the property of antiviral activity beside its use to decrease the hypercoagulabilty that happens due to COVID infection in addition to the property of promoting type I interferon (IFN) responses and protect mice from viral pneumonia [30]. Rolitetracycling is an amazing in its binding mode in the active site of the protease pocket it seemed as it is tailored to be buried in that pocket. Mopidamol and rosuvastatin are slightly better than the co-crystallized ligand N3 and darunavir in binding mode which nominate the as COVID-19 protease inhibitors. Hopefully this study will help in the repurposing a drug for the treatment of COVID-19.
https://chemrxiv.org/articles/Molecular_Docking_Reveals_the_Potential_of_Aliskiren_Dipyridamole_Mopidamol_Rosuvastatin_Rolitetracycline_and_Metamizole_to_Inhibit_COVID-19_Virus_Main_Protease/12061302

DIAGNOSTIC DEVELOPMENT

- Here is a UK paper that examines the use of Loop-Mediated Isothermal Amplification (LAMP) to PCR. [**note: you need to read the paper if you want to understand the technology**] We tested reverse transcription loop mediated isothermal amplification (RT-LAMP), a method which can produce results in under 30 minutes, alongside standard methods in a real-life clinical setting. Methods: This service improvement project piloted a research RT-LAMP method on nasal and pharyngeal swabs on 21 residents in an NHS Category 1 care home, with two index COVID-19 cases, and compared it to multiplex tandem reverse transcription polymerase chain reaction (RT-PCR). We calculated the sensitivity, specificity, positive and negative predictive values of a single RT-LAMP swab compared to RT-PCR, as per STARD guidelines. We also recorded vital signs of patients to correlate clinical and laboratory information. Findings: The novel method accurately detected 8/10 PCR positive cases and identified a further 3 positive cases. Eight further cases were negative using both methods. Using repeated RT-PCR as a 'gold standard', the sensitivity and specificity of the novel test were 80% and 73% respectively. Positive predictive value (PPV) was 73% and negative predictive value (NPV) was 83%. We also observed hypothermia to be a significant early clinical sign in a number of COVID-19 patients in this setting. Interpretation: RT-LAMP testing for SARS-CoV-2 was found to be promising, fast, easy to use and to work equivalently to RT-PCR methods. Definitive studies to evaluate this method in larger cohorts are underway. RT-LAMP has the potential to transform COVID-19 detection, bringing rapid and accurate testing to the point of care. This method could be deployed in mobile testing units in the community, care homes and hospitals to detect disease early and prevent spread. https://www.medrxiv.org/content/10.1101/2020.04.01.20047357v1

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2020-04-05

For today's musical selection, I've moved over to the pop world. I am a closeted Taylor Swift fan so we have the great music video (great for the depiction of girl power) 'Bad Blood' - https://www.youtube.com/watch?v=QcIy9NiNbmo There is a cameo VIP appearance by someone whose marriage I may or may not have broken up about 25 years ago (that's a story for another day).

Sunday's are always a slow news day, so there is not a lot new to report on.

The drug of the day is ivermectin. An Australian in vitro test shows high potency against SARS-CoV-2 so of course the Internet is all abuzz in how it should be used. Here's the abstract: https://www.sciencedirect.com/science/article/pii/S0166354220302011?via%3Dihub#! Just what we need another huge community trial.

MODELING

- Nothing new here. Lots of interactive Internet models and unless I see something really novel, I will drop this category in future emails.

NEWLY REGISTERED CLINICAL TRIALS

- Here is an interesting proposed trial from UCSF (my daughter works at Children's Hospital in SF!). This individually randomized telemedicine-based trial aims to evaluate the efficacy of a single dose of azithromycin for prevention of progression of COVID-19 in patients with mild/moderate symptomatic COVID-19 with a recent positive SARS-CoV-2 test. Participants will get a single 1g dose of the antibiotic. NCT04332107
- As one who has been coughing for the past four weeks, likely a result of seasonal tree pollen allergies, I find this study intriguing! An open access study that will define and collect digital measures of coughing in multiple populations and public spaces using various means of audio data collection. They are looking for enrollees who have coronavirus infections, hay fever, asthma, COPD, influenza, common cold, URIs and healthy individuals. NCT04326309

CLINICAL TRIAL RESULTS

- Maybe patients should be screened for metformin use before being given hydroxychloroquine. Here is troubling animal safety data. we report a cautionary note on the potential fatal toxicity of chloroquine (CQ) or hydroxychloroquine (HCQ) in combination with anti-diabetic drug metformin. We observed that the combination of CQ or HCQ and metformin, which were used in our studies as potential anti-cancer drugs, killed 30-40% of mice. While our observations in mice may not translate to toxicity in humans, the reports that CQ or HCQ has anti-COVID-19 activity, the use of CQ resulting in toxicity and at least one death, and the recent Emergency Use Authorization (EUA) for CQ and HCQ by the US Food and Drug Administration (FDA) prompted our report. Here we report the lethality of CQ or HCQ in combination with metformin as a warning of its potential serious clinical toxicity. We hope that our report will be helpful to stimulate pharmacovigilance and monitoring of adverse drug reactions with the use of CQ or HCQ, particularly in combination with metformin.
  https://www.biorxiv.org/content/10.1101/2020.03.31.018556v1
- Interesting conjecture about susceptibility of lupus patients to SARS-CoV-2. we suggest that patients with systemic lupus erythematous might be especially prone to severe COVID-19 independent of their immunosuppressed state from lupus treatment. Specially, we provide evidence in lupus to suggest hypomethylation and overexpression of ACE2, which is located on the X chromosome and encodes a functional receptor for the SARS-CoV-2 spike glycoprotein. Oxidative stress induced by viral infections exacerbates the DNA methylation defect in lupus, possibly resulting in further ACE2 hypomethylation and enhanced viremia. In addition, demethylation of interferon-regulated genes, NFκB, and key cytokine genes in lupus patients might exacerbate the immune response to SARS-CoV-2 and increase the likelihood of cytokine storm. These arguments suggest that inherent epigenetic dysregulation in lupus might facilitate viral entry, viremia, and an excessive immune response to SARS-CoV-2. Further, maintaining disease remission in lupus patients is critical to prevent a vicious cycle of demethylation and increased oxidative stress, which will exacerbate susceptibility to SARS-CoV-2 infection during the current pandemic. Epigenetic control of the ACE2 gene might be a target for prevention and therapy in COVID-19. [**note: I wonder if those lupus patient on antimalarial therapy are protected?**] https://www.medrxiv.org/content/10.1101/2020.03.30.20047852v1

- It was just a question of when (I need to inject some humor into these posts!). Chinese researchers showed no viral migration of SARS-CoV-2 to the testes or in semen. To examine whether there is sexual transmission from male, we employed realtime polymerase chain reaction testing (RT-PCR) to detect 2019-nCov in semen or testicular biopsy specimen. Findings: The age range of the 12 patients in recovery was 22-38 years. None of the patients developed severe COVID-19 pneumonia. As of March 14, 2020, ten patients discharged from the hospital while the rest 2 had developed into recovery stage. All of the patients in recovery tested negative for 2019-nCoV RNA in semen samples. Another died patient was 67 years old, who died in March 10, 2020 and tissue sample via testicular biopsy was tested negative for viral RNA. Conclusion: No positive RT-PCR result was found in the semen or testicular biopsy specimen. The results from this study show no evidence of sexual transmission of 2019-nCov from males. https://www.medrxiv.org/content/10.1101/2020.03.31.20042333v1

DRUG DEVELOPMENT

- Nothing new here

DIAGNOSTIC DEVELOPMENT

- Nothing New but here is a nice article on shipment of the Abbott quick test kits. As we all know, it takes time to ramp up production and there is only a small number of kits being shipped: https://www.fiercebiotech.com/medtech/trump-touted-abbott-s-quick-covid-19-test-hhs-document-shows-only-5-500-are-way-to-entire-u