2020-11-23

Welcome to Week 36 of the Pandemic Newsletter

We are going to stay with opera for one last day before moving on as I had an extra clip worth watching. Here is the sleepwalking scene 'Ah! Non credea mirarti' from Bellini's La Sonambula. I'm constantly amazed at how many fine arias Bellini wrote in his short life. Here is the wonderful Italian soprano, Rosa Feola: https://www.youtube.com/watch?v=BmIRn6HAZl4 and as an extra special treat, here is a masterclass taught by Joyce DiDonato with soprano Alexandra Nowakowski with one of the other arias from La Sonambula: https://www.youtube.com/watch?v=5rCWXu3iMTY I was stunned when she commented to Ms. DiDonato that this was the first time she has sung this aria in a performance setting!

Another vaccine candidate reports in as highly effective. The AstraZeneca/Oxford adenovirus vectored Spike protein data is in from an interim analysis of UK and Brazil trials. This is good news. It may be another month or two, but we should see the data for Novavax and Johnson & Johnson. The AstraZeneca/Oxford vaccine can be stored at normal refrigerator temperatures. What I don't understand is the differing responses to the dose regimen. Giving a half dose followed by a full dose 28 days later was more potent than two full doses. The vaccine's developer, Sara Gilbert, said it may be a priming effect but that more research is necessary. There were no serious safety effects observed in the trial.

The Washington Post notes that there is a lot of holiday travel going on and the this may increase the spread of COVID-19.

The New York Times comments that there are enough ventilators right now but perhaps not enough trained critical care personnel to deal with the large numbers of hospitalized COVID-19 patients. Here is a story about the efforts of Bill Gates and his Foundation in funding vaccine research and development. This story discusses the US vaccine distribution plans.

STAT note that hospitalized patients are surviving at higher rates but the surge in cases might roll this back. Here is their take on the AstraZeneca/Oxford vaccine.

Nature have a story on the discovery of coronaviruses in bats outside of China. Two lab freezers in Asia have a coronavirus close related to SARS-CoV-2. *The virus in Cambodia was found in two Shamel's horseshoe bats (Rhinolophus shameli) captured in the country's north in 2010. The virus's genome has not yet been fully sequenced — nor its discovery published — making its full significance to the pandemic hard to ascertain. The other virus, called Rc-o319, identified in a little Japanese horseshoe bat (Rhinolophus cornutus) captured in 2013. That virus shares 81% of its genome with SARS-CoV-2, according to a paper[1] published on 2 November — which makes it too distant to provide insights into the pandemic's origin, says Edward Holmes, a virologist at the University of Sydney in Australia.*

As is usual for Monday, there are few articles posted on the preprint servers. This will be a short week for newsletters because of the Thanksgiving holiday. I won't be sending one out on Thursday.

MODELING

- The determination of the infection fatality rate (IFR) for the novel SARS-CoV-2 coronavirus is a key aim for many of the field studies that are currently being undertaken in response to the pandemic. The IFR together with the basic reproduction number R0, are the main epidemic parameters describing severity and transmissibility of the virus, respectively. *The IFR can be also used as a basis for estimating and monitoring the number of infected individuals in a population, which may be subsequently used to inform policy decisions relating to public health interventions and lockdown strategies. The interpretation of IFR measurements requires the calculation of confidence intervals. We present a number of statistical methods that are relevant in this context and develop an inverse problem formulation to determine correction factors to mitigate time-dependent effects that can lead to biased IFR estimates. We also review a number of methods to combine IFR estimates from multiple independent studies, provide example calculations throughout this note and conclude with a summary and "best practice" recommendations. The developed code is available online.* [**note: calculating the true infection rate is important for getting accurate values of the fatality rate from COVID-19. There is still a struggle in light of imprecise knowledge of how many people have actually been infected. Here is a model from the UK that might prove useful.**]
  https://www.medrxiv.org/content/10.1101/2020.11.19.20235036v1

NEWLY REGISTERED CLINICAL TRIALS

- Alert readers will know that I checked yesterday.

CLINICAL TRIAL RESULTS

- Nothing today

DRUG DEVELOPMENT

- Nothing today

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Here we report that COVID-19 hospitalisation rates follow an exponential relationship with age, doubling for every 16 years of age or equivalently increasing by 4.5% per year of life (R2=0.98). This mirrors the well studied exponential decline of both thymus volume and T-cell production, which halve every 16 years. COVID-19 can therefore be added to the list of other diseases with this property, including those caused by MRSA, West Nile virus, Streptococcus Pneumonia and certain cancers, such as chronic myeloid leukemia and brain cancers. In addition, *incidence of severe disease and mortality due to COVID-19 are both higher in men, consistent with the degree to which thymic involution (and the decrease in T-cell production with age) is more severe in men compared to women. For under 20s, COVID-19 incidence is remarkably low. A Bayesian analysis of daily hospitalisations, accounting for contact-based and environmental transmission, indicates that non-adults are the only age group to deviate significantly from the exponential relationship. Our model fitting suggests under 20s have 49-75% additional immune protection beyond that predicted by strong thymus function alone, consistent with increased juvenile cross-immunity from other viruses. We found no evidence for differences between age groups in susceptibility to overall infection, or, relative infectiousness to others. The strikingly simple inverse relationship between COVID-19 risk and thymic T-cell output reported here begs a mechanistic understanding*

and suggests that T-cell based therapies may be a promising target. **[note: more on the importance of the immune system and how aging may result in severe COVID-19.**] https://www.medrxiv.org/content/10.1101/2020.08.25.20181487v2

DIAGNOSTIC DEVELOPMENT

- Nothing today

>>

2020-11-24

Today we finally step away from opera (if I had my druthers, it would be vocal music every day but I might see mass desertion among my readers!!!). Here is a home recital by Hilary Hahn of some new solo cadenzas to the Mozart Violin Concerto in A major. These were commissioned by the Philharmonic Society of Orange County. These are all quite wonderful: https://www.youtube.com/watch?v=00lLwGRBxDY

The Washington Post reports that the Russian COVID-19 vaccine is also 95% effective and cheaper than others. This manufacturer of medical gloves is shutting 28 manufacturing facilities because of a COVID-19 outbreak. I have a surprising ally in Pope Francis who has criticized anti-mask protesters!!! This strike by Washington urgent care doctors was predictable.

This New York Times story reminds me of one of my favorite Frank Zappa songs, 'Montana'. Four experts weigh in on how to have a safe Thanksgiving. Here is a story on the type of events that are causing COVID-19 transmission. This is a good op-ed on the need for better COVID-19 reporting. The early 614G mutation of SARS-CoV-2 may have led to a more contagious virus (I thought it first appeared in Italy, but it now looks like it arose in Eastern China. The outbreak in Washington State resulted from the original strain and it was the East Coast outbreak that was caused by 614G.). Film production in New York City seems to be moving forward! A big shout out to Australian airline Qantas who plan to make COVID-19 vaccination mandatory for all travelers once they become available.

ProPublica has a good story of two school districts in Georgia with different requirements for mask wearing. It is no surprise the school that mandated masks had no school-related transmissions of COVID-19.

The Infectious Disease Society of America (IDSA) has updated their treatment guidelines for COVID-19.

Derek Lowe discusses the AZ/Oxford vaccine data. Here is a Nature article on the same topic.

MODELING

- Understanding changes in infectiousness during COVID-19 infections is critical to assess the effectiveness of public health measures such as contact tracing. Data from known source-recipient pairs can be used to estimate the average infectiousness profile of infected individuals, and to evaluate the proportion of presymptomatic transmissions. Here, we infer the infectiousness profile of COVID-19 infections using a mechanistic approach, and show that this method provides an improved fit to data from source-recipient pairs compared to previous

studies. *Our results indicate a higher proportion of presymptomatic transmissions than previously thought, with many transmissions occurring shortly before symptom onset. High infectiousness immediately prior to symptom onset highlights the importance of contact tracing, even if contacts from a short time window before symptom onset alone are traced*. [**note: it is probably too late in the pandemic to implement sound contact tracing. This was identified as a key issue way back when but events have eclipsed public health measures.**] https://www.medrxiv.org/content/10.1101/2020.11.20.20235754v1

- In late 2019 and through 2020, the COVID-19 pandemic swept the world, presenting both scientific and medical challenges associated with understanding and treating a previously unknown disease. To help address the need for great understanding of COVID-19, the scientific community mobilized and banded together rapidly to characterize SARS-CoV-2 infection, pathogenesis and its distinct disease trajectories. The urgency of COVID-19 provided a pressing use-case for leveraging relatively new tools, technologies, and nascent collaborative networks. Single-cell biology is one such example that has emerged over the last decade as a powerful approach that provides unprecedented resolution to the cellular and molecular underpinnings of biological processes. Early foundational work within the single-cell community, including the Human Cell Atlas, utilized published and unpublished data to characterize the putative target cells of SARS-CoV-2 sampled from diverse organs based on expression of the viral receptor ACE2 and associated entry factors TMPRSS2 and CTSL (Muus et al., 2020; Sungnak et al., 2020; Ziegler et al., 2020). This initial characterization of reference data provided an important foundation for framing infection and pathology in the airway as well as other organs. However, initial community analysis was limited to samples derived from uninfected donors and other previously-sampled disease indications. This report provides an overview of a single-cell data resource derived from samples from COVID-19 patients along with initial observations and guidance on data reuse and exploration. [**note: here is another large scale effort to provide data on COVID-19. This is single cell profiling of patients and provides data from multiple tissues.**] https://www.medrxiv.org/content/10.1101/2020.11.20.20227355v1
- The measles-mumps-rubella (MMR) vaccine has been theorized to provide protection against coronavirus disease 2019 (COVID-19). Our aim was to determine whether any MMR IgG titers are inversely correlated with severity in recovered COVID-19 patients previously vaccinated with MMR II. We divided 80 subjects into two groups, comparing MMR titers to recent COVID-19 severity levels. The MMR II group consisted of 50 subjects who would primarily have MMR antibodies from the MMR II vaccine, and a comparison group of 30 subjects consisted of those who would primarily have MMR antibodies from sources other than MMR II, including prior measles, mumps, and/or rubella illnesses. There was a significant inverse correlation ($r_s = -0.71$, $P < 0.001$) between mumps virus titers (mumps titers) and COVID-19 severity within the MMR II group. There were no significant correlations between mumps titers and severity in the comparison group, between mumps titers and age in the MMR II group, or between severity and measles or rubella titers in either group. *Within the MMR II group, mumps titers of 134 to 300 arbitrary units (AU)/ml (*n *= 8) were found only in those who were functionally immune or asymptomatic; all with mild symptoms had mumps titers below 134 AU/ml (*n *= 17); all with moderate symptoms had mumps titers below 75 AU/ml (*n *= 11); all who had been hospitalized and had required oxygen had mumps titers below 32 AU/ml (*n *= 5). Our results demonstrate that there is a significant inverse correlation between mumps titers from MMR II and COVID-19*

severity. [**note: the anti-vax community may not like the results of this paper.** https://mbio.asm.org/content/11/6/e02628-20

NEWLY REGISTERED CLINICAL TRIALS

- Did you really expect to see anything in this section?

CLINICAL TRIAL RESULTS

- Type III interferons have been touted as promising therapeutics in outpatients with coronavirus disease 2019 (COVID-19). We conducted a randomized placebo-controlled trial in 120 patients with mild to moderate COVID-19 to determine whether a single, 180 mcg subcutaneous dose of Peginterferon Lambda-1a (Lambda) could shorten the duration of viral shedding (primary endpoint) or symptoms (secondary endpoint, NCT04331899). In both the 60 patients receiving Lambda and the 60 receiving placebo, the median time to cessation of viral shedding was 7 days (hazard ratio [HR] = 0.81; 95% confidence interval [CI] 0.56 to 1.19). Symptoms resolved in 8 and 9 days in Lambda and placebo, respectively (HR 0.94; 95% CI 0.64 to 1.39). At enrollment; 41% of subjects were SARS-CoV-2 IgG seropositive; compared to placebo, lambda tended to delay shedding cessation in seronegatives (aHR 0.66, 95% CI 0.39-1.10) and to hasten shedding cessation in seropositives (aHR 1.58, 95% CI 0.88-2.86; p for interaction = 0.03). Liver transaminase elevations were more common in the Lambda vs. placebo arm (15/60 vs 5/60; p = 0.027). *In this study, a single dose of subcutaneous Peginterferon Lambda-1a neither shortened the duration of SARS-CoV-2 viral shedding nor improved symptoms in outpatients with uncomplicated COVID-19*. [**note: here are the results of a Stanford clinical trial of Peginterferon Lambda-1a. Sadly, it seems not to have worked on outpatients with uncomplicated COVID-19.**] https://www.medrxiv.org/content/10.1101/2020.11.18.20234161v1

DRUG DEVELOPMENT

- Here, we describe Newcastle disease virus (NDV) vector vaccines expressing the spike protein of SARS-CoV-2 in its wild type format or a membrane-anchored format lacking the polybasic cleavage site. *All described NDV vector vaccines grow to high titers in embryonated chicken eggs. In a proof of principle mouse study, the immunogenicity and protective efficacy of these NDV-based vaccines were investigated*. [**note: this new vaccine candidate which is a live viral vector based on Newcastle disease virus comes from the busy group at Mt. Sinai. The only drawback is that it relies on embryonated eggs for production. This is the same method that the yearly flu vaccine is based.**] https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(20)30508-9/fulltext
- Drug repurposing provides a rapid approach to meet the urgent need for therapeutics to address COVID-19. To identify therapeutic targets relevant to COVID-19, we conducted Mendelian randomization (MR) analyses, deriving genetic instruments based on transcriptomic and proteomic data for 1,263 actionable proteins that are targeted by approved drugs or in clinical phase of drug development. *Using summary statistics from the Host Genetics Initiative and the Million Veteran Program, we studied 7,554 patients hospitalized with COVID-19 and >1 million controls. We found significant Mendelian randomization results for three proteins (ACE2: P=1.6x10^-6, IFNAR2: P=9.8x10^-11, and IL-10RB: P=1.9x10^-14) using cis-eQTL genetic instruments that also had strong evidence for colocalization with COVID-19 hospitalization. To*

disentangle the shared eQTL signal for IL10RB and IFNAR2, we conducted phenome-wide association scans and pathway enrichment analysis, which suggested that IFNAR2 is more likely to play a role in COVID-19 hospitalization. Our findings prioritize trials of drugs targeting IFNAR2 and ACE2 for early management of COVID-19. [**note: new approaches to drug development are still going on. A genome-wide Mendelian randomization approach suggests targeting IFNAR2 along with ACE2.**] https://www.medrxiv.org/content/10.1101/2020.11.19.20234120v1

- Epidemiological studies suggest that the Bacillus Calmette-Guerin (BCG) vaccine may have protective effects against coronavirus disease 2019 (COVID-19); and, there are now more than 15 ongoing clinical trials seeking to determine if BCG vaccination can prevent or reduce the severity of COVID-19 (1). However, the mechanism by which BCG vaccination can induce a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) specific T cell response is unknown. Here, in silico, we identify 8 BCG derived peptides with significant sequence homology to either SARS-CoV-2 NSP3 or NSP13 derived peptides. *Using an in vitro co-culture system, we show that human CD4+ and CD8+ T cells primed with a BCG derived peptide developed enhanced reactivity to its corresponding SARS-CoV-2 derived peptide. As expected, HLA differences between individuals meant that not all persons developed immunogenic responses to all 8 BCG derived peptides. Nevertheless, all of the 20 individuals that were primed with BCG derived peptides developed enhanced T cell reactivity to at least 7 of 8 SARS-CoV-2 derived peptides. These findings provide a mechanistic basis for the epidemiologic observation that BCG vaccination confers protection from COVID-19; and supports the use of BCG vaccination to induce cross-reactive SARS-CoV-2 specific T cell responses*. [**note: this is an interesting finding about some peptides derived from BCG vaccine conferring cross immunity to SARS-CoV-2. I still have not seen results of the BCG clinical trials that are taking place.**] https://www.medrxiv.org/content/10.1101/2020.11.21.20236018v1
- Two proteases produced by the SARS-CoV-2 virus, Mpro and PLpro, are essential for viral replication and have become the focus of drug development programs for treatment of COVID-19. We screened a highly focused library of compounds containing covalent warheads designed to target cysteine proteases to identify new lead scaffolds for both Mpro and PLpro proteases. These efforts identified a small number of hits for the Mpro protease and no viable hits for the PLpro protease. *Of the Mpro hits identified as inhibitors of the purified recombinant protease, only two compounds inhibited viral infectivity in cellular infection assays. However, we observed a substantial drop in antiviral potency upon expression of TMPRSS2, a transmembrane serine protease that acts in an alternative viral entry pathway to the lysosomal cathepsins. This loss of potency is explained by the fact that our lead Mpro inhibitors are also potent inhibitors of host cell cysteine cathepsins. To determine if this is a general property of Mpro inhibitors, we evaluated several recently reported compounds and found that they are also effective inhibitors of purified human cathepsin L and B and showed similar loss in activity in cells expressing TMPRSS2. Our results highlight the challenges of targeting Mpro and PLpro proteases and demonstrate the need to carefully assess selectivity of SARS-CoV-2 protease inhibitors to prevent clinical advancement of compounds that function through inhibition of a redundant viral entry pathway*. [**note: these Stanford researchers discuss the challenges of targeting SARS-CoV-2 proteases as a therapeutic strategy.**] https://www.biorxiv.org/content/10.1101/2020.11.21.392753v1

- Viruses thrive by exploiting the cells they infect but must also produce viral proteins to replicate and infect other cells. As a consequence, they are also susceptible to exploitation by defective versions of themselves that do not produce such proteins. A defective viral genome with deletions in protein-coding genes could still replicate in cells coinfected with full-length viruses, and even replicate faster due to its shorter size, interfering with the replication of the virus. We have created a synthetic defective interfering version of SARS-CoV-2, the virus causing the recent Covid-19 pandemic, assembling parts of the viral genome that do not code for any functional protein but enable it to be replicated and packaged. This synthetic defective genome replicates three times faster than SARS-CoV-2 in coinfected cells, and interferes with it, reducing the viral load of a cell by half in 24 hours. *The synthetic genome is transmitted as efficiently as the full-length genome, confirming the location of the putative packaging signal of SARS-CoV-2. A version of such a synthetic construct could be used as a self-promoting antiviral therapy: by enabling replication of the synthetic genome, the virus promotes its own demise*. [**note: I was wondering when someone would come up with this type of 'Trojan Horse' virus. These Penn State researchers have created a synthetic SARS-CoV-2 that is missing some genes but can still replicate in co-infected cells. I look forward to seeing continued development of this.**] https://www.biorxiv.org/content/10.1101/2020.11.22.393587v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Abstract: An improved understanding of the immunity offered by the antibodies developed against SARS-CoV-2 is critical for the development of diagnostic tests and vaccines. Our study aimed at the longitudinal analysis of antibody persistence and its dynamic trend over a period of eight months in a group of COVID-19 recovered patients who tested positive by real-time quantitative PCR for SARS-CoV-2 in the period between the 18th and 30th of March, 2020. The subjects were divided into two groups based on disease severity: mild and moderately-severe. The MAGLUMI 2019-nCoV lgM/lgG chemiluminescent analytical system (CLIA) assay was used to analyse the antibody titres. *Robust IgG antibody persistency was demonstrated in 76.7 % of the subjects (23 out of 30) at eight months post infection. The results of this study highlight an important point in terms of the association between humoral immune response and disease severity. Patients who might have experienced a relatively moderate-severe infection may develop a robust immunity that could persist for a longer duration*. [**note: I think it's pretty clear that robust immunity to SARS-CoV-2 appears to hold for long periods of time post-infection. This paper is from Italy and looks at antibody levels at eight months post infection. Almost every paper that is doing such surveillance is coming up with similar results. I'm not going to cover this any longer.**] https://www.medrxiv.org/content/10.1101/2020.11.21.20236117v1

DIAGNOSTIC DEVELOPMENT

- Not a thing today.

>>

2020-11-25

I have featured Yo-Yo Ma in the past but why not post another video clip as he always provides welcome relief for me. Here is a music video (yes, classical musicians are taking a cue from the pop stars and

beginning to do this with increasing frequency. Here Ma is with pianist Kathryn Stott performing an arrangement of 'Over the Rainbow': https://www.youtube.com/watch?v=03GpPfOsFkQ this is from a recording of "Songs of Comfort and Hope. Enjoy this one!

The Washington Post has an op-ed advocating school closures during the winter. I don't know what side to come down on here as there are schools that have handled things quite well. Why should they be penalized? Her is the Post story on the Pfizer/BioNTech vaccine distribution. I guess this was predictable; Comcast is raising prices for Internet customers. I have had no word on whether my carrier Verizon will follow. Chinese vaccine company Sinopharm is requesting approval for their COVID-19 vaccine from that country's regulatory authority. In what is not shocking news to me, Sweden's top epidemiologist admits immunity isn't slowing down that country's second wave. So much for the herd immunity theory. I believe there is truth to this story that pandemic coverage tends to focus on 'bad news.'

The New York Times discusses what is known about the confounding results of the AstraZeneca/Oxford vaccine. Here is the first comment on distribution of the Pfizer/BioNTech vaccine, 6.4 million doses going out in mid-December. I wish this consortium of African countries good luck in their clinical trial effort!! It should have turned out much better; officials are giving up on contact tracing.

My Yahoo news feed points to this study on masks!

STAT discusses burnout among healthcare workers. Here is a story of a New Jersey hospital that hopes this time will be different from the Spring outbreak.

The Lacet has a piece discussing the two views on 'herd immunity for COVID-19.'

Kaiser Health News discusses the pandemic strain on hospital nurses. As we give thanks tomorrow, let us salute all the healthcare workers who have spent hours upon hours battling the pandemic!

The New England Journal of Medicine has the results of a Spanish cluster trial of HCQ. *Postexposure therapy with hydroxychloroquine did not prevent SARS-CoV-2 infection or symptomatic Covid-19 in healthy persons exposed to a PCR-positive case patient. (Funded by the crowdfunding campaign YoMeCorono and others; BCN-PEP-CoV2.* Here is a study of the genomewide association of severe COVID-19 with respiratory failure. *We identified a 3p21.31 gene cluster as a genetic susceptibility locus in patients with Covid-19 with respiratory failure and confirmed a potential involvement of the ABO blood-group system. (Funded by Stein Erik Hagen and others.)* Here is an accompanying editorial on this research. This is good stuff and we are leaning so much about the genetic aspects of both the virus and the human response to it.

The Annals of Internal Medicine have an Ontario study on the association between type O and Rh- blood groups on SARS-CoV-2 infection. *The O and Rh− blood groups may be associated with a slightly lower risk for SARS-CoV-2 infection and severe COVID-19 illness*.

MODELING

- To compare trends and undertake statistical analyses of differences in public health performance (confirmed cases and fatalities) of Nordic countries; Denmark, Finland, Norway and

Sweden, and New Zealand, in response to the COVID-19 pandemic. Methods: Per capita trends in total cases and per capita fatalities were analysed and difference-in-difference statistical tests undertaken to assess whether differences in stringency of mandated social distancing (SD) measures, testing rates and border closures explain cross-country differences. Results: Sweden is a statistical outlier, relative to its Nordic neighbours, for both per capita cases and per capita fatalities associated with COVID-19 but not in terms of the reduction in economic growth. Sweden's public health differences, compared to its Nordic neigbours, are partially explained by differences in terms of international border closures and the level of stringency of SD measures (including testing) implemented from early March to June 2020. Conclusions: *We find that: one, early imposition of full international travel restrictions combined with high levels of government-mandated stringency of SD reduced the per capita cases and per capita fatalities associated with COVID-19 in 2020 in the selected countries and, two, in Nordic countries, less stringent government-mandated SD is not associated with higher quarterly economic growth*. [**note: here is an analysis of public health and economic performance of Nordic Countries in response to the COVID-19 pandemic. This is useful as Sweden have been looked at as one model while their neighbors have elected to go down a different path.]**
https://www.medrxiv.org/content/10.1101/2020.11.23.20236711v1

- The knowledge of clinically relevant markers distribution might become a useful tool in COVID-19 therapy using personalized approach in the lack of unified recommendations for COVID-19 patients management during pandemic. We aimed to identify the frequencies and distribution patterns of rs11385942 and rs657152 polymorphic markers, associated with severe COVID-19, among populations of the world, as well at the national level within Russia. The study was also dedicated to reveal whether population frequencies of both polymorphic markers are associated with COVID-19 cases, recovery and death rates. Methods. We genotyped 1883 samples from 91 ethnic populations from Russia and neighboring countries by rs11385942 and rs657152 markers. Local populations which were geographically close and genetically similar were pooled into 28 larger groups. In the similar way we compiled a dataset on the other regions of the globe using genotypes extracted or imputed from the available datasets (32 populations worldwide). The differences in alleles frequencies between groups were estimated and the frequency distribution geographic maps have been constructed. We run the correlation analysis of both markers frequencies in various populations with the COVID-19 epidemiological data on the same populations. Findings. *The cartographic analysis revealed that distribution of rs11385942 follows the West Eurasian pattern: it is frequent in Europeans, West Asians, and particularly in South Asians but rare or absent in all other parts of the globe. Notably, there is no abrupt changes in frequency across Eurasia but the clinal variation instead. The distribution of rs657152 is more homogeneous. Higher population frequencies of both risk alleles correlated positively with the death rate. For the rs11385942 we can state the tendency only (r=0.13, p=0.65), while for rs657152 the correlation was significantly high (r=0.59, p=0.02). These reasonable correlations were obtained on the Russian dataset, but not on the world dataset. Interpretation. Using epidemiological statistics on Russia and neighboring countries we revealed the evident correlation of the risk alleles frequencies with the death rate from COVID-19. The lack of such correlations at the world level should be attributed to the differences in the ways epidemiological data have been counted in different countries. So that, we believe that genetic differences between populations make small but real contribution into the heterogeneity of the*

pandemic worldwide. New studies on the correlations between COVID-19 recovery/mortality rates and population's gene pool are urgently needed. [**note: this is from Russia and looks at the variation in genome sites associated with severe COVID-19 across populations. The authors note that more data is needed but there does appear to be a small but real genetic effect (not a surprising finding, but honing in on the exact locus will take a lot of data).**] https://www.medrxiv.org/content/10.1101/2020.11.22.20236414v1

NEWLY REGISTERED CLINICAL TRIALS

- Don't even ask about this section today!

CLINICAL TRIAL RESULTS

- There is growing recognition of the burden of COVID-19 among Asian Americans, but data on outcomes among Asian ethnic subgroups remain extremely limited. We conducted a retrospective analysis of 85,328 patients tested for COVID-19 at New York City's public hospital system between March 1 and May 31, 2020, to describe characteristics and COVID-19 outcomes of Asian ethnic subgroups compared to Asians overall and other racial/ethnic groups. South Asians had the highest rates of positivity and hospitalization among Asians, second only to Hispanics for positivity and Blacks for hospitalization. Chinese patients had the highest mortality rate of all groups and were nearly 1.5 times more likely to die than Whites. The high burden of COVID-19 among South Asian and Chinese Americans underscores the urgent needs for improved data collection and reporting as well as public health program and policy efforts to mitigate the disparate impact of COVID-19 among these communities. [**note: this data is from New York City and breaks out COVID-19 cases and outcomes among Asian Americans whining the public hospital system.**] https://www.medrxiv.org/content/10.1101/2020.11.23.20233155v1
- South Korea was one of the epicenters for both the 2015 MERS and 2019 COVID-19 outbreaks. However, there has been a lack of published literature, especially using the EMR records, that provides a comparative summary of the prognostic factors present in the coronavirus-derived diseases patients. Therefore, in this study, we aimed to compare and evaluate the distinct clinical traits between the patients of different coronaviruses, including the lesser pathogenic HCoV strains, SARS-CoV, MERS-CoV, and SARS-CoV-2. We also conducted observed the risk factors by the COVID severity to investigate the extent of resemblance in clinical features between the disease groups and to identify unique factor that may influence the prognosis of the COVID-19 patients. Here, we utilize the common data model (CDM), which is the database that houses the EMR records transformed into the common format to be used by the multiple institutions. For the comparative analyses between the disease groups, we used independent t-test, Scheffe post-hoc test, and Games-howell post-hoc test and for the continuous variables, chi-square test and Fisher exact test. Based on the analyses, we selected the variables with p-values less than 0.05 to predict COVID-19 severity by nominal logistic regression with adjustments to age and gender. *From the study, we observed diabetes, cardio and cerebrovascular diseases, cancer, pulmonary disease, gastrointestinal disease, and renal disease in all patient groups. Of all, the proportions of cancer patients were highest in all groups with no statistical significance. Most interestingly, we observed a high degree of clinical similarity between the COVID-19 and SARS patients with more than 50% of measured clinical variables to*

show statistical similarities between two groups. Our research reflects the great significance within the bioinformatics field that we were able to effectively utilize the integrated CDM to reflect real-world challenges in the context of coronavirus. We expect the results from our study to provide clinical insights that can serve as predicator of risk factors from the future coronavirus outbreak as well as the prospective guidelines for the clinical treatments. [**note: this is from South Korea and looks at all three novel coronaviruses for risk factors and clinical comparisons.**] https://www.medrxiv.org/content/10.1101/2020.11.23.20237487v1

DRUG DEVELOPMENT

- Rocaglates, a class of plant-derived cyclopenta[b]benzofurans, exhibit broad-spectrum antiviral activity against positive- and negative-sense RNA viruses. This compound class inhibits eukaryotic initiation factor 4A (eIF4A)-dependent mRNA translation initiation, resulting in strongly reduced viral RNA translation. The synthetic rocaglate CR-31-B (-) has previously been shown to inhibit the replication of human coronaviruses, such as HCoV-229E and MERS-CoV, as well as Zika-, Lassa-, Crimean Congo hemorrhagic fever virus in primary cells. Here, we assessed the antiviral activity of CR-31-B (-) against SARS-CoV-2 using both in vitro and ex vivo cell culture models. In African green monkey Vero E6 cells, CR-31-B (-) inhibited SARS-CoV-2 replication with an EC50 of ~1.8 nM. In line with this, viral protein accumulation and replication/transcription complex formation were found to be strongly reduced by this compound. In an ex vivo infection system using human airway epithelial cells, CR-31-B (-) was found to cause a massive reduction of SARS-CoV-2 titers by about 4 logs to nearly non-detectable levels. The data reveal a potent anti-SARS-CoV-2 activity by CR-31-B (-), corroborating previous results obtained for other coronaviruses and supporting the idea that rocaglates may be used in first-line antiviral intervention strategies against novel and emerging RNA virus outbreaks. [**note: this paper is from Germany. This compound comes from a class of natural products found in plants that have diverse biological activities.**]
  https://www.biorxiv.org/content/10.1101/2020.11.24.389627v1
- We recently discovered a superantigen-like motif, similar to Staphylococcal enterotoxin B (SEB), near the S1/S2 cleavage site of SARS-CoV-2 Spike protein, which might explain the multisystem-inflammatory syndrome (MIS-C) observed in children and cytokine storm in severe COVID-19 patients. *We show here that an anti-SEB monoclonal antibody (mAb), 6D3, can bind this viral motif, and in particular its PRRA insert, to inhibit infection by blocking the access of host cell proteases, TMPRSS2 or furin, to the cleavage site. The high affinity of 6D3 for the furin-cleavage site originates from a poly-acidic segment at its heavy chain CDR2, a feature shared with SARS-CoV-2-neutralizing mAb 4A8. The affinity of 6D3 and 4A8 for this site points to their potential utility as therapeutics for treating COVID-19, MIS-C, or common cold caused by human coronaviruses (HCoVs) that possess a furin-like cleavage site*. [**note: this is an interesting finding of a similar antigen motif on the cleavage site of the S protein that is similar to Staphylococcal enterotoxin B.]** https://www.biorxiv.org/content/10.1101/2020.11.24.395079v1
- Face masks have globally been accepted to be an effective protective tool to prevent bacterial and viral transmission, especially against indoor aerosol transmission. However, commercial face masks contain filters that are made of materials that are not capable of inactivating neither SARS-CoV-2 nor multidrug-resistant bacteria. Therefore, symptomatic and asymptomatic individuals can infect other people even if they wear them because some viable viral or bacterial

loads can escape from the masks. Furthermore, viral or bacterial contact transmission can occur after touching the mask, which constitutes an increasing source of contaminated biological waste. Additionally, bacterial pathogens contribute to the SARS-CoV-2 mediated pneumonia disease complex and their resistance to antibiotics in pneumonia treatment is increasing at an alarming rate. *In this regard, herein, we report the development of a novel protective non-woven face mask filter fabricated with a biofunctional coating of benzalkonium chloride that is capable of inactivating SARS-CoV-2 in one minute of contact, and the life-threatening methicillin-resistant Staphylococcus aureus and Staphylococcus epidermidis. Nonetheless, despite the results obtained, further studies are needed to ensure the safety and correct use of this technology for the mass production and commercialization of this broad-spectrum antimicrobial face mask filter. Our novel protective non-woven face mask filter would be useful for many health care workers and researchers working in this urgent and challenging field*. [**note: here is the design for an antimicrobial face mask using benzalkonium chloride. This compound is present in many commercial cleaning solutions.**]
https://www.biorxiv.org/content/10.1101/2020.11.24.396028v1

- In order to produce proteins essential for their propagation, many pathogenic human viruses, including SARS-CoV-2 the causative agent of COVID-19 respiratory disease, commandeer host biosynthetic machineries and mechanisms. Three major structural proteins, the spike, envelope and membrane proteins, are amongst several SARS-CoV-2 components synthesised at the endoplasmic reticulum (ER) of infected human cells prior to the assembly of new viral particles. Hence, the inhibition of membrane protein synthesis at the ER is an attractive strategy for reducing the pathogenicity of SARS-CoV-2 and other obligate viral pathogens. Using an in vitro system, we demonstrate that the small molecule inhibitor ipomoeassin F (Ipom-F) potently blocks the Sec61-mediated ER membrane translocation/insertion of three therapeutic protein targets for SARS-CoV-2 infection; the viral spike and ORF8 proteins together with angiotensin-converting enzyme 2, the host cell plasma membrane receptor. Our findings highlight the potential for using ER protein translocation inhibitors such as Ipom-F as host-targeting, broad-spectrum, antiviral agents. [**note: this is from England and offeres another possible drug candidate that blocks the virus. This is a natural product derived from Morning Glories and appears to be quite toxic in its native form.**]
https://www.biorxiv.org/content/10.1101/2020.11.24.390039v1
- The SARS-CoV-2 macrodomain (Mac1) within the non-structural protein 3 (Nsp3) counteracts host-mediated antiviral ADP-ribosylation signalling. This enzyme is a promising antiviral target because catalytic mutations render viruses non-pathogenic. Here, we report a massive crystallographic screening and computational docking effort, identifying new chemical matter primarily targeting the active site of the macrodomain. Crystallographic screening of diverse fragment libraries resulted in 214 unique macrodomain-binding fragments, out of 2,683 screened. An additional 60 molecules were selected from docking over 20 million fragments, of which 20 were crystallographically confirmed. X-ray data collection to ultra-high resolution and at physiological temperature enabled assessment of the conformational heterogeneity around the active site. Several crystallographic and docking fragment hits were validated for solution binding using three biophysical techniques (DSF, HTRF, ITC). Overall, the 234 fragment structures presented explore a wide range of chemotypes and provide starting points for development of potent SARS-CoV-2 macrodomain inhibitors. [**note: this is a study of the Nsp3**

protein of SARS-CoV-2. I think this is the first study to explicitly look at this enzyme. Perhaps this will be a good therapeutic target.]
https://www.biorxiv.org/content/10.1101/2020.11.24.393405v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- SARS-CoV-2 genome accumulates point mutations in a constant manner. Whether the accumulation of point mutations is correlated with milder manifestations of COVID-19 remains unknown. **Methods:** We performed SARS-CoV-2 genome sequencing in 90 patients with COVID-19 infection treated at a tertiary medical center in Tokyo between March and August 2020. The possible association between disease severity and viral haplotype was then assessed by counting the number of mutations in addition to performing phylogenic tree analysis, comparative amino acid sequence analysis among β-coronaviruses, and mathematical prediction of the functional relevance of amino acid substitutions. **Results:** The number of non-synonymous mutations was inversely correlated with COVID-19 severity, as defined by requiring oxygen supplementation. Phylogenic tree analysis identified two predominant groups which were separated by a set of 6 single nucleotide substitutions, including four leading to non-synonymous amino acid substitutions. Among those four, Pro108Ser in 3 chymotrypsin-like protease ($3CL^{pro}$) and Pro151Leu in nucleocapsid protein occurred at conserved locations and were predicted to be deleterious. Patients with Pro108Ser in $3CL^{pro}$ and Pro151Leu in nucleocapsid protein had a lower odds ratio for developing hypoxia requiring supplemental oxygen (odds ratio of 0.24 [95% confidence interval of 0.07-0.88, P-value = 0.032]) after adjustments for age and sex, compared with patients lacking this haplotype in Clade 20B. **Conclusion:** *Viral genome sequencing in 90 patients treated in the Tokyo Metropolitan area showed that the accumulation of point mutations, including Pro108Ser in $3CL^{pro}$ and Pro151Leu in nucleocapsid protein, was inversely correlated with COVID-19 severity. Further in vitro research is awaited*. [**note: this is from Tokyo and looks at point mutations in the virus relative to disease severity in patients at a tertiary hospital.**]
https://www.medrxiv.org/content/10.1101/2020.11.24.20235952v1
- SARS-CoV-2 mortality has been extensively studied in relationship to a patient's predisposition to the disease. However, how sequence variations in the SARS-CoV-2 genome affect mortality is not understood. *To address this issue, we used a whole-genome sequencing (WGS) association study to directly link death of SARS-CoV-2 patients with sequence variation in the viral genome. Specifically, we analyzed 3,626 single stranded RNA-genomes of SARS-CoV-2 patients in the GISAID database (Elbe and Buckland-Merrett, 2017; Shu and McCauley, 2017) with reported patient's health status from COVID-19, i.e. deceased versus non-deceased. In total, evaluating 28,492 loci of the viral genome for association with patient/host mortality, two loci, 12,053bp and 25,088bp, achieved genome-wide significance (p-values of 1.24e-12, and 1.24e-26, respectively). Mutations at 25,088bp occur in the S2 subunit of the SARS-CoV-2 spike protein, which plays a key role in viral entry of target host cells. Additionally, mutations at 12,053bp are within the ORF1ab gene, in a region encoding for the protein nsp7, which is necessary to form the RNA polymerase complex responsible for viral replication and transcription. Both mutations altered amino acid coding sequences, potentially imposing structural changes that could enhance viral infectivity and symptom severity, and may be important to consider as targets for therapeutic development*. [**note: here is another study of mutations in SARS-CoV-2 and the**

linkage to COVID-19 mortality.]
https://www.biorxiv.org/content/10.1101/2020.11.17.386714v1

DIAGNOSTIC DEVELOPMENT

- Nothing striking today.

>>

2020-11-27

How did I go so long with music selections without acknowledging Nina Simone? Too long, that's how long! Here is Ms. Simone in a live performance from Morehouse College in 1969 with 'Take Me to the Water': https://www.youtube.com/watch?v=N1xWFo8xEu8

I'm not going to link to the endless stories about the current outbreak unless there is something unique. I could spend all day in frustration reading about overcrowded hospitals and excessive deaths. As I've said in the past, this could have been a much different trajectory. Here is the latest CDC forecast.

The New York Times comments on issues related to the AstraZeneca/Oxford vaccine trial. The FDA will sort this out but right now things look problematic for this vaccine. Amazon has hired a lot of workers because of home shopping during the pandemic. Yes, the virus will continue to evolve, and this is one of the reasons I would like to see more focus on vaccines with the N protein as an added antigen.

The Washington Post discusses the 5-4 Supreme Court decision blocking New York State's attempt to curb attendance at religious institutions. I understand the Constitution pretty well but the Justices who sided against New York clearly do not understand what protection of the public health means. Are some people going to get new treatments for COVID-19 because of their political standing? When new COVID-19 treatments are in short supply who will decision on who gets them be made? This virus zapping robot, although costly, is a pretty cool invention. I want one for my home!!!

STAT have an opinion piece on COVID-19 related risks to football players.

JAMA have a report on the estimated seroprevalence of COVID-19 in the US. *In this repeated, cross-sectional study of 177 919 residual clinical specimens, the estimated percentage of persons in a jurisdiction with detectable SARS-CoV-2 antibodies ranged from fewer than 1% to 23%. Over 4 sampling periods in 42 of 49 jurisdictions with calculated estimates, fewer than 10% of people had detectable SARS-CoV-2 antibodies.* [**note: the survey covers the period from July to September of this year and does not have data from the current wave. 'If' we assume the herd immunity level is 50-70%, there is a long way to go before transmission dies down nationwide. This is why some of the models being used by policymakers paint a bleak picture.**] Here is a good commentary on this matter. Here is a paper from Johns Hopkins regarding psychological distress and COVID-19 related stressors reported in the US in April and July. *Reported prevalence of serious psychological distress among US adults was 13.6% in April 2020 and 13% in July 2020. Persistent distress increases risk of psychiatric disorders, which the Kessler 6 scale predicts.[3] High prevalence at both time points suggests that the pandemic's longer-term disruptions are important drivers of distress. More than 60% of adults with serious distress reported that pandemic-related disruptions to education, employment, and finances negatively affected their mental health. These stressors may be particularly salient to young adults, about a quarter of whom reported serious distress in both April and July. Thirty-five percent of adults with serious distress cited*

inability to obtain health care as a contributing factor, highlighting the need to facilitate safe and affordable health care access during the pandemic and beyond.[4,5]

STAT have a story of a Kentucky woman who took precautions but came down with both the flu and COVID-19 at the same time. I still do not understand mask resistance.

The Lancet's editor, Richard Horton, writes about the struggle in Europe in dealing with COVID-19. Here is a commentary on the role of remdesivir in COVID-19 treatment. It is a useful drug but not the 'magic bullet' that we need.

MODELING

- Human Challenge Trials (HCTs) are a potential method to accelerate development of vaccines and therapeutics. However, HCTs for COVID-19 pose ethical and practical challenges, in part due to the unclear and developing risks. In this paper, we introduce an interactive model for exploring some risks of a SARS-COV-2 dosing study, a prerequisite for any COVID-19 challenge trials. The risk estimates we use are based on a Bayesian evidence synthesis model which can incorporate new data on infection fatality rates (IFRs) to patients, and infer rates of hospitalization. We have also created a web tool to explore risk under different study design parameters and participant scenarios. Finally, we use our model to estimate individual risk, as well as the overall mortality and hospitalization risk in a dosing study. Based on the Bayesian model we expect IFR for someone between 20 and 30 years of age to be 17.5 in 100,000, with 95% uncertainty interval from 12.8 to 23.6. *Using this estimate, we find that a simple 50-person dosing trial using younger individuals has a 99.1% (95% CI: 98.8% to 99.4%) probability of no fatalities, and a 92.8% (95% CI: 90.3% to 94.6%) probability of no cases requiring hospitalization. However, this IFR will be reduced in an HCT via screening for comorbidities, as well as providing medical care and aggressive treatment for any cases which occur, so that with stronger assumptions, we project the risk to be as low as 3.1 per 100,000, with a 99.85% (95% CI: 99.7% to 99.9%) chance of no fatalities, and a 98.7% (95% CI: 97.4% to 99.3%) probability of no cases requiring hospitalization*. [**note: for those who support human challenge trials for vaccine development, here is a model exploring the risks. This comes from the group 1 Day Sooner that advocates for such trials.**]
  https://www.medrxiv.org/content/10.1101/2020.11.19.20234658v1

NEWLY REGISTERED CLINICAL TRIALS

- It's not being updated today.

CLINICAL TRIAL RESULTS

- Lots of people took naps yesterday because of eating too much turkey.

DRUG DEVELOPMENT

- The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the ongoing pandemic coronavirus disease 2019 (COVID-19) has triggered worldwide concerted efforts in an attempt to identify effective therapies. In the present study, we have identified two candidate agents with potential activity against SARS-CoV-2 which can be administered intranasally, namely, xylitol and grape seed fruit extract (GSE). A commercially available nasal spray (Xlear)

combining xylitol and GSE has been available for years, but the antiviral effects of this solution have not been documented. This in vitro study examined the virucidal effect of Xlear against SARS-CoV-2. To this end, two independent sets of experiments were carried out to test the hypothesis that Xlear is an effective (Experiment I) and replicable (Experiment II) means to deactivate SARS-CoV-2. When tested against SARS-CoV-2, the test compound GSE 0.2% was the only compound effective at reducing >3 log10 CCID50 infectious virus from, 3.67 log10 CCID50/0.1 mL to an undetectable amount of infectious virus. The present results validated by two independent sets of experiments, performed by different labs, on different viral strains, provide early evidence to encourage further pilot and clinical studies aimed at investigating the use of Xlear as a potential treatment for COVID-19 [**note: here's another approach for all of you naturopathic medicine believers. This product is available without a prescription!!!! Give it a try.**] https://www.biorxiv.org/content/10.1101/2020.11.23.394114v1

- Receptor recognition and subsequent membrane fusion are essential for the establishment of successful infection by SARS-CoV-2. Halting these steps can cure COVID-19. Here we have identified and characterized a potent human monoclonal antibody, HB27, that blocks SARS-CoV-2 attachment to its cellular receptor at sub-nM concentrations. Remarkably, HB27 can also prevent SARS-CoV-2 membrane fusion. Consequently, a single dose of HB27 conferred effective protection against SARS-CoV-2 in two established mouse models. Rhesus macaques showed no obvious adverse events when administrated with 10-fold of effective dose of HB27. *Cryo-EM studies on complex of SARS-CoV-2 trimeric S with HB27 Fab reveal that three Fab fragments work synergistically to occlude SARS-CoV-2 from binding to ACE2 receptor. Binding of the antibody also restrains any further conformational changes of the RBD, possibly interfering with progression from the prefusion to the postfusion stage. These results suggest that HB27 is a promising candidate for immuno-therapies against COVID-19*. [**note: here is a potent mAb from China that warrants clinical trials.**]
https://www.biorxiv.org/content/10.1101/2020.11.24.393629v1
- Six pathogenic human coronaviruses, likely zoonotic viruses, cause the common cold in humans. A new emerging coronavirus, SARS-CoV-2, become a crucial etiology for the Coronavirus-induced disease 19 (COVID-19). However, effective therapeutics and vaccines against multiple coronaviruses remain unavailable. *This study aimed to investigate an antiviral molecule, single chain variable fragment (scFv), against SARS-CoV-2 and other coronaviruses. 3D8, a recombinant scFv, exhibits broad-spectrum antiviral activity against DNA and RNA viruses owing to its nucleic acid-hydrolyzing property. Here, we report that 3D8 scFv inhibited the replication of SARS-CoV-2, human coronavirus OC43 (HCoV-OC43), and porcine epidemic diarrhea virus (PEDV). Our results revealed the prophylactic and therapeutic effects of 3D8 scFv against SARS-CoV-2 in Vero E6 cells. Immunoblot and plaque assays showed the absence of coronavirus nucleoproteins and infectious particles in 3D8 scFv-treated cells, respectively. In addition, we observed the antiviral effects of 3D8 against HCoV-OC43 and PEDV. In conclusion, this study provides insights into the broad-spectrum antiviral agent of 3D8 scFv; thus, it could be considered a potential antiviral countermeasure against SARS-CoV-2 and zoonotic coronaviruses*. [**note: this is from South Korea and looks at a single chain variable fragment that has been studied against a number of animal pathogens in the past. Whether it is useful against SARS-CoV-2 *in vivo* remains to be determined.**] https://www.biorxiv.org/content/10.1101/2020.11.25.398909v1

- Until an effective vaccine against SARS-CoV-2 is available on a widespread scale, the control of the COVID-19 pandemic is reliant upon effective pandemic control measures. The ability of SARS-CoV-2 to remain viable on surfaces and in aerosols, means indirect contact transmission can occur and so there is an opportunity to reduce transmission using effective disinfectants in public and communal spaces. Virusend (TX-10), a novel disinfectant, has been developed as a highly effective disinfectant against a range of microbial agents. Here we investigate the ability of VirusEnd (TX-10) to inactivation SARS-CoV-2. Using surface and solution inactivation assays, we show that VirusEnd (TX-10) is able to reduce SARS-CoV-2 viral titre by 4log10 PFU/mL within 1 minute of contact. Ensuring disinfectants are highly effective against SARS-CoV-2 is important in eliminating environmental sources of the virus to control the COVID-19 pandemic. [**note: another disinfectant for surfaces. There are so many choices, that a new one is not necessarily big news.**] https://www.biorxiv.org/content/10.1101/2020.11.25.394288v1
- The emergence of SARS-CoV-2 virus has resulted in a worldwide pandemic, but an effective antiviral therapy has yet to be discovered. To improve treatment options, we conducted a high-throughput drug repurposing screen to uncover compounds that block the viral activity of SARS-CoV-2. A minimally pathogenic human betacoronavirus (OC43) was used to infect physiologically-relevant human pulmonary fibroblasts (MRC5) to facilitate rapid antiviral discovery in a preclinical model. Comprehensive profiling was conducted on more than 600 compounds, with each compound arrayed at 10 dose points (ranging from 20 µM to 1 nM). Our screening revealed several FDA-approved agents that act as novel antivirals that block both OC43 and SARS-CoV-2 viral replication, including lapatinib, doramapimod, and 17-AAG. Importantly, lapatinib inhibited SARS-CoV-2 replication by over 50,000-fold without any toxicity and at doses readily achievable in human tissues. Further, both lapatinib and doramapimod could be combined with remdesivir to dramatically improve antiviral activity in cells. These findings reveal novel treatment options for people infected with SARS-CoV-2 that can be readily implemented during the pandemic. [**note: another *in vitro* study shows lapatinib is an antiviral agent. This is not the first tyrosine kinase inhibitor that works against SARS-CoV-2. Maybe this would be a good one to look at as a combination therapy. It's also an oral drug.**] https://www.biorxiv.org/content/10.1101/2020.11.25.398859v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Fine scale delineation of epitopes recognized by the antibody response to SARS-CoV-2 infection will be critical to understanding disease heterogeneity and informing development of safe and effective vaccines and therapeutics. The Serum Epitope Repertoire Analysis (SERA) platform leverages a high diversity random bacterial display library to identify epitope binding specificities with single amino acid resolution. We applied SERA broadly, across human, viral and viral strain proteomes in multiple cohorts with a wide range of outcomes from SARS-CoV-2 infection. *We identify dominant epitope motifs and profiles which effectively classify COVID-19, distinguish mild from severe disease, and relate to neutralization activity. We identify a repertoire of epitopes shared by SARS-CoV-2 and endemic human coronaviruses and determine that a region of amino acid sequence identity shared by the SARS-CoV-2 furin cleavage site and the host protein ENaC-alpha is a potential cross-reactive epitope. Finally, we observe decreased epitope signal for mutant strains which points to reduced antibody response to mutant SARS-CoV-2. Together, these findings indicate that SERA enables high resolution of antibody epitopes*

that can inform data-driven design and target selection for COVID-19 diagnostics, therapeutics and vaccines. [**note: this is a multi-author paper that looks at viral epitopes. I think this type of research is quite valuable and we will learn more about the relationship between SARS-CoV-2 and other coronaviruses.**]
https://www.medrxiv.org/content/10.1101/2020.11.23.20235002v1

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19. SARS-CoV-2 relies on cellular RNA-binding proteins (RBPs) to replicate and spread, although which RBPs control SARS-CoV-2 infection remains largely unknown. *Here, we employ a multi-omic approach to identify systematically and comprehensively which cellular and viral RBPs are involved in SARS-CoV-2 infection. We reveal that the cellular RNA-bound proteome is remodelled upon SARS-CoV-2 infection, having widespread effects on RNA metabolic pathways, non-canonical RBPs and antiviral factors. Moreover, we apply a new method to identify the proteins that directly interact with viral RNA, uncovering dozens of cellular RBPs and eight viral proteins. Amongst them, several components of the tRNA ligase complex, which we show regulate SARS-CoV-2 infection. Furthermore, we discover that available drugs targeting host RBPs that interact with SARS-CoV-2 RNA inhibit infection. Collectively, our results uncover a new universe of host-virus interactions with potential for new antiviral therapies against COVID-19*. [**note: this is from the UK and shows some new interactions that may regulate infection.**]
https://www.biorxiv.org/content/10.1101/2020.11.25.398008v1
- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of the ongoing coronavirus disease 19 (COVID-19) pandemic. Despite the urgent need, we still do not fully understand the molecular basis of SARS-CoV-2 pathogenesis and its ability to antagonize innate immune responses. Here, we use RNA-sequencing and ribosome profiling along SARS-CoV-2 infection and comprehensively define the mechanisms that are utilized by SARS-CoV-2 to shutoff cellular protein synthesis. *We show SARS-CoV-2 infection leads to a global reduction in translation but that viral transcripts are not preferentially translated. Instead, we reveal that infection leads to accelerated degradation of cytosolic cellular mRNAs which facilitates viral takeover of the mRNA pool in infected cells. Moreover, we show that the translation of transcripts whose expression is induced in response to infection, including innate immune genes, is impaired, implying infection prevents newly transcribed cellular mRNAs from accessing the ribosomes. Overall, our results uncover the multipronged strategy employed by SARS-CoV-2 to commandeer the translation machinery and to suppress host defenses*. [**note: this is from Israel and examines the multipronged strategy the virus uses to suppress host protein synthesis. The virus is indeed devious!**] https://www.biorxiv.org/content/10.1101/2020.11.25.398578v1

DIAGNOSTIC DEVELOPMENT

- Nothing today.

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

2020-11-28

Like him or hate him, Tom Jones was one of the biggest recording stars from the time he broke onto the scene in the mid-1960s. Other than classical, there was not a single genre that he did not attack with gusto. He had a good run as a star entertainer in Las Vegas and was still singing until a couple of years

ago. It seems fitting to see him in this live performance singing, 'You'll Never Walk Alone' from Carousel: https://www.youtube.com/watch?v=BEgtX1RgIeA that serves as a reminder that we all (maybe mostly all) are in this together.

This Washington Post story shows how the country's priorities are ass-backwards. Athletes get tested for COVID-19 and nurses don't. What is wrong here? Will the two shot COVID-19 vaccine regimen pose difficulties for the inoculation program?

The New York Times provides further evidence on the crises in hospitals in areas hard hit by COVID-19. This op-ed writer has some questions about masks. The one key answer is to put it on when you go out into areas where there are other people! Will ski resorts in Europe open this winter?

The European Medicines Agency issued a drug safety warning on chloroquine and hydroxychloroquine. *EMA's safety committee (PRAC) has recommended updating the product information for all chloroquine or hydroxychloroquine-containing medicines following a review of all available data that confirmed a link between the use of these medicines and the risk of psychiatric disorders and suicidal behaviour*.

MODELING

- Introduction New York City (NYC) has the largest public school system in the United States (US). During the SARS-CoV-2 pandemic, NYC was the first major US city to open schools for in-person learning in the 2020-2021 academic year. Several policies were implemented to reduce the risk of in-school transmission, including infection control measures (facemasks, physical distancing, enhanced indoor ventilation, cohorting of small groups, and hand hygiene), option of all-remote instruction, alternative options for how class schedules would rotate in-person and remote instruction, daily symptom screening, and testing 10-20% of students and staff weekly or monthly depending on local case rates. We sought to determine which of these policies had the greatest impact on reducing the risk of in-school transmission. Methods We evaluated the impact of each policy by referring to global benchmarks for the secondary attack rate (SAR) of SARS-CoV-2 in school settings and by simulating the potential for transmission in NYC's rotating cohort schedules, in which teachers could act as "bridges" across rotating cohorts. We estimated the impact of (1) infection control measures, (2) providing an option of all-remote instruction, (3) choice of class scheduling for in-person learners, (4) daily symptom screening, (5) testing to curtail transmission, and (6) testing to identify school outbreaks. Each policy was assessed independently of other policies, with the exception of symptom screening and random testing, which were assessed both independently and jointly. Results *Among the policies analyzed, the greatest transmission reduction was associated with the infection control measures, followed by small class cohorts with an option for all-remote instruction, symptom screening, and finally randomly testing 10-20% of school attendees. Assuming adult staff are the primary source of within-school SARS-CoV-2 transmission, weekly testing of staff could be at least as effective as symptom screening, and potentially more so if testing days occur in the beginning of the workweek with results available by the following day. A combination of daily symptom screening and testing on the first workday of each week could reduce transmission by 70%. Conclusions Adherence to infection control is the highest priority for safe school re-opening. Further transmission reduction can be achieved through small rotating class cohorts with an*

option for remote learning, widespread testing at the beginning of the work week, and daily symptom screening and self-isolation. Randomly testing 10-20% of attendees weekly or monthly does not meaningfully curtail transmission and may not detect outbreaks before they have spread beyond a handful of individuals. School systems considering re-opening during the SARS-CoV-2 pandemic or similarly virulent respiratory disease outbreaks should consider these relative impacts when setting policy priorities. [**note: this is a study of various virus control procedures in the New York City schools.**]
https://www.medrxiv.org/content/10.1101/2020.11.24.20237305v1

- To determine if the observed change in reported norovirus outbreaks in the United States was best explained by underreporting, seasonal trends, or reduced exposure due to NPIs. We also aimed to assess if the change in reported norovirus outbreaks varied by setting. Design: An ecologic, interrupted time series analysis of norovirus outbreaks from nine states reported to the National Outbreak Reporting System (NORS) from July 2012-July 2020. Setting: Surveillance data from Massachusetts, Michigan, Minnesota, Ohio, Oregon, South Carolina, Tennessee, Virginia, and Wisconsin were included in the analysis. Participants: 9,226 reports of acute gastroenteritis outbreaks with norovirus as an epidemiologically suspected or laboratory-confirmed etiology were included in the analysis, resulting in more than 8 years of follow up. Outbreak reports from states that participated in NoroSTAT for at least 4 years were included in the analysis (range: 4-8 years). Exposure: The main exposure of interest was time period: before (July 2012-February 2020) or after (April 2020-July 2020) the start of NPIs in the United States Main outcome: The main outcome of interest was monthly rate of reported norovirus outbreaks. As a secondary outcome, we also examined the average outbreak size. Results: We found that the decline in norovirus outbreak reports was significant for all 9 states considered (pooled incidence rate ratio (IRR) comparing April 2020-July 2020 vs. all pre-COVID months for each state= 0.14, 95% CI: 0.098, 0.21; P=<0.0001), even after accounting for typical seasonal decline in incidence during the summer months. These patterns were similar across a variety of settings, including nursing homes, child daycares, healthcare settings, and schools. The average outbreak size was also reduced by 61% (95% CI: 56%, 42.7%; P=<0.0001), suggesting that the decline does not reflect a tendency to report only more severe outbreaks due to strained surveillance systems, but instead reflects a decline in incidence. Conclusions and relevance: *While NPIs implemented during the spring and summer of 2020 were intended to reduce transmission of SARS-CoV-2, these changes also appear to have impacted the incidence of norovirus, a non-respiratory pathogen. These results suggest that NPIs may provide benefit for preventing transmission of other human pathogens, reducing strain to health systems during the continued SARS-CoV-2 pandemic*. [**note: measures to control SARS-CoV-2 transmission also controlled infections from norovirus.**]
https://www.medrxiv.org/content/10.1101/2020.11.25.20237115v1

NEWLY REGISTERED CLINICAL TRIALS

- Check back tomorrow and you will be surprised.

CLINICAL TRIAL RESULTS

- COVID-19 clinical presentation ranges from asymptomatic to fatal outcome. This variability is due in part to host genome specific mutations. Recently, two families in which COVID-19

segregates like an X-linked recessive monogenic disorder environmentally conditioned by SARS-CoV-2 have been reported leading to identification of loss-of-function variants in TLR7. Objective: We sought to determine whether the two families represent the tip of the iceberg of a subset of COVID-19 male patients. Methods: We compared male subjects with extreme phenotype selected from the Italian GEN-COVID cohort of 1178 SARS-CoV-2-infected subjects (<60y, 79 severe cases versus 77 control cases). We applied the LASSO Logistic Regression analysis, considering only rare variants on the young male subset, picking up TLR7 as the most important susceptibility gene. Results: Rare TLR7 missense variants were predicted to impact on protein function in severely affected males and in none of the asymptomatic subjects. We then investigated a similar white European cohort in Spain, confirming the impact of TRL7 variants. A gene expression profile analysis in peripheral blood mononuclear cells after stimulation with TLR7 agonist demonstrated a reduction of mRNA level of TLR7, IRF7, ISG15, IFN-α and IFN-γ in COVID-19 patients compared with unaffected controls demonstrating an impairment in type I and II INF responses. Conclusion: *Young males with TLR7 loss-of-function mutations and severe COVID-19 in the two reported families represent only a fraction of a broader and complex host genome situation. Specifically, missense mutations in the X-linked recessive TLR7 disorder may significantly contribute to disease susceptibility in up to 4% of severe COVID-19*. [**note: here is some good genetic sleuthing from Italy about host genomic mutations in male subjects from two families. A variant in Toll-like receptor 7 may be associated with severe COVID-19.**] https://www.medrxiv.org/content/10.1101/2020.11.19.20234237v1

- Acquired somatic mutations in hematopoietic stem and progenitor cells (clonal hematopoiesis or CH) are associated with advanced age, increased risk of cardiovascular and malignant diseases, and decreased overall survival. These adverse sequelae may be mediated by altered inflammatory profiles observed in patients with CH. A pro-inflammatory immunologic profile is also associated with worse outcomes of certain infections, including SARS-CoV-2 and its associated disease Covid-19. Whether CH predisposes to severe Covid-19 or other infections is unknown. *Among 515 individuals with Covid-19 from Memorial Sloan Kettering (MSK) and the Korean Clonal Hematopoiesis (KoCH) consortia, we found that CH was associated with severe Covid-19 outcomes (OR=1.9, 95%=1.2-2.9, p=0.01). We further explored the relationship between CH and risk of other infections in 14,211 solid tumor patients at MSK. CH was significantly associated with risk of Clostridium Difficile (HR=2.0, 95% CI: 1.2-3.3, p=6x10-3) and Streptococcus/Enterococcus infections (HR=1.5, 95% CI=1.1-2.1, p=5x10-3). These findings suggest a relationship between CH and risk of severe infections that warrants further investigation*. [**note: here is another example of a relation to severe COVID-19. In this case it is somatic mutations in hematopoietic stem and progenitor cells.**] https://www.medrxiv.org/content/10.1101/2020.11.25.20233163v1
- Objective: Patients with autoimmune diseases were advised to shield to avoid COVID-19, but information on their prognosis is lacking. We characterised 30-day outcomes and mortality after hospitalisation with COVID-19 among patients with prevalent autoimmune diseases, and compared outcomes after hospital admissions among similar patients with seasonal influenza. Design: Multinational network cohort study Setting: Electronic health records data from Columbia University Irving Medical Center (CUIMC) (NYC, United States [US]), Optum [US], Department of Veterans Affairs (VA) (US), Information System for Research in Primary Care-Hospitalisation Linked Data (SIDIAP-H) (Spain), and claims data from IQVIA Open Claims (US) and

Health Insurance and Review Assessment (HIRA) (South Korea). Participants: All patients with prevalent autoimmune diseases, diagnosed and/or hospitalised between January and June 2020 with COVID-19, and similar patients hospitalised with influenza in 2017-2018 were included. Main outcome measures: 30-day complications during hospitalisation and death Results: We studied 133,589 patients diagnosed and 48,418 hospitalised with COVID-19 with prevalent autoimmune diseases. The majority of participants were female (60.5% to 65.9%) and aged ≥50 years. The most prevalent autoimmune conditions were psoriasis (3.5 to 32.5%), rheumatoid arthritis (3.9 to 18.9%), and vasculitis (3.3 to 17.6%). Amongst hospitalised patients, Type 1 diabetes was the most common autoimmune condition (4.8% to 7.5%) in US databases, rheumatoid arthritis in HIRA (18.9%), and psoriasis in SIDIAP-H (26.4%). Compared to 70,660 hospitalised with influenza, those admitted with COVID-19 had more respiratory complications including pneumonia and acute respiratory distress syndrome, and higher 30-day mortality (2.2% to 4.3% versus 6.3% to 24.6%). Conclusions: *Patients with autoimmune diseases had high rates of respiratory complications and 30-day mortality following a hospitalization with COVID-19. Compared to influenza, COVID-19 is a more severe disease, leading to more complications and higher mortality. Future studies should investigate predictors of poor outcomes in COVID-19 patients with autoimmune diseases*. [**note: this is another large study that arose from a protocol developed by OHDSI and looks at patients with prevalent autoimmune diseases. COVID-19 is a more severe disease in this cohort than common influenza.**]
https://www.medrxiv.org/content/10.1101/2020.11.24.20236802v1

DRUG DEVELOPMENT

- The *a priori* T cell repertoire and immune response against SARS-CoV-2 viral antigens may explain the varying clinical course and prognosis of patients having a mild COVID-19 infection as opposed to those developing more fulminant multisystem organ failure and associated mortality. Using a novel SARS-Cov-2-specific artificial antigen presenting cell (aAPC), coupled with a rapid expansion protocol (REP) as practiced in tumor infiltrating lymphocytes (TIL) therapy, we generate an immune catalytic quantity of Virus Induced Lymphocytes (VIL). Using T cell receptor (TCR)-specific aAPCs carrying co-stimulatory molecules and major histocompatibility complex (MHC) class-I immunodominant SARS-CoV-2 peptide-pentamer complexes, we expand virus-specific VIL derived from peripheral blood mononuclear cells (PBMC) of convalescent COVID-19 patients up to 1,000-fold. This is achieved in a clinically relevant 7-day vein-to-vein time-course as a potential adoptive cell therapy (ACT) for COVID-19. *We also evaluate this approach for other viral pathogens using Cytomegalovirus (CMV)-specific VIL from donors as a control. Rapidly expanded VIL are enriched in virus antigen-specificity and show an activated, polyfunctional cytokine profile and T effector memory phenotype which may contribute to a robust immune response. Virus-specific T cells can also be delivered allogeneically via MHC-typing and patient human leukocyte antigen (HLA)-matching to provide pragmatic treatment in a large-scale therapeutic setting. These data suggest that VIL may represent a novel therapeutic option that warrants further clinical investigation in the armamentarium against COVID-19 and other possible future pandemics*. [**note: this may be a possible cellular therapy for COVID-19. Virus induced lymphocytes.**]
https://www.biorxiv.org/content/10.1101/2020.11.26.400390v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- SARS-CoV-2 is a novel ssRNA+ virus from the *Coronaviridae* family, which has caused the global COVID-19 pandemic. The genome of SARS-CoV-2 is one of the largest of RNA viruses, comprising of 26 known protein-coding loci. This study aimed to explore the coding potential of negative-strand RNA intermediate for its potential to contain additional protein coding-loci. Surprisingly, we have found several putative ORFs and one brandt new functional SARS-CoV-2 protein-coding loci and called it *Avo1* (Ambient viral ORF1). *This sequence is located on negative-sense RNA intermediate and* bona fide *coding for 81 amino acid residues long protein and contains strong Kozak sequence for translation on eukaryotic ribosomes.* In silico *translated protein Avo1 has a predominantly alpha-helical structure. The existence of* Avo1 *gene is supported also by its evolutionarily and structural conservation in RaTG13 bat coronavirus. The nucleotide sequence of* Avo1 *also contains a unique SREBP2 binding site which is closely related to the so-called cytokine storm in severe COVID-19 patients. Altogether, our results suggest the existence of still undescribed SARS-CoV-2 protein, which may play an important role in the viral lifecycle and COVID-19 pathogenesis*. [**note: here is an interesting paper from the Czech Republic on a possible new SARS-CoV-2 protein. We will need to see further confirmation of this finding but it may have implications for disease progression.**]
  https://www.biorxiv.org/content/10.1101/2020.11.27.400788v1
- The efficacy of virus-specific T cells in clearing pathogens involves a fine balance between their antiviral and inflammatory features. SARS-CoV-2-specific T cells in individuals who clear SARS-CoV-2 infection without symptoms or disease could reveal non-pathological yet protective characteristics. We therefore compared the quantity and function of SARS-CoV-2-specific T cells in a cohort of asymptomatic individuals (n=85) with that of symptomatic COVID-19 patients (n=76), at different time points after antibody seroconversion. We quantified T cells reactive to structural proteins (M, NP and Spike) using ELISpot assays, and measured the magnitude of cytokine secretion (IL-2, IFN-γ, IL-4, IL-6, IL-1β, TNF-α and IL-10) in whole blood following T cell activation with SARS-CoV-2 peptide pools as a functional readout. Frequencies of T cells specific for the different SARS-CoV-2 proteins in the early phases of recovery were similar between asymptomatic and symptomatic individuals. *However, we detected an increased IFN-γ and IL-2 production in asymptomatic compared to symptomatic individuals after activation of SARS-CoV-2-specific T cells in blood. This was associated with a proportional secretion of IL-10 and pro-inflammatory cytokines (IL-6, TNF-α and IL-1β) only in asymptomatic infection, while a disproportionate secretion of inflammatory cytokines was triggered by SARS-CoV-2-specific T cell activation in symptomatic individuals. Thus, asymptomatic SARS-CoV-2 infected individuals are not characterized by a weak antiviral immunity; on the contrary, they mount a robust and highly functional virus-specific cellular immune response. Their ability to induce a proportionate production of IL-10 might help to reduce inflammatory events during viral clearance*. [**note: from Singapore, more information on the immune response in asymptomatic people. It appears they mount a significant cellular immune response that is specific for the virus while producing little antibody response.**]
  https://www.biorxiv.org/content/10.1101/2020.11.25.399139v1

DIAGNOSTIC DEVELOPMENT

- Nothing today.

>>

2020-11-29

For reflection Sunday, I offer up Beethoven's Missa Solemnis that was written around the time of his Ninth Symphony. The performance is by the Frankfurt Radio Symphony under the direction of Andrés Orozco-Estrada. The setting is the Kloster Eberbach, a former monastery in Eltville, Hesse Germany. Enjoy this one: https://www.youtube.com/watch?v=hnrFUFVcDmc&t=19s

The Washington Post covers Rhode Island's decision to close bars and gyms and keep schools open. This is the right choice. Here is how to safely engage in various sports; I'm partial to solitary walking as the risks of contracting COVID-19 are quite small. Here is a nice article on COVID-19 tracking apps. We have them on our Android phones.

The New York Times has a story of how Baltimore is trying to move back to in class teaching.

MODELING

- Universities play a central role in a rural or small town's economy. They are often the main forms of enrichment to the lives of the longtime residents, the students, and the employees. *Unfortunately, during a global pandemic, the migration and movement of young people in these communities can likely cause a rapid infection spike and drive spread easily, especially relative to larger urban areas. The current study investigates the relationship between COVID-19 case growth, university-county rurality, and time at the beginning of the Fall 2020 academic semester. Findings showed that small metro and non-metro counties with universities had a dramatic infection spike near the beginning of the semester and infection growth remained significantly higher than their large and medium metro counterparts for the duration of the study. Suggestions to slow the spread in rural communities are discussed*. [**note: here is a study that shows COVID-19 infection rates at small metro and non-metro counties was higher than at large metro areas. This was a result of young people moving into the area.**] https://www.medrxiv.org/content/10.1101/2020.11.25.20238642v1
- Understanding how location-specific variations in non-pharmaceutical epidemic control policies and behaviors contributed to disease transmission will be key for designing effective strategies to avoid future resurgences. We offer a statistical analysis of the relative effectiveness of the timing of both official stay-at-home orders and population mobility reductions, offering a distinct (but complementary) dimension of evidence gleaned from more traditional mechanistic models of epidemic dynamics. Specifically, we use a Bayesian hierarchical model fit to county-level mortality data from the first wave of the pandemic from Jan 21 2020 through May 10 2020 to establish how timing of stay-at-home orders and population mobility changes impacted county-specific epidemic growth. We find that population mobility reductions generally preceded stay-at-home orders, and among 356 counties with a pronounced early local epidemic between January 21 and May 10 (representing 195 million people and 32,000 observed deaths), a 10 day delay in population mobility reduction would have added 16,149 (95% credible interval [CI] 9,517 24,381) deaths by Apr 20, whereas shifting mobility reductions 10 days earlier would have saved 13,571 (95% CI 8,449 16,930) lives. *Analogous estimates attributable to the timing of explicit stay-at-home policies were less pronounced, suggesting that mobility changes were the clearer drivers of epidemic dynamics. Our results also suggest that the timing of mobility reductions and policies most impacted epidemic dynamics in larger, urban counties compared*

with smaller, rural ones. Overall, our results suggest that community behavioral changes had greater impact on curve flattening during the Spring wave compared with stay at home orders. Thus, community engagement and buy-in with precautionary policies may be more important for predicting transmission risk than explicit policies. [**note: I don't find this conclusion surprising at all. The goal of pandemic control is always to change people's behavior to minimize the chance of viral transmission. Unfortunately, large swathes of the public did not buy into the precautionary policies.**] https://www.medrxiv.org/content/10.1101/2020.11.24.20238055v1

- Different combinations of targeted quarantine and broad scale social distancing are equally capable of stemming the transmission of a virus like SARS-CoV-2. *Finding the optimal balance between these policies can be operationalized by minimizing the total amount of social isolation needed to achieve a target reproductive number. This results in a risk threshold for triggering quarantine that depends strongly on disease prevalence in a population, suggesting that very different disease control policies should be used at different times or places. Very aggressive quarantine is warranted given low disease prevalence, while populations with a higher base rate of infection should rely more on broad social distancing. Total cost to a society can be greatly reduced given modestly more information about individual risk of infectiousness*. [**note: this is similar to the above paper and argues that quarantines offer a marginal value.**] https://www.medrxiv.org/content/10.1101/2020.11.24.20238204v1

NEWLY REGISTERED CLINICAL TRIALS

- This is a multicenter, open-label, controlled, randomized phase 2 study designed to evaluate the safety and efficacy profile of GNS561 in patients with COVID-19. [**note: this trial is being sponsored by Genoscience Pharma and is taking place in France. I don't know anything about this compound other than it is an oral drug.**] NCT04637828
- This expanded access use program will provide a botanical drug of T89 for treatment use in an intermediate-size population infected with SARS-CoV-2 who have severe COVID-19, or who are judged by a healthcare provider to be at high risk of progression to severe or life-threatening condition. T89 capsule is a botanical drug product for oral use. The drug substance of T89 capsule is the water extract of two widely used herb medicines: Danshen (Radix Saliva Miltiorrhize Bge., RSM) and Sanqi (Radix Notoginseng, RN). [**note: this is for all you herbal medicine fans. The sponsor is Tasly Pharmaceuticals.**] NCT04646031
- This is a single-center, randomized double blind placebo controlled trial to evaluate the efficacy and safety of novel PAI-1 inhibitor (TM5614) for high-risk patients hospitalized with severe COVID-19 at Northwestern Memorial Hospital. The patients will be randomized in a 1:1 ratio to receive standard of care plus TM5614 or standard of care plus placebo. This project will evaluate the efficacy and safety of a novel small molecule therapy targeting PAI-1 (TM5614) for patients with severe COVID-19. This is a randomized (1:1), double-blinded trial that will enroll adult patients (> 65 years OR <65 years with at least one major cardiometabolic comorbidity [diabetes, hypertension, or cardiovascular disease]) with COVID-19 requiring supplemental oxygen. The study intervention will be a small molecule inhibitor of PAI-1, TM5614, up to 180 mg, compared to matching placebo for up to 7 days. [**note: this is a single center trial at Northwestern.**] NCT04634799
- Study objective is to evaluate the efficacy of the combination of masitinib and isoquercetin in adult hospitalized patients with moderate and severe COVID-19. Many patients with moderate and severe COVID-19, develop a "cytokine storm" that leads to severe pulmonary inflammation

and various thrombotic events associated with acute respiratory distress syndrome (ARDS) and potentially death. The combination of masitinib and isoquercetin may prevent the development of these two complications. Masitinib is a potent blocker of mast cells and macrophages that are contributors to the cytokine storm. Isoquercetin inhibits disulfide isomerase (PDI), an enzyme directly involved in the formation of clots, and also decreases D-Dimer, a predictor of COVID-19 thrombosis severity. [**note: this is another French trial of two combination drugs. Masitinib is a tyrosine kinase inhibitor and several of these are in trials.**] NCT04622865

- Patients who are admitted to hospitalization in hcor and who have the confirmed diagnosis of corona virus, will be asked to consent to participate in this study that intends to study the effectiveness of the remote intercession prayer in combating this disease. [**note: this is from Sao Paulo and I include it for completeness sake. Maybe it will help but I am unsure how one runs an appropriate control group.**] NCT04631380

CLINICAL TRIAL RESULTS

- A prospective case-control study determined by admittance to the hospital based on bed availability. Participants: Eighteen patients with COVID-19 infection (laboratory confirmed) severe pneumonia admitted to hospital between 20th March and 19th April 2020. Patients admitted to the hospital during the study period were assigned to different beds based on bed availability. Depending on the bed the patient was admitted, the treatment was ozone autohemotherapy or standard treatment. Patients in the case group received ozonated blood twice daily starting on the day of admission for a median of four days. Each treatment involved administration of 200 mL autologous whole blood enriched with 200 mL of oxygen-ozone mixture with a 40 µg/mL ozone concentration. Main Outcomes: The primary outcome was time from hospital admission to clinical improvement. Results: Nine patients (50%) received ozonated autohemotherapy beginning on the day of admission. Ozonated autohemotherapy was associated with shorter time to clinical improvement (median [IQR]), 7 days [6-10] vs 28 days [8-31], p=0.04) and better outcomes at 14-days (88.8% vs 33.3%, p=0.01). In risk-adjusted analyses, ozonated autohemotherapy was associated with a shorter mean time to clinical improvement (-11.3 days, p=0.04, 95% CI -22.25 to -0.42). *Conclusion: Ozonated autohemotherapy was associated with a significantly shorter time to clinical improvement in this prospective case-control study. Given the small sample size and study design, these results require evaluation in larger randomized controlled trials*. [**note: this is a small trial of ozonated blood but the sample size is too small to draw any conclusions about the efficacy of this treatment.**] https://www.medrxiv.org/content/10.1101/2020.06.03.20117994v4

DRUG DEVELOPMENT

- Nothing today

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Natural selection adaptation in the coronavirus can occur during coronavirus amplification in vivo in farmed minks. Natural selection in such viruses is observed by introduction of mutations in SARS-CoV-2 that are not observed during the growth process in humans. Infection with a mutant (Y453F) of SARS-CoV-2 from farmed minks is known to widely spread among humans. *We investigated the virological characteristics of this SARS-CoV-2 mutant (Y453F) using three-*

dimensional protein structural analysis. Our experimental study suggests that virus variants with the Y453F mutation partially escaped detection by four neutralizing monoclonal antibodies. The spread of SARS-CoV-2 variants mediated by millions of infected farmed minks is uncontrolled; consequently, raising a concern that infection of SARS-CoV-2 mutants that cause serious symptoms in humans may spread globally. [**note: another good reason not to farm minks!!! It's still not known whether this is a significant reservoir for virus recombination but we know from influenza that viral jumping between pigs, ducks and humans leads to mutations that can result in more infectious virus.**]
https://www.biorxiv.org/content/10.1101/2020.11.27.401893v1

- Understanding immune responses following SARS-CoV-2 infection in relation to COVID-19 severity is critical to predicting the effects of long-term immunological memory on viral spread. Here we longitudinally assessed systemic and airway immune responses against SARS-CoV-2 in a well-characterized cohort of 147 infected individuals representing the full spectrum of COVID-19 severity; from asymptomatic infection to fatal disease*. High systemic and airway antibody responses were elicited in patients with moderate to severe disease, and while systemic IgG levels were maintained after acute disease, airway IgG and IgA declined significantly. In contrast, individuals with mild symptoms showed significantly lower antibody responses but their levels of antigen-specific memory B cells were comparable with those observed in patients with moderate to severe disease. This suggests that antibodies in the airways may not be maintained at levels that prevent local virus entry upon re-exposure and therefore protection via activation of the memory B cell pool is critical*. [**note: this Swedish study shows that airway antibodies wane with time but that B cell memory can remain which is important for continuing immunity.**]
https://www.medrxiv.org/content/10.1101/2020.11.25.20238592v1

DIAGNOSTIC DEVELOPMENT

- Nothing today