Welcome to Week 37 as the coming vaccines give us all a promise of return to normalcy

Today we will return to one of my favorite jazz bands, the Sant Andreu group conducted by Joan Chamorro. Here is Andrea Motis singing 'Blame it on My Youth' with some great ensemble playing along with a fabulous flute solo from Joan Marti: https://www.youtube.com/watch?v=m4eGgRd440E I am constantly amazed at how these kids play with such enthusiasm.

The Washington Post reports on how poor rural states may have difficulty in distributing COVID-19 vaccines. Here is an interesting article on the limits of various laboratory tests. This op-ed pieces discusses the challenges that some college students are experiencing. Some really good news!! Moderna is submitting a request for an Emergency Use Application for their COVID-19 vaccine to the FDA. Here is an on the ground report about an Eau Claire Wisconsin hospital's battle to find enough beds for COVID-19 patients.

The New York Times reports on how some early slip ups made the outbreak in Bergamo worse than it should have been. Seriously, there are American mink farms? Yes there are and the minks are showing up with COVID-19. PETA must have been asleep at the wheel. Mayor de Blasio cannot make up his mind. Elementary schools in New York City will now be opening on December 7. Lockdowns are a last resort but they do work as data from England show.

STAT has an article on Thanksgiving travel and whether there will be a spike in COVID-19 cases. Here is their article on the Moderna vaccine application.

Nature has an interesting article on Iceland's work on dealing with SARS-CoV-2.

MODELING

- Decision makers with the responsibility of managing policy for the COVID-19 epidemic have faced difficult choices in balancing the competing claims of saving lives and the high economic cost of shutdowns. In this paper we formulate a model with both epidemiological and economic content to assist this decision making process. We consider two ways to handle the balance between economic costs and deaths. *First, we use the statistical value of life, which in Canada is about C\$7 million, to optimise over a single variable, which is the sum of the economic cost and the value of lives lost. Our second method is to calculate the Pareto optimal front when we look at the two variables -- deaths and economic costs. In both cases we find that, for most parameter values, the optimal policy is to adopt an initial shutdown level which reduces the reproduction number of the epidemic to close to 1. This level is then reduced once a vaccination program is underway. Our model also indicates that an oscillating policy of strict and mild shutdowns is less effective than a policy which maintains a moderate shutdown level*. [**note: here is a good paper for all my economist friends who read the newsletter! These Canadian researchers look at both epidemiological and economic issues as part of the decision-making process.** https://www.medrxiv.org/content/10.1101/2020.11.25.20239004v1
- Workplaces requiring in-person attendance of employees for ongoing operations may be susceptible to SARS-CoV-2 outbreaks that impact workers as well as their close contacts. To understand industry sectors impacted by workplace outbreaks in the first wave of the pandemic, and the additional burden of illness through household transmission, we analyzed public health

declared workplace outbreaks between January 21 to June 30, 2020, and their associated cases from January 21 to July 28. Methods: Number, size and duration of outbreaks were described by sector, and outbreak cases were compared to sporadic cases in the same time frame. Address matching identified household cases with onset ≥2 days before, ≥2 days after, or within 1 day of the workplace outbreak case. Results: *There were 199 outbreaks with 1245 cases, and 68% of outbreaks and 80% of cases belonged to i) Manufacturing, ii) Agriculture, Forestry, Fishing, Hunting, iii) Transportation and Warehousing. Median size of outbreaks was 3 cases (range: 1-140), and lasted median 7days (range: 0-119). Outbreak cases were significantly more likely to be male, younger, healthier, and have better outcomes. There were 608 household cases associated with 339 (31%) outbreak cases with valid addresses, increasing the burden of illness by 56%. The majority of household cases (368, 60%) occurred after the outbreak case. Conclusions: Workplace outbreaks primarily occurred in three sectors. COVID-19 prevention measures should target industry sectors at risk by preventing introduction from exposed employees, spread in the workplace, and spread outside of the workplace*. [**note: I have not seen a study that relates COVID-19 to industrial sector with the degree of granularity of this Ontario study.** https://www.medrxiv.org/content/10.1101/2020.11.25.20239038v1

- On 30 July 2020, a total number of 301,530 diagnosed COVID-19 cases were reported in Iran, with 261,200 recovered and 16,569 dead. The COVID-19 pandemic started with 2 patients in Qom city in Iran on 20 February 2020. Accurate prediction of the end of the COVID-19 pandemic and the total number of populations affected is challenging. In this study, several widely used models, including Richards, Gompertz, Logistic, Ratkowsky, and SIRD models, are used to project dynamics of the COVID-19 pandemic in the future of Iran by fitting the present and the past clinical data. Iran is the only country facing a second wave of COVID-19 infections, which makes its data difficult to analyze. The present study's main contribution is to forecast the near-future of COVID-19 trends to allow non-pharmacological interventions (NPI) by public health authorities and/or government policymakers. We have divided the COVID-19 pandemic in Iran into two waves, Wave I, from February 20, 2020 to May 4, 2020, and Wave II from May 5, 2020, to the present. Two statistical methods, i.e., Pearson correlation coefficient (R) and the coefficient of determination (R2), are used to assess the accuracy of studied models. Results for Wave I Logistic, Ratkowsky, and SIRD models have correctly fitted COVID-19 data in Iran. SIRD model has fitted the first peak of infection very closely on April 6, 2020, with 34,447 cases (The actual peak day was April 7, 2020, with 30,387 active infected patients) with the re-production number R0=3.95. Results of Wave II indicate that the SIRD model has precisely fitted with the second peak of infection, which was on June 20, 2020, with 19,088 active infected cases compared with the actual peak day on June 21, 2020, with 17,644 cases. In Wave II, the re-production number R0=1.45 is reduced, indicating a lower transmission rate. We aimed to provide even a rough project future trends of COVID-19 in Iran for NPI decisions. Between 180,000 to 250,000 infected cases and a death toll of between 6,000 to 65,000 cases are expected in Wave II of COVID-19 in Iran. There is currently no analytical method to project more waves of COVID-19 beyond Wave II. [**note: here is a model of the outbreak in Iran that was especially hard hit. One of our neighbors went back home for the funeral of his 85 year old mother last February and got caught in the pandemic and only returned to the US two weeks ago as flights in and out of Iran were constantly being cancelled.**]
https://www.medrxiv.org/content/10.1101/2020.11.29.20240580v1

NEWLY REGISTERED CLINICAL TRIALS

- You got your present yesterday.

CLINICAL TRIAL RESULTS

- Purpose: This small-scale, prospective cohort study nested within a randomized controlled trial aimed to investigate the possible associations between physical activity levels and clinical outcomes among hospitalized patients with severe COVID-19. Methods: Hospitalized patients with severe COVID-19 were recruited from Clinical Hospital of the School of Medicine of the University of Sao Paulo (a quaternary referral teaching hospital), and from Ibirapuera Field Hospital, both located in Sao Paulo, Brazil. Physical activity levels were assessed by Baecke Questionnaire of Habitual Physical Activity. The primary outcome was hospital length of stay. The secondary outcomes were: mortality, admission to the intensive care unit (ICU), and mechanical ventilation requirement. Results: Mean hospital length of stay was 8.5 (7.1) days; 3.3% of patients died, 13.8% were admitted to ICU, and 8.6% required mechanical ventilation. Linear regression models showed that physical activity indexes were not associated with hospital length of stay (work index: B=-0.57 [95%CI: -1.80 to 0.65], p=0.355; sport index: B=0.43 [95%CI: -0.94 to 1.80], p=0.536; leisure-time index: B=1.18 [95%CI: -0.22 to 2.59], p=0.099; total activity index: B=0.20 [95%CI: -0.48 to 0.87], p=0.563. Physical activity indexes were not associated with mortality, admission to ICU and mechanical ventilation requirement (all p>0.05). Conclusions: Among hospitalized patients with COVID-19, physical activity did not associate with hospital length of stay or any other clinically-relevant outcomes. These findings suggest that previous physical activity levels may not change the prognosis of severe COVID-19. [**note: this small nested trial is from Brazil and shows the level of pre-COVID-19 physical activity does not change the prognosis for severe disease. I'm still going to keep exercising as it's good for other things and you should too.**]
  https://www.medrxiv.org/content/10.1101/2020.11.25.20237925v1
- Background: Acute and chronic alcohol abuse have adverse impacts on both the innate and adaptive immune response, which may result in reduced resistance to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection and promote the progression of coronavirus disease 2019 (COVID-19). However, there are no large population-based data evaluating potential causal associations between alcohol consumption and COVID-19. Method: We conducted a Mendelian randomization study using data from UK Biobank to explore the association between alcohol consumption and risk of SARS-CoV-2 infection and serious clinical outcomes in patients with COVID-19. A total of 12,937 participants aged 50-83 who tested for SARS-CoV-2 between 16 March to 27 July 2020 (12.1% tested positive) were included in the analysis. The exposure factor was alcohol consumption. Main outcomes were SARS-CoV-2 positivity and death in COVID-19 patients. We generated weighted and unweighted allele scores using three genetic variants (rs1229984, rs1260326, and rs13107325) and applied the allele scores as the instrumental variables to assess the effect of alcohol consumption on outcomes. Analyses were conducted separately for white participates with and without obesity. Results: Of the 12,937 participants, 4,496 were never or infrequent drinkers and 8,441 were frequent drinkers. (including 1,156 light drinkers, 3,795 moderate drinkers, and 3,490 heavy drinkers). Both logistic regression and Mendelian randomization analyses found no evidence that alcohol consumption was associated with risk of SARS-CoV-2 infection in participants either with

(OR=0.963, 95%CI 0.800-1.159; q =1.000) or without obesity (OR=0.891, 95%CI 0.755-1.053; q =.319). However, frequent drinking (HR=1.565, 95%CI 1.012-2.419; q =.079), especially heavy drinking (HR=2.071, 95%CI 1.235-3.472; q =.054), was associated with higher risk of death in patients with obesity and COVID-19, but not in patients without obesity. Notably, the risk of death in frequent drinkers with obesity increased slightly with the average amount of alcohol consumed weekly (HR=1.480, 95%CI 1.059-2.069; q =.099). Conclusions: Our findings suggested alcohol consumption may had adverse effects on the progression of COVID-19 in white participants with obesity, but was not associate with susceptibility to SARS-CoV-2 infection. [**note: obesity and alcohol consumption are not good things if you want to avoid severe COVID-19.**] https://www.medrxiv.org/content/10.1101/2020.11.25.20238915v1

DRUG DEVELOPMENT

- Nothing new today.

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- A new SARS-CoV-2 clade (GV) characterized by S substitution A222V, first reported from Spain in March, is rapidly spreading across Europe. To establish the A222V variant involvement in the infection rise in Italy, all GISAID sequences from Italy and those from our Laboratory (Lazio) in the period June-October were analysed. A222V, first recognized in August, represents 11.2% of sequences in this period, reaching 100% of autochthonous sequences in October, supporting increased GV circulation in Italy. [**note: it's not surprising that a new mutation has appeared and is spreading. It is not known whether this is more infectious that the parental strain.**] https://www.medrxiv.org/content/10.1101/2020.11.28.20237016v1
- Comorbid medical illnesses, such as obesity and diabetes, are associated with more severe COVID-19, hospitalization, and death. However, the role of the immune system in mediating these clinical outcomes has not been determined. We used multi-parameter flow cytometry and systems serology to comprehensively profile the functions of T cells and antibodies targeting spike, nucleocapsid, and envelope proteins in a convalescent cohort of COVID-19 subjects who were either hospitalized (n=20) or not hospitalized (n=40). To avoid confounding, subjects were matched by age, sex, ethnicity, and date of symptom onset. *Surprisingly, we found that the magnitude and functional breadth of virus-specific CD4 T cell and antibody responses were consistently higher among hospitalized subjects, particularly those with medical comorbidities. However, an integrated analysis identified more coordination between polyfunctional CD4 T-cells and antibodies targeting the S1 domain of spike among subjects that were not hospitalized. These data reveal a functionally diverse and coordinated response between T cells and antibodies targeting SARS-CoV-2 which is reduced in the presence of comorbid illnesses that are known risk factors for severe COVID-19. Our data suggest that isolated measurements of the magnitudes of spike-specific immune responses are likely insufficient to anticipate vaccine efficacy in high-risk populations*. [**note: here is a Univ of Washington study on T-cell and antibody response. The see a higher response among hospitalized patients (this has been observed by others) and isolated measurements of magnitudes of these two may not anticipate vaccine efficacy in high-risk populations.**] https://www.medrxiv.org/content/10.1101/2020.11.25.20235150v1

- SARS-CoV-2 infection takes a mild or clinically inapparent course in the majority of humans who contract this virus. After such individuals have cleared the virus, only the detection of SARS-CoV-2-specific immunological memory can reveal the exposure, and hopefully the establishment of immune protection. With most viral infections, the presence of specific serum antibodies has provided a reliable biomarker for the exposure to the virus of interest. SARS-CoV-2 infection, however, does not reliably induce a durable antibody response, especially in sub-clinically infected individuals. Consequently, it is plausible for a recently infected individual to yield a false negative result within only a few months after exposure. Immunodiagnostic attention has therefore shifted to studies of specific T cell memory to SARS-CoV-2. *Most reports published so far agree that a T cell response is engaged during SARS-CoV-2 infection, but they also state that in 20-81% of non- SARS-CoV-2-exposed individuals, T cells respond to SARS-CoV-2 antigens (mega peptide pools), allegedly due to T cell cross-reactivity with coronaviruses causing Common Cold (CCC), or other antigens. Here we show that by introducing irrelevant mega peptide pools as negative controls to account for chance cross-reactivity, and by establishing the antigen dose-response characteristic of the T cells, one can clearly discern between cognate T cell memory induced by SARS-CoV-2 infection vs. cross-reactive T cell responses in individuals who had not been infected with SARS-CoV-2*. [**note: here is an interesting report from Cellular Technologies Ltd. That untangles the T-cell response to SARS-CoV-2 from cross reactivity to other coronaviruses.**] https://www.biorxiv.org/content/10.1101/2020.11.29.402677v1

DIAGNOSTIC DEVELOPMENT

- Nothing new today.

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2020-12-01

As I am focusing on some all-time favorites, why not take a second look at the Chairman of the Board, Mr. Frank Sinatra? There is a dedicated YouTube channel that has loads of clips and full-length videos of his song stylings. Here are two at random that I picked out. The first is 'I've Got You Under my Skin' from a concert film: https://www.youtube.com/watch?v=OqH7VwpSwBo Wow, did he have style with the three piece sporty outfit with matching pocket square. I still occasionally dress up and look in the mirror, remembering how things used to be.😉 The second choice is a great duet with Ella Fitzgerald, 'The Lady is a Tramp': https://www.youtube.com/watch?v=xafBWOxqssg It doesn't get much better than this!!!

The Washington Post covers a Missouri doctor who petitioned the governor to implement a state-wide mask mandate. I support this! Things did not end well at this Hong Kong dance studio. Two vaccines head for FDA Advisory Committee meetings, this is really good news!!! President Trump's coronavirus advisor has resigned. Here is a story about how getting COVID-19 changed one man's behavior. Given past history as a superspreading site, this White House decision may not be such a good idea (though I am unlikely to receive an invitation, I would decline if I did).

The New York Times comments on the obvious; young children pose a much lower risk of viral transmission and in-person teaching is safer than with older ones.

The COVID Tracking Project over at The Atlantic does not have good news.

Kaiser Health News has a good story on how traveling nurses tending to COVID-19 patients can make as much as $8K/week. However, resurgence of the virus in some areas is causing high stress levels in nurses. Failed contact tracing is leaving diners in the dark.

MODELING

- The number of secondary cases is an important parameter for the control of infectious diseases. When individual variation in disease transmission is present, like for COVID-19, the number of secondary cases is often modelled using a negative binomial distribution. However, this may not be the best distribution to describe the underlying transmission process. We propose the use of three other offspring distributions to quantify heterogeneity in transmission, and we assess the possible bias in estimates of the offspring mean and its overdispersion when the data generating distribution is different from the one used for inference. *We find that overdispersion estimates may be biased when there is a substantial amount of heterogeneity, and that the use of other distributions besides the negative binomial should be considered. We revisit three previously analysed COVID-19 datasets and quantify the proportion of cases responsible for 80\% of transmission, $p_{80\%}$, while acknowledging the variation arising from the assumed offspring distribution. We find that the number of secondary cases for these datasets is better described by a Poisson-lognormal distribution*. [**note: I am always a sucker for innovative statistical analyses of the pandemic. It forces me to pull out my old college stat textbook and refresh my mind! Here is an attempt to quantify superspreading events using Poisson mixture distribution.**] https://www.medrxiv.org/content/10.1101/2020.11.27.20239657v1
- Encounters with rats in urban areas increase risk of human exposure to rat-associated zoonotic pathogens and act as a stressor associated with psychological distress. The frequency and nature of human-rat encounters may be altered by social distancing policies to mitigate the COVID-19 pandemic. For example, restaurant closures may reduce food availability for rats and promote rat activity in nearby residential areas, thus increasing public health risks during a period of public health crisis. In this study, we aimed to identify factors associated with increased perceived exposure to rats during a stay-at-home order, describe resident encounters with rats relevant to their health and well-being, and identify factors associated with increased use of rodent control. Methods: Urban residents in Chicago, a large city with growing concerns about rats and health disparities, completed an online questionnaire including fixed response and open-ended questions during the spring 2020 stay-at-home order. Analyses included ordinal multivariate regression, spatial analysis, and thematic analysis for open-ended responses. Results: Overall, 21% of respondents (n=835) reported an increase in rat sightings around their homes during the stay-at-home order and increased rat sightings was positively associated with proximity to restaurants, low-rise apartment buildings, and rat feces in the home ($p \leq 0.01$). Many respondents described feeling unsafe using their patio or yard, and afraid of rats entering their home or spreading disease. Greater engagement with rodent control was associated with property ownership, information about rat control, and lower incomes ($p \leq 0.01$). Conclusions: *More frequent rat encounters may be an unanticipated public health concern during periods of social distancing, especially in restaurant-dense areas or in low-rise apartment buildings. Rat presence may also limit resident ability to enjoy nearby outdoor spaces, which otherwise might buffer stress experienced during a stay-at-home order. Proactive rat control may be needed to*

mitigate rat-associated health risks during future stay-at-home orders. [**note: YIKES!!!!!!!!!!!! 😱 Where is the Pied Piper of Hamelin when we really need him???? Chicago is calling.**] https://www.medrxiv.org/content/10.1101/2020.11.25.20238741v1

- This research measures the epidemiological and economic impact of COVID-19 spread in the US under different mitigation scenarios, comprising of non-pharmaceutical interventions. A detailed disease model of COVID-19 is combined with a model of the US economy to estimate the direct impact of labor supply shock to each sector arising from morbidity, mortality, and lock down, as well as the indirect impact caused by the interdependencies between sectors*. During a lockdown, estimates of jobs that are workable from home in each sector are used to modify the shock to labor supply. Results show trade-offs between economic losses, and lives saved and infections averted are non-linear in compliance to social distancing and the duration of lockdown. Sectors that are worst hit are not the labor-intensive sectors such as Agriculture and Construction, but the ones with high valued jobs such as Professional Services, even after the teleworkability of jobs is accounted for. Additionally, the findings show that a low compliance to interventions can be overcome by a longer shutdown period and vice versa to arrive at similar epidemiological impact but their net effect on economic loss depends on the interplay between the marginal gains from averting infections and deaths, versus the marginal loss from having healthy workers stay at home during the shutdown*. [**note: here is another model for the economists to look at.**] https://www.medrxiv.org/content/10.1101/2020.11.28.20239517v1
- There is growing evidence of cluster transmission and superspreading of SARS-CoV-2, implying heterogeneous dispersion. We discuss the successful containment of COVID-19 local outbreak in Bcharreh, the small town of 4500 inhabitants, in Northern Lebanon. We look at the dynamics of cluster transmission and viral load evolution throughout the outbreak. SARS-CoV-2 PCR test was proposed to all exposed individuals. Persons under investigation that tested negative by PCR were periodically retested. We define: a cluster as more than 3 people with a common suspicious or confirmed SARS-CoV-2 positive contact, clinical cure as the resolution of symptoms, and virologic cure as SARS-CoV-2 PCR Cycle threshold(Ct) >35. We analyzed all obtained Ct into corresponding clusters and performed a time series analysis. A total of 713/871 SARS-CoV-2 PCR tests were performed at Saint George Hospital University Medical Center (SGHUMC) from April 5th 2020 -June 14th 2020. We used the LightMix; Modular SARS-CoV-2 (COVID19) E, N, and RdRP-genes (Tib Molbiol, Berlin, Germany). Week one of epidemiologic surveillance began on March 31st when the first case was detected. A strict lockdown was imposed on Bcharreh village 5 days later, on top of the national lockdown. We identified 4 different clusters ranging from 3 to 27 cases and 3 sporadic unrelated cases. Almost 70% of each cluster was diagnosed within 7 days. After 2 weeks, we saw a significant increase in the average initial diagnostic Ct 27.9 to 34.72 ($P<0.0001$). A total of 73/74 SARS-CoV-2 PCR positive individuals achieved cure (98.6%). We recorded one death of a 90-year-old man with multiple comorbidities. In explosive new epidemics, we can derive from previous experience and not be blinded by it. To safely navigate out of the lockdown, focus on where new transmission is likely to emerge and accordingly target available diagnostic technologies. [**note: yes, it is a very small Lebanese village but public health is public health. In this case, they do isolate an outbreak, analyze and take remedial steps to eliminate it. Pretty easy, correct?**] https://www.medrxiv.org/content/10.1101/2020.11.28.20240077v1

- There is increasing evidence that the 2020 COVID-19 pandemic has been influenced by variations in air temperature and humidity. However, the impact that these environmental parameters have on survival of the SARS-CoV-2 virus has not been fully characterised. Therefore an analytical study was undertaken using published data to develop a psychrometric model to predict the biological decay rate of the virus in aerosols. This revealed that it is possible to predict with a high degree of accuracy (R2 = 0.718, p<0.001) the biological decay constant for SARS-CoV-2 using a regression model with enthalpy, vapour pressure and specific volume as predictors. *Applying this to historical meteorological data from London, Paris and Milan over the pandemic period, produced results which indicate that the average half-life of the virus in aerosols was in the region 13-21 times longer in March 2020, when the outbreak was accelerating, than it was in August 2020 when epidemic in Europe was at its nadir. As such, this suggests that changes in virus survivability due the variations in the psychrometric qualities of the air might influence the transmission of COVID-19.* [**note: yes, there are lots of physical chemical equations that even I as a lapsed chemist understand (they did leave out the entropic considerations which I found to be weird as that can govern dispersion). However, this still does not explain why there were large outbreaks in Arizona and Florida, both warm states but differing in relative humidity. In short, I don't particularly find this convincing.**] https://www.medrxiv.org/content/10.1101/2020.11.29.20240408v1

NEWLY REGISTERED CLINICAL TRIALS

- You have wasted precious seconds if you read this sentence.

CLINICAL TRIAL RESULTS

- Dietary supplements may provide nutrients of relevance to ameliorate SARS-CoV-2 infection, although scientific evidence to support a role is lacking. We investigate whether the regular use of dietary supplements can reduce the risk of testing positive for SARS-CoV-2 infection in around 1.4M users of the COVID Symptom Study App who completed a supplement use questionnaire. **Design:** Longitudinal app-based community survey and nested case control study. **Setting:** Subscribers to an app that was launched to enable self-reported information related to SARS-CoV-2 infection for use in the general population in three countries. **Main Exposure:** Self-reported regular dietary supplement usage since the beginning of the pandemic. **Main Outcome Measures:** SARS-CoV-2 infection confirmed by viral RNA polymerase chain reaction test (RT-PCR) or serology test. A secondary outcome was new-onset anosmia. **Results:** In an analysis including 327,720 UK participants, the use of probiotics, omega-3 fatty acids, multivitamins or vitamin D was associated with a lower risk of SARS-CoV-2 infection by 14%(95%CI: [8%,19%]), 12%(95%CI: [8%,16%]), 13%(95%CI: [10%,16%]) and 9%(95%CI: [6%,12%]), respectively, after adjusting for potential confounders. No effect was observed for vitamin C, zinc or garlic supplements. When analyses were stratified by sex, age and body mass index (BMI), the protective associations for probiotics, omega-3 fatty acids, multivitamins and vitamin D were observed in females across all ages and BMI groups, but were not seen in men. The same overall pattern of association was observed in both the US and Swedish cohorts. Results were further confirmed in a sub-analysis of 993,365 regular app users who were not tested for SARS-CoV-2 with cases (n= 126,556) defined as those with new onset anosmia (the strongest COVID-19 predictor). **Conclusion:** *We observed a modest but significant association between use of probiotics, omega-3 fatty acid,*

multivitamin or vitamin D supplements and lower risk of testing positive for SARS-CoV-2 in women. No clear benefits for men were observed nor any effect of vitamin C, garlic or zinc for men or women. Randomised controlled trials of selected supplements would be required to confirm these observational findings before any therapeutic recommendations can be made. [**note: this is a large longitudinal study on the use of dietary supplements and possible links to COVID-19 protection. This type of study does not replace a controlled clinical trial.**] https://www.medrxiv.org/content/10.1101/2020.11.27.20239087v1

- Abstract Background: Qualitative olfactory (smell) dysfunctions are a common side effect of post-viral illness and known to impact on quality of life and health status. Evidence is emerging that taste and smell loss are common symptoms of Covid-19 that may emerge and persist long after initial infection. The aim of the present study was to document the impact of post Covid-19 alterations to taste and smell. Methods: We conducted passive and active thematic analysis of user-generated text from 9000 users of the AbScent Covid-19 Smell and Taste Loss moderated Facebook support group from March 24 to 30th September 2020. Results: Participants reported difficulty understanding, explaining and managing altered taste and smell; a lack of interpersonal and professional explanation or support; altered eating; appetite loss, weight change; loss of pleasure in food, eating and social engagement; altered intimacy and an altered relationship to self and others. Conclusions: *Our findings suggest altered taste and smell with Covid-19 lead to a severe disruption to daily living that impacts on psychological well-being and health. Moreover, this impact is broad, spanning flavour perception; desire and ability to eat and prepare food; weight gain, loss and nutritional sufficiency; emotional wellbeing; professional practice; intimacy; social bonding and erosion of peoples very sense of reality. Our findings should inform the training, assessment and treatment practices of health care professionals working with long Covid*. [**note: here is a paper covering one of the more concerning side effects of COVID-19, the loss of taste and smell. Fortunately, it seems to return in most people who have had these symptoms.**] https://www.medrxiv.org/content/10.1101/2020.11.26.20239152v1
- Background Hydroxychloroquine is an antimalarial drug that received worldwide news and media attention in the treatment of COVID-19 patients. This drug was used based on its antimicrobial and antiviral properties despite lack of definite evidence of clinical efficacy. In this study, we aim to assess the efficacy and safety of using Hydroxychloroquine in treatment of COVID-19 patients who are admitted in acute care hospitals in Bahrain. Methodology We conducted retrospective cohort study on a random sample of admitted COVID19 patients between 24 February and 31 July 2020. The study was conducted in four acute care COVID19 hospitals in Bahrain. Data was extracted from the medical records. The primary endpoint was the requirement of non-invasive ventilation, intubation or death. Secondary endpoint was length of hospitalization for survivors. Three methods of analysis were used to control for confounding factors: logistic multivariate regression, propensity score adjusted regression and matched propensity score analysis. Results A random sample of 1571 patients were included, 440 of which received HCQ (treatment group) and 1131 did not receive it (control group). Our results showed that HCQ did not have a significant effect on primary outcomes due to COVID-19 infection when compared to controls after adjusting for confounders (OR 1.43 95% CI 0.85 to 2.37, P value=0.17). Co-administration of azithromycin had no effect on primary outcomes (OR 2.7 95% CI 0.82 to 8.85 P value =0.10). HCQ was found to be associated with increased risk of

hypoglycemia (OR 10.9 95% CI 1.72 - 69.49, P value =0.011) and diarrhea(OR 2.8, 95% CI 1.4-5.5, P value =0.003), but not QT prolongation(OR=1.92, 95% CI 0.95-3.9, P value =0.06) or cardiac arrhythmia.(OR=1.06, 95% CI 0.55-2.05, P value =0.85). Conclusion *Our results showed no significant beneficial effect of using hydroxychloroquine on the outcome of COVID-19 patients. Moreover, the risk of hypoglycemia due to hydroxychloroquine would possess a significant risk for out of hospital use*. [**note: this study from Bahrain also shows HCQ does not work. I include this for the sake of completeness of the story. They also observe another adverse event in patients, hypoglycemia.**]
https://www.medrxiv.org/content/10.1101/2020.11.25.20234914v1

DRUG DEVELOPMENT

- *This short paper reports a Bayesian analysis of the publicly available COVID-19 trial results. The analysis casts some doubts on whether the half+full dose regime of the AstraZeneca COVID-19 vaccine is truly (much) more effective than the 2x full dose regime. The 95% posterior interval for the effectiveness of the half+full dose regime is 66-96%, while for the 2x full dose regime it is 39-74%. The estimated effectiveness for the Pfizer vaccine is 89-97% and for Moderna 86-97%. These results should be interpreted with care though, since this analysis does not account for differences in for instance trial population, COVID-19 testing, and storage requirements for the various vaccines*. [**note: it's always fun to see a paper analyze the efficacy of something without having access to the full dataset. I'm not sure this paper is worth much other than being an interesting artifiact.**]
https://www.medrxiv.org/content/10.1101/2020.11.30.20240671v1
- *In this work we have developed, by employing lambda superstrings, a map of candidate vaccines against SARS-CoV-2 with lengths between 9 and 200, based on estimations of the immunogenicity of the epitopes and the binding affinity of epitopes to MHC class I molecules using tools from the IEDB Analysis Resource, as well as the overall predictions obtained using the VaxiJen tool. We have synthesized one of the peptides, specifically the one of length 22, and we have carried out an immunogenicity assay and a cytokine assay, which has given positive results in both cases*. [**note: this is from the Basque region of Spain and presents a candidate vaccine derived from AI and computational tools. The come up with a single epitope candidate.**]
https://www.biorxiv.org/content/10.1101/2020.11.30.403824v1
- The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) continues to infect people globally. The increased COVID-19 cases and no licensed vaccines highlight the need to develop safe and effective vaccines against SARS-CoV-2 infection. Multiple vaccines candidates are under pre-clinical or clinical trails with different strengths and weaknesses. Here we developed a pilot scale production of a recombinant subunit vaccine (RBD-Fc Vacc) with the Receptor Binding Domain of SARS-CoV-2 S protein fused with the Fc domain of human IgG1. RBD-Fc Vacc induced SARS-CoV-2 specific neutralizing antibodies in non-human primates and human ACE2 transgenic mice. *The antibodies induced in macaca fascicularis neutralized three divergent SARS-CoV2 strains, suggesting a broader neutralizing ability. Three times immunizations protected Macaca fascicularis (20ug or 40ug per dose) and mice (10ug or 20ug per dose) from SARS-CoV-2 infection respectively. These data support clinical development of SARS-CoV-2 vaccines for humans. RBD-Fc Vacc is currently being assessed in randomized controlled phase 1/II human clinical trails* [**note: here is yet another vaccine candidate from China, this one is a fusion compound**

consisting of the RBD protein fused with the Fc domain of human IgG1. It appears to generate broad neutralizing antibodies.]]
https://www.biorxiv.org/content/10.1101/2020.11.29.402339v1

- The outbreak of 2019 coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a global pandemic. Despite intensive research including several clinical trials, currently there are no completely safe or effective therapeutics to cure the disease. Here we report a strategy incorporating neutralizing antibodies conjugated on the surface of a photothermal nanoparticle to actively capture and inactivate SARS-CoV-2. *The photothermal nanoparticle is comprised of a semiconducting polymer core and a biocompatible polyethylene glycol surface decorated with neutralizing antibodies. Such nanoparticles displayed efficient capture of SARS-CoV-2 pseudoviruses, excellent photothermal effect, and complete inhibition of viral entry into ACE2-expressing host cells via simultaneous blocking and inactivating of the virus. This photothermal nanoparticle is a flexible platform that can be readily adapted to other SARS-CoV-2 antibodies and extended to novel therapeutic proteins, thus providing a broad range of protection against multiple strains of SARS-CoV-2.* [**note: here is a nice bit of work from Univ of Chicago on a linking neutralizing antibodies to a photothermal nanoparticle.**] https://www.biorxiv.org/content/10.1101/2020.11.30.404624v1
- In this report, we describe the initial development and proof-of-concept studies for UB-612, the first multitope protein-peptide vaccine against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the pathogen responsible for the Coronavirus Disease of 2019 (COVID-19). UB-612 consists of eight components rationally designed for induction of high neutralizing antibodies and broad T cell responses against SARS-CoV-2: the S1-RBD-sFc fusion protein, six synthetic peptides (one universal peptide and five SARS-CoV-2-derived peptides), a proprietary CpG TLR-9 agonist, and aluminum phosphate adjuvant. *Through immunogenicity studies in guinea pigs and rats, we optimized the design of protein/peptide immunogens and selected an adjuvant system, yielding a vaccine that provided excellent S1-RBD binding and high neutralizing antibody responses, robust cellular responses, and a Th1-oriented response at low doses of the vaccine. Our candidate vaccine was then advanced into challenge studies, in which it reduced viral load and prevented development of disease in a mouse challenge model and in nonhuman primates (NHP, immunogenicity part is completed, challenge is ongoing). A GLP-compliant toxicity study has shown a favorable safety profile for the vaccine. With the Phase 1 trial ongoing in Taiwan and additional trials planned worldwide, UB-612 is a highly promising and differentiated vaccine candidate for prevention of SARS-CoV-2 transmission and COVID-19 disease*. [**note: the vaccine research isn't stopping! Here is a new approach in what these COVAXX researchers call a multitope protein/peptide vaccine candidate. This is an interesting company with lots of research expertise from past vaccine work. I don't know if this effort is too late in the game.**] https://www.biorxiv.org/content/10.1101/2020.11.30.399154v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- The effect of SARS-CoV-2 mutations and viral load on the severity of COVID-19 is not well understood. The possibility of reinfection with SARS-CoV-2 has already been reported, but dual infection with SARS-CoV-2 is poorly described and is currently under discussion. We describe a study of two strains of SARS-CoV-2 detected in the same patient during the same disease presentation. Methods: Two nasopharyngeal swabs were obtained eight days apart from the

patient in their 90s, diagnosed with lobar pneumonia (J18.1). Both tests were positive for SARS-CoV-2 with high viral load (Ct = 13). We have performed high-throughput sequencing of SARS-CoV-2 genomes from both swabs. Findings: Genomic analysis of SARS-CoV-2 revealed the presence of two genetically distant strains in both swabs. Detected strains belong to different phylogenetic clades (GH and GR) and differ in the seven nucleotide positions. The relative abundance of strains was 70% (GH) and 30% (GR) in the first swab, and 3% (GH) and 97% (GR). Interpretation: *Our findings suggest that the patient was infected by two genetically distinct SARS-CoV-2 strains at the same time. One of the possible explanations is that the second infection occurred in the hospital. Change of the dominant strain ratio during disease manifestation could be explained by the advantage or higher virulence of the strain belonging to the clade GR*. [**note: this is an interesting paper from Russia that looks at a 90 year old patient who had two distinct genetic strains of SARS-CoV-2 from swabs.**] https://www.medrxiv.org/content/10.1101/2020.11.29.20238402v1

- Nucleocapsid protein (N) is the most abundant viral protein encoded by SARS-CoV-2, the causative agent of COVID-19. N plays key roles at different steps in the replication cycle and is used as a serological marker of infection. Here we characterize the biochemical properties of SARS-CoV-2 N. *We define the N domains important for oligomerization and RNA binding that are associated with spherical droplet formation and suggest that N accessibility and assembly may be regulated by phosphorylation. We also map the RNA binding interface using hydrogen-deuterium exchange mass spectrometry. Finally, we find that the N protein C-terminal domain is the most immunogenic by sensitivity, based upon antibody binding to COVID-19 patient samples from the US and Hong Kong. Together, these findings uncover domain-specific insights into the significance of SARS-CoV-2 N and highlight the diagnostic value of using N domains as highly specific and sensitive markers of COVID-19*. [**note: this is from Washington Univ in St. Louis and shows that the nucleocapsid protein C-terminal domain is the most immunogenic part of the protein.**] https://www.biorxiv.org/content/10.1101/2020.11.30.404905v1

DIAGNOSTIC DEVELOPMENT

- Nothing new today.

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2020-12-02

One of my favorite symphonies is the ebullient Mendelssohn Symphony #4 in A major (Italian). From the opening Allegro vivace movement, this symphony gets things moving forward for me. It was also the theme music from the classic film 'Breaking Away' that those of us who attended Indiana University deeply cherish! Here is the Leipzig Gewandhaus Orchestra conducted by Kurt Mazur: https://www.youtube.com/watch?v=XMLyJNgd6LA

The Washington Post discusses health officials concerns about a pandemic Christmas. This story from Ohio is disturbing and tells you everything that is wrong with the pandemic response! This op-ed by a WaPo columnist and doctor urges us to cancel holiday travel plans now. We didn't have any to cancel. We are looking forward to a family Zoom book club meeting to discuss one of my favorite books, 'The Transit of Venus' by Shirley Hazzard. If any of my readers have read this send me a note, I would like to hear your take on the book. I just read it for the third time! 😄 The CDC vaccines committee met

yesterday and recommended health-care workers and nursing home residents should be the first vaccine recipients. Here is the UK decision on Pfizer's vaccine. The question for the FDA is why they couldn't have scheduled the Advisory Committee sooner after Pfizer filed for the EUA. I know that Thanksgiving holiday was an interruption but we are in the midst of a public health crisis. Iceland will allow travelers from the Schengen area if they have already contracted COVID-19. Here are some games you can play over Zoom!!! Get out that graph paper, Battleship is one of the chosen games.

The New York Times discusses whether COVID-19 test kits work reliably in children. It appears that politics are again intruding on the FDA's mission. SARS-CoV-2 may have been in the US as early as December 13 of last year, or perhaps not. HERE is a link to the full paper. My take is that while this is of historical interest it has no bearing on the pandemic and the morbidity and mortality that the country has endured. The UK approved the Pfizer COVID-19 vaccine.

The Atlantic's Sarah Zhang writes about how vaccine trials can surprise us.

STAT have a special report on COVID-19 vaccines. STAT weighs in on the UK approval of the Pfizer vaccine.

The Lancet have a case report on a double lung transplant from a donor previously infected with SARS-CoV-2. I suspect this is not routine surgery.

Nature ask the question whether COVID-19 delirium can bring on dementia. YIKES!!!! All those weird dreams I have been having are now beginning to, hmmmmmm, I forgot what I was going to say. Someone please remind me. BTW, during the pandemic it is quite common to forget what day it is. This is NOT a sign of impending dementia.

MODELING

- Nothing today.

NEWLY REGISTERED CLINICAL TRIALS

- Why are you even asking?

CLINICAL TRIAL RESULTS

- Alas, no news. I wonder how the favipiravir, ivermectin, and other small molecule trials are going? It's been enough time for some results to come out.

DRUG DEVELOPMENT

- Antibodies are widely used in biology and medicine, and there has been considerable interest in multivalent antibody formats to increase binding avidity and enhance signaling pathway agonism. However, there are currently no general approaches for forming precisely oriented antibody assemblies with controlled valency. We describe the computational design of two-component nanocages that overcome this limitation by uniting form and function. One structural component is any antibody or Fc fusion and the second is a designed Fc-binding homo-oligomer that drives nanocage assembly. Structures of 8 antibody nanocages determined by electron microscopy spanning dihedral, tetrahedral, octahedral, and icosahedral architectures with 2, 6, 12, and 30 antibodies per nanocage match the corresponding

computational models. *Antibody nanocages targeting cell-surface receptors enhance signaling compared to free antibodies or Fc-fusions in DR5-mediated apoptosis, Tie2-mediated angiogenesis, CD40 activation, and T cell proliferation; nanocage assembly also increases SARS-CoV-2 pseudovirus neutralization by α-SARS-CoV-2 monoclonal antibodies and Fc-ACE2 fusion proteins. We anticipate that the ability to assemble arbitrary antibodies without need for covalent modification into highly ordered assemblies with different geometries and valencies will have broad impact in biology and medicine*. [**note: from the Hutch in Seattle, this is pretty cool research. I don't know if it will have a marked therapeutic impact or not.]** https://www.biorxiv.org/content/10.1101/2020.12.01.406611v1

- Plant extracts are rich in bioactive compounds, such as polyphenols, sesquiterpenes and triterpenes, with potential antiviral activities. As the dramatic outbreak of the pandemic COVID-19, caused by the SARS-CoV-2 virus, thousands of scientists are working tirelessly trying to understand the biology of this new virus and the disease pathophysiology, with the main goal to discover effective preventive treatments and therapeutic agents. *Plant-derived secondary metabolites may play key roles in preventing and counteracting the rapid spread of SARS-CoV-2 infections by inhibiting the activity of several viral proteins, in particular those involved in the virus entry into the host cells and its replication. In this study, by using different in vitro approaches, we uncovered the role of a pomegranate peel extract in attenuating the interaction between the SARS-CoV-2 Spike glycoprotein and the human Angiotensin-Converting Enzyme 2 (ACE2) receptor, and in inhibiting the activity of the virus 3CL protease. Although further studies will be determinant to assess the efficacy of this extract in vivo, our results open up new promising opportunities to employ natural extracts for the development of effective and innovative therapies in the fight against SARS-CoV-2*. [**note: I did notice pomegranates for sale at the market last week. I'll have to go back and see if any are still left and start doing some home chemistry on the extracting compounds from the peel. DIY pharmacy work looks good during the pandemic.**] https://www.biorxiv.org/content/10.1101/2020.12.01.406116v1
- SARS-CoV-2 is detectable in saliva from asymptomatic individuals, suggesting the potential necessity for the use of mouth rinses to suppress viral load to reduce virus spread. Published studies on anti-SARS-CoV-2 activities of antiseptics determined by virus-induced cytotoxic effects cannot exclude antiseptic-associated cytotoxicity. Here, we determined the effect of commercially available mouth rinses and antiseptic povidone-iodine on the infectivity of pseudotyped SARS-CoV-2 virus. We first determined the effect of mouth rinses on cell viability to ensure that antiviral activity was not a consequence of mouth rinse-induced cytotoxicity. Colgate Peroxyl (hydrogen peroxide) exhibited the most cytotoxicity, followed by povidone-iodine-10% solution, chlorhexidine gluconate-0.12% (CHG), and Listerine (essential oils and alcohol). Analysis of the anti-viral activity of mouth rinses at non-cytotoxic concentrations showed that 1.5% (v/v) diluted CHG was a potent inhibitor when present in cells during infection, but the potency was reduced when CHG was removed after viral attachment, suggesting that the prolonged effect of mouth rinses on cells impacts the anti-viral activity. *To minimalize mouth rinse-associated cytotoxicity, we pelleted treated-viruses to remove most of the mouth rinse prior to infection of cells. Colgate Peroxyl or povidone-iodine at 5% (v/v) completely blocked the viral infectivity. Listerine or CHG at 5% (v/v) had a moderate suppressive effect on the virus, and 50% (v/v) Listerine or CHG blocked the viral infectivity completely. Prolonged incubation of virus with mouth rinses was not required to block viral infectivity. Our*

results indicate that mouth rinses can significantly reduce virus infectivity, suggesting their potential use to reduce SARS-CoV-2 spread. [**note: here's a paper for all you mouthwash fans out there. Get fresh breath and kill viruses in one rinse. Maybe we will see mouthwash dispensers right next to the hand sanitizer (where you spit the rinse out is the still to be solved problem).**] https://www.biorxiv.org/content/10.1101/2020.12.01.405662v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- As a member of RNA viruses, the glycosylation of envelope glycoprotein plays the crucial role in protein folding, evasing host immune system, invading host cell membrane, even affecting host preference. Therefore, detail glyco-related researches have been adopted in the Spike protein (S-protein) of SARS2 CoV from the bioinformatic perspective. *Phylogenic analysis of S-protein sequences revealed the evolutionary relationship of N-glycosylation sites in different CoVs. Structural comparation of S-proteins indicated their similarity and distributions of N-glycosylation sites. Further potential sialic acid or galactose affinity domains have been described in the S-protein by docking analysis. Molecular dynamic simulation for the glycosylated complexus of S-protein-ACE2 implied that the complicate viral binding of receptor-binding domain may be influenced by peripheric N-glycans from own and adjacent monoers. These works will contribute to investigate the N-glycosylation in S-protein and explain the highly contagious of COVID-19*. [**note: here is some research on the glycosylation sites and glycan binding of the N protein.**] https://www.biorxiv.org/content/10.1101/2020.12.01.406025v1
- The envelopes surrounding these viruses are decorated with spike proteins, whose receptor binding domains (RBDs) initiate invasion by binding to the human angiotensin-converting enzyme 2 (ACE2). Subtle changes at the interface with ACE2 seem to be responsible for the enhanced affinity for the receptor of the SARS-CoV-2 RBD compared to SARS-CoV RBD. Here, we use Elastic Network Models (ENMs) to study the response of the viral RBDs and ACE2 upon dissassembly of the complexes. We identify a dominant detachment mode, in which the RBD rotates away from the surface of ACE2, while the receptor undergoes a conformational transition which stretches the active-site cleft. Using the Structural Perturbation Method, we determine the network of residues, referred to as the Allostery Wiring Diagram (AWD), which drives the large-scale motion activated by the detachment of the complex. *The AWD for SARS-CoV and SARS-CoV-2 are remarkably similar, showing a network that spans the interface of the complex and reaches the active site of ACE2, thus establishing an allosteric connection between RBD binding and receptor catalytic function. Informed in part by the AWD, we used Molecular Dynamics simulations to probe the effect of interfacial mutations in which SARS-CoV-2 residues are replaced by their SARS-CoV counterparts. We focused on a conserved glycine (G502 in SARS-CoV-2, G488 in SARS-CoV) because it belongs to a region that initiates the dissociation of the complex along the dominant detachment mode, and is prominent in the AWD. Molecular Dynamics simulations of SARS-CoV-2 wild-type and G502P mutant show that the affinity for the human receptor of the mutant is drastically diminished. Our results suggest that in addition to residues that are in direct contact with the interface those involved in long range allosteric communication are also a determinant of the stability of the RBD-ACE2 complex*. [**note: from Univ of Texas more work on the binding dynamics of the virus to the ACE2 receptor.**] https://www.biorxiv.org/content/10.1101/2020.11.30.405340v1

- Antibodies are becoming a frontline therapy for SARS-CoV-2, but the risk of viral evolutionary escape remains unclear. Here we map how all mutations to SARS-CoV-2's receptor-binding domain (RBD) affect binding by the antibodies in Regeneron's REGN-COV2 cocktail and Eli Lilly's LY-CoV016. These complete maps uncover a single amino-acid mutation that fully escapes the REGN-COV2 cocktail, which consists of two antibodies targeting distinct structural epitopes. The maps also identify viral mutations that are selected in a persistently infected patient treated with REGN-COV2, as well as in lab viral escape selections. Finally, the maps reveal that mutations escaping each individual antibody are already present in circulating SARS-CoV-2 strains. Overall, these complete escape maps enable immediate interpretation of the consequences of mutations observed during viral surveillance. [**note: more good work from the Hutch in Seattle on mapping of viral mutations that escape antibodies to treat COVID-19.**] https://www.biorxiv.org/content/10.1101/2020.11.30.405472v1
- Sex differences in the risk of SARS-CoV-2 infection have been controversial and the underlying mechanisms of COVID-19 sexual dimorphism remain understudied. Here we inspected sex differences in SARS-CoV-2 positivity, hospitalization, admission to the intensive care unit (ICU), sera immune profiling, and two single-cell RNA-sequencing (snRNA-seq) profiles from nasal tissues and peripheral blood mononuclear cells (PBMCs) of COVID-19 patients with varying degrees of disease severity. Our propensity score-matching observations revealed that male individuals have a 29% increased likelihood of SARS-CoV-2 positivity, with a hazard ration (HR) 1.32 (95% confidence interval [CI] 1.18-1.48) for hospitalization and HR 1.51 (95% CI 1.24-1.84) for admission to ICU. Sera from male patients at hospital admission had decreased lymphocyte count and elevated inflammatory markers (C-reactive protein, procalcitonin, and neutrophils). *We found that SARS-CoV-2 entry factors, including ACE2, TMPRSS2, FURIN and NRP1, have elevated expression in nasal squamous cells from males with moderate and severe COVID-19. Cell-cell network proximity analysis suggests possible epithelium-immune cell interactions and immune vulnerability underlying a higher mortality in males with COVID-19. Monocyte-elevated expression of Toll like receptor 7 (TLR7) and Bruton tyrosine kinase (BTK) is associated with severe outcomes in males with COVID-19. These findings provide basis for understanding immune responses underlying sex differences, and designing sex-specific targeted treatments and patient care for COVID-19*. [**note: here is a nice paper from the Cleveland Clinic on an analysis of sex differences in the human immune system and how this impacts COVID-19.**] https://www.biorxiv.org/content/10.1101/2020.12.01.407007v1
- Sexual dimorphisms in immune responses contribute to coronavirus disease 2019 (COVID-19) outcomes, yet the mechanisms governing this disparity remain incompletely understood. We carried out sex-balanced sampling of peripheral blood mononuclear cells from confirmed COVID-19 inpatients and outpatients, uninfected close contacts, and healthy controls for 36-color flow cytometry and single cell RNA-sequencing. *Our results revealed a pronounced reduction of circulating mucosal associated invariant T (MAIT) cells in infected females. Integration of published COVID-19 airway tissue datasets implicate that this reduction represented a major wave of MAIT cell extravasation during early infection in females. Moreover, female MAIT cells possessed an immunologically active gene signature, whereas male counterparts were pro-apoptotic. Collectively, our findings uncover a female-specific protective MAIT profile, potentially shedding light on reduced COVID-19 susceptibility in females*. [**note:**

and from Duke another paper exploring sex related differences.]
https://www.biorxiv.org/content/10.1101/2020.12.01.407148v1

DIAGNOSTIC DEVELOPMENT

- No new approaches.

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2020-12-03

One of the new groups that I have discovered during the writing of the newsletter is the NOVA Quartet that specializes in Bossa Nova and Samba music. Laura Vall's vocals are always arresting. They have been doing a quarantine series over the recent months that feature some of my favorite pieces. 'Summer Samba' was just recently uploaded: https://www.youtube.com/watch?v=F8A-BezgZHY From the pre-pandemic (remember that?) here is the great Jobim composition, 'Desafinado': https://www.youtube.com/watch?v=1Rhq53sCfRU and finally, a reprise of one of my favorites that I posted a while back that warrants another listen, 'Corcovado': https://www.youtube.com/watch?v=wl6NVR88kgQ this is for a very special reader of my newsletters and you know who you are!!!!

The COVID-19 illness and mortality statistics continue to be grim. By my rough calculation the Case Fatality Rate (CFR) is just a shade under 2% based on documented cases of the illness. We do not know how many asymptomatic cases have not been diagnosed (the CDC estimated last week it could be 8X the current number). As you know, my own rough estimate for the CFR has been somewhere between 0.3-0.6% based on the novelty of the virus and data on past influenza epidemics. Regardless, we will see increasing morbidity and mortality over the next two months as the vaccine(s) are made available in the US.

The Washington Post notes that super-cold freezers are in high demand. I wonder why? CDC director Robert Redfield says January and February will be very difficult times and may be the biggest public health challenge the country has faced. Perhaps it is the beginning of the end of the pandemic.

The New York Times tells us why the UK approved the Pfizer vaccine before the US. Here are some common questions about the vaccine rollout. We should not forget that lab techs are under a lot of pressure these days. As NBA players return to training camps, almost one tenth have tested positive for COVID-19.

If it is Thursday, there must be some papers worth noting in The New England Journal of Medicine and sure enough there are. Here is a report from the WHO Solidarity Trial Consortium on repurposed antiviral drugs for COVID-19. They studied remdesivir, HCQ, lopinavir, and interferon beta-1a. *These remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had little or no effect on hospitalized patients with Covid-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay*. Here is an accompanying editorial on this paper and also a paper from the FDA Division of Antivirals that approved remdesivir (I wonder if this was solicited by the Journal). I was not persuaded that this is a mainstream therapy for COVID-19 and would have preferred to have seen this moved to a Treatment IND while more data was acquired. The drug is quite expensive, and the benefit marginal based on the submitted data, but this is just my opinion of course; I will let my readers draw their own

conclusions on this conundrum. Here is a commentary on placebo-controlled trials of COVID-19 vaccines and why we still need them from the WHO Ad Hoc Expert Group. Finally, a short letter on the rapid response to an outbreak in Qingdao, China.

STAT discusses a potential 'Black Market' for COVID-19 vaccines. Here is an opinion piece on a better way to roll out COVID-19 vaccines: focus on hot zones.

JAMA look at race/ethnicity in children who come down with COVID-19 associated Multisystem Inflammatory Syndrome in New York City. *We present population-based data highlighting a disproportionate burden of MIS-C among Black and Hispanic children in NYC. It is unclear whether this finding represents a phenomenon distinct from the increased burden of COVID-19 in Black and Hispanic communities, because we also observed a disproportionate burden of COVID-19 hospitalizations among Black and Hispanic children. This analysis is limited by missing race/ethnicity data for most confirmed, nonhospitalized, and nonfatal COVID-19 cases in NYC, which prohibits evaluating the excess burden of MIS-C and COVID-19 hospitalizations among children of color*.

Kaiser Health News has a nice photo montage by Heidi de Marco of Los Angeles under lockdown. I should have done something like this for our area; it would have provided some pandemic relief. OSHA fell down on the job in terms of reporting worker deaths from COVID-19.

Lots of reading today!!!!

MODELING

- Public health experts have confirmed that airborne transmission of SARS-CoV-2 (COVID-19) is one of the primary mechanisms of infection (CDC, 2020). In addition to social distancing, mask wearing and hand washing, experts now recommend increasing the ventilation and filtration of indoor air. While there is widespread consensus on this general approach, to date there are no published guidelines for the levels of ventilation, filtration, etc. that are required to control the pandemic. This is an urgent concern because colder weather in the Northern Hemisphere has moved social activity indoors where the risk of infection is higher. We propose a Guideline that provides a Criterion for integrating the effects of engineering and administrative controls with personal protective equipment (PPE) for indoor environments. *The Guideline takes into account ventilation, filtration, temperature control, humidity control, masks, occupant density, occupancy category and activity. The design of the Guideline integrates recently published research regarding COVID-19 characteristics (a topic of ongoing scientific investigation) with well-established models for contaminant accumulation and infection risk (Wells-Riley), and is informed by the SIR model of epidemic dynamics. We mathematically determine a minimum threshold for the loss rate (combination of air change rate, removal rate by filtration, inactivation rate, and settling rate) that will keep the expected number of secondary infections from a single infected person less than 1.0 over the sequence of activities performed by the infected person while they are infectious. If the expected number of secondary infections is less than 1.0, then the number of infections at the population level will decrease. We show how the Guideline can be used in conjunction with existing tabulated air quality standards. We also illustrate the importance of masks and occupant density. Though the Guideline has been*

developed with SARS-CoV-2 in mind, it could also be applied to future epidemics and other pathogens using different pathogen-specific characteristics. [**note: lots of office buildings are still empty because of the pandemic. Moving to a healthy inside building environment is not only important during the pandemic but also post-pandemic. This is a very useful paper in that regard.**] https://www.medrxiv.org/content/10.1101/2020.11.30.20241406v1

- Covid-19 mitigation commonly involves contact tracing (CT) and social distancing. Due to its high economic toll and its impact on personal freedom, we need to ease social distancing and deploy alternative measures, while preventing further waves of infections. While reliable mass testing (for virus RNA) would require too many resources to be effective, CT, which focuses on isolating symptomatic cases and their contacts, has been implemented in many countries. However, the latter approach has reduced efficiency when high numbers of positive patients are burdening the tracing centers. Moreover, CT misses transmissions by asymptomatic cases. Therefore, its effect in reducing the reproduction number has a theoretical limit. To improve effectiveness of contact tracing, we propose to complement it with a strategy relying on identifying and testing symptom free subgroups with a significantly higher than average virus prevalence. *We call this smart testing (ST). By testing everybody in these subgroups, in addition to symptomatic cases, also large fractions of pre- and asymptomatic persons can be identified, which enhances the effectiveness of contact tracing. High prevalence subgroups can be found in different ways, which are discussed in this paper. A particularly efficient way is via preselection using cheap and fast virus antigen tests, as proposed recently. Mathematical modeling quantifies the potential reduction of the reproduction number by such a two-stage ST strategy. In addition to global scenarios, also more realistic local applications of two-stage ST have been investigated, that is, within counties, institutions, schools, companies, etc., where members have internal as well as external contacts. All involved model parameters have been varied within realistic ranges and results are presented with probabilities. Even with the most pessimistic parameter set, these results suggest that the effect of two-stage ST on the reproduction number would clearly outweigh its economic cost. Two-stage ST is technically and logistically feasible. Further, it is locally effective also when only applied within small local subpopulations. Thereby, two-stage ST efficiently complements the portfolio of mitigation strategies, which allow easing social distancing without compromising public health*. [**note: this one is from researchers at Albert Einstein's alma mater in Zurich so you know it has to be good! They proposed a smart testing regime that can complement other mitigation strategies.**]
  https://www.medrxiv.org/content/10.1101/2020.11.30.20239566v1
- Background Until pharmaceutical measures are widely available to slow the spread of SARS-CoV-2, social distancing strategies are key to avert overwhelmed health systems. Since schools host large numbers of students in enclosed spaces, they are feared to produce infection clusters. With school closures coming at high social and economic costs, social distancing measures within schools are needed to make them as safe as possible. One widely discussed distancing measure in the school context is to use cohorting strategies, i.e., to split larger clusters such as classrooms into smaller groups that are instructed separately. In addition to facilitating social distancing within these cohorts, cohorting strategies also aim to prevent transmission across cohorts. However, little is known about which cohorting strategies are particularly effective to prevent disease transmission between cohorts in schools. Methods Using nationally representative data on adolescents in classrooms in four European countries, we simulate how

four different cohorting strategies can mitigate the spread of SARS-CoV-2 in high schools. We model the effect of forming two cohorts randomly, splitting cohorts by gender, optimizing cohorts by minimizing students' out-of-school cross-cohort contacts, and approximating this optimization strategy by network chains. The rationale of all non-random cohorting strategies is to prevent the spread of SARS-CoV-2 from one cohort to the other by reducing cross-cohort out-of-school contact. We also compare the overall effect of cohorting to no cohorting and differentiate between a rota-system in which cohorts receive in-person instruction in alternating weeks and a system with separate but same-day in-person instruction for both cohorts. Data were collected between 2010 and 2011 as part of the CILS4EU project, a network panel study of 14-15-year-olds in England, Germany, the Netherlands, and Sweden. Across all four countries, we model the transmission of SARS-CoV-2 in 507 classrooms, capturing a total of 12,291 students. Findings Our simulations suggest that all four cohorting strategies reduce the spread of SARS-CoV-2 in classrooms, but vary in their effectiveness. Relative to random cohorting, all strategies that factor in out-of-school cross-cohort ties have particularly strong effects on the frequency of cross-cohort transmission but also substantively reduce the total number of infections and the share of students in quarantine when transmission dynamics are strong. *Cohorting that explicitly minimizes out-of-school contact between students in different cohorts is most effective, but network-based approximation also breaks many cross-cohort ties and thus performs well. Because adolescents' out-of-school contacts tend to be strongly segregated by gender, dividing classrooms by gender also outperforms random cohorting but is less effective than directly using network information. For all cohorting strategies, rota-systems with instruction in alternating weeks contain outbreaks more effectively than same-day in-person instruction. Interpretation Cohorting of school classes as a social distancing measure can help to effectively curb SARS-CoV-2 outbreaks in the school context. If schools consider splitting up classes into two smaller cohorts, factoring in out-of-school contacts can help achieve a more effective separation of cohorts. The paper proposes effective cohorting strategies that outperform naive random cohorting in preventing the spread of SARS-CoV-2. These strategies may limit outbreaks to one cohort, keep the size of infection clusters low, and reduce the number of students in quarantine if an index case occurs in the student body. Our findings thus suggest that if schools consider cohorting, they should assign students who meet after school to the same cohort. In particular, cohorting on the basis of gender or network chains is effective and may be successfully implemented within the constraints posed by the classroom context*. [**note: it's always fun reading new modeling papers on how to keep schools open. Here is one that focuses on high schools.**] https://www.medrxiv.org/content/10.1101/2020.11.30.20241166v1

- Although many COVID-19 patients quarantine and recover at home, the dispersal of SARS-CoV-2 onto surfaces and dust within the home environment remains poorly understood. To investigate the distribution and persistence of SARS-CoV-2 in a quarantine home, samples were collected from a household with two confirmed COVID-19 cases (one adult and one child). Home surface swab and dust samples were collected two months after symptom onset (and one month after symptom resolution) in the household. The strength of the SARS-CoV-2 molecular signal in fomites varied as a function of sample location, surface material and cleaning practices. Notably, the SARS-CoV-2 RNA signal was detected at several locations throughout the household although cleaning appears to have attenuated the signal on many surfaces. Of the 24 surfaces sampled, 46% were SARS-CoV-2 positive at the time of sampling. The SARS-CoV-2

concentrations in dust recovered from floor and HVAC filter samples ranged from 104-105 N2 gene copies/g dust. While detection of viral RNA does not imply infectivity, this study confirms that the SARS-CoV-2 RNA signal can be detected at several locations within a COVID-19 quarantine home and can persist after symptoms have resolved. In addition, the concentration of SARS-CoV-2 (normalized per unit mass of dust) recovered in home HVAC filters may prove useful for estimating SARS-CoV-2 airborne levels in homes. [**note: this is from Univ of Texas and looks at a variety of surfaces in a home with COVID-19 positive occupants. I'm still unsure that the detection of viral RNA implies that there is infectious virus on the surface.**] https://www.medrxiv.org/content/10.1101/2020.11.30.20234393v1

- The emergence of coronavirus disease 2019 (COVID-19) has infected more than 37 million people worldwide. The control responses varied across countries with different outcomes in terms of epidemic size and social disruption. In this study, we presented an age-specific susceptible-exposed-infected-recovery-death model that considers the unique characteristics of COVID-19 to examine the effectiveness of various non-pharmaceutical interventions (NPIs) in New York City (NYC). Numerical experiments from our model show that the control policies implemented in NYC reduced the number of infections by 72% (IQR 53-95), and the number of deceased cases by 76% (IQR 58-96) by the end of 2020, respectively. *Among all the NPIs, social distancing for the entire population and the protection for the elderly in the public facilities is the most effective control measure in reducing severe infections and deceased cases. School closure policy may not work as effectively as one might expect in terms of reducing the number of deceased cases. Our simulation results provide novel insights into the city-specific implementation of NPIs with minimal social disruption considering the locations and population characteristics*. [**note: here is some work from Chinese researchers on the impact of non-pharmaceutical interventions on the control of the pandemic in New York City.**] https://www.medrxiv.org/content/10.1101/2020.12.01.20242347v1
- In the COVID-19 pandemic, among the more controversial issues is the use of face coverings. To address this we show that the underlying physics ensures particles with diameters (> 1 micron) are efficiently filtered out by a simple cotton or surgical mask. For particles in the submicron range the efficiency depends on the material properties of the masks, though generally the filtration efficiency in this regime varies between 30 to 60 % and multi-layered cotton masks are expected to be comparable to surgical masks. Respiratory droplets are conventionally divided into coarse droplets (> 5-10 micron) responsible for droplet transmission and aerosols (< 5-10 micron) responsible for airborne transmission. *Masks are thus expected to be highly effective at preventing droplet transmission, with their effectiveness limited only by the mask fit, compliance and appropriate usage. By contrast, knowledge of the size distribution of bioaerosols and the likelihood that they contain virus is essential to understanding their effectiveness in preventing airborne transmission. We argue from literature data on SARS-CoV-2 viral loads that the finest aerosols (< 1 micron) are unlikely to contain even a single virion in the majority of cases; we thus expect masks to be effective at reducing the risk of airborne transmission in most settings*. [**note: from the Univ of Bristol, face masks work! Interesting that they hypothesize that very fine aerosols are unlikely to contain even a single virus particle.**] https://www.medrxiv.org/content/10.1101/2020.12.01.20241992v1
- The recent publication of the Great Barrington Declaration (GBD), which calls for relaxing all public health interventions on young, healthy individuals, has brought the question of herd

immunity to the forefront of COVID-19 policy discussions, and is partially based on unpublished research that suggests low herd immunity thresholds (HITs) of 10-20%. *We re-evaluate these findings and correct a flawed assumption leading to COVID-19 HIT estimates of 60-80%. If policymakers were to adopt a herd immunity strategy, in which the virus is allowed to spread relatively unimpeded, we project that cumulative COVID-19 deaths would be five times higher than the initial estimates suggest. Our re-estimates of the COVID-19 HIT corroborate strong signals in the data and compelling arguments that most of the globe remains far from herd immunity, and suggest that abandoning community mitigation efforts would jeopardize the welfare of communities and integrity of healthcare systems*. [**note: maybe Scott Atlas read this paper before deciding to leave as the coronavirus advisor to President Trump. In addition to reducing mortality, NPIs are necessary to keep hospitals from being overloaded.**]
https://www.medrxiv.org/content/10.1101/2020.12.01.20242289v1

- As long as effective medical treatment and vaccination are not available, non-pharmaceutical interventions such as social distancing, self-isolation and quarantine as well as far-reaching shutdowns of economic activity and public life are the only available strategies to prevent the virus from spreading. These interventions must meet conflicting requirements where some objectives, like the minimization of disease-related deaths or the impact on health systems, demand for stronger counter-measures, while others, such as social and economic costs, call for weaker counter-measures. *Therefore, finding the optimal compromise of counter-measures requires the solution of a multi-objective optimization problem that is based on accurate prediction of future infection spreading for all combinations of countermeasures under consideration. We present a strategy for construction and solution of such a multi-objective optimization problem with real-world applicability. The strategy is based on a micro-model allowing for accurate prediction via a realistic combination of person-centric data-driven human mobility and behavior, stochastic infection models and disease progression models including micro-level inclusion of governmental intervention strategies. For this micro-model, a surrogate macro-model is constructed and validated that is much less computationally expensive and can therefore be used in the core of a numerical solver for the multi-objective optimization problem. The resulting set of optimal compromises between countermeasures (Pareto front) is discussed and its meaning for policy decisions is outlined*. [**note: wow, lots of models today. This one is right up my wheelhouse as it uses my favorite, a stochastic infection model along with the classic Pareto approach!**]
https://www.medrxiv.org/content/10.1101/2020.12.01.20241885v1
- In the wake of the rapid surge in the Covid-19 infected cases seen in Southern and West-Central USA in the period of June-July 2020, there is an urgent need to develop robust, data-driven models to quantify the effect which early reopening had on the infected case count increase. In particular, it is imperative to address the question: *How many infected cases could have been prevented, had the worst affected states not reopened early? To address this question, we have developed a novel Covid-19 model by augmenting the classical SIR epidemiological model with a neural network module. The model decomposes the contribution of quarantine strength to the infection timeseries, allowing us to quantify the role of quarantine control and the associated reopening policies in the US states which showed a major surge in infections. We show that the upsurge in the infected cases seen in these states is strongly co-related with a drop in the quarantine/lockdown strength diagnosed by our model. Further, our results demonstrate that in*

the event of a stricter lockdown without early reopening, the number of active infected cases recorded on 14 July could have been reduced by more than 40% in all states considered, with the actual number of infections reduced being more than 100,000 for the states of Florida and Texas. As we continue our fight against Covid-19, our proposed model can be used as a valuable asset to simulate the effect of several reopening strategies on the infected count evolution; for any region under consideration. [**note: here is a model from MIT that looks at the impact of the road not chosen in some states regarding delaying reopenings.**]
https://www.medrxiv.org/content/10.1101/2020.12.01.20242172v1

- In the year 2020 COVID-19 pandemic was a global issue that changed mankind's lifestyle. Since then, when we will control the pandemic and recover our normal life has become the paramount question to be answered, and it needs to be solved. One problem is that there are wealthy countries, with very good health care systems and scientific resources while others barely dedicate 100 US $ per citizen per year, rich countries could cooperate at different levels with poorer ones. In such a diverse context classic epidemiology models, excellent for predicting short term evolution of the pandemic at a local level are not as suitable for long term predictions at a global scale specially if the data they use are of questionable accuracy. Alternatively, big data and AI approaches have been tried. There is an option that can be more effective. Physics applies predictive models about the duration of an event based on analysing the dynamics of the time evolution of the event itself. These models can be used alongside with probabilistic and game theory models that consider different degrees of cooperation. *By means of the physics Delta-t argument and a game theory model (cooperate versus defector) we calculate when different countries may control COVID-19 pandemic. In a non-cooperate model, those countries with more resources and best manage the pandemic will have it under control between May and September 2021, whereas those with no resources will suffer the pandemic until at least October 2023. On the other hand, a strong cooperative model will allow that the majority could control the COVID-19 pandemic between October 2021 and November 2022*. [**note: any paper with 'Is the end near?' in the title gets a shout out from me. Unfortunately, this game theory model presents a bleak case unless there is cooperation.**]
https://www.medrxiv.org/content/10.1101/2020.12.01.20242099v1

NEWLY REGISTERED CLINICAL TRIALS

- You can safely look away.

CLINICAL TRIAL RESULTS

- An uncontrolled increase in cytokine production may lead to systemic hyperinflammation, vascular hypo-responsiveness, increased endothelial permeability, hypercoagulation, multi-organ dysfunction and eventually death in moderate to severely ill COVID-19 patients. Targeting T-cells, an important driver of the hyperinflammatory response, in the treatment of COVID-19, could potentially reduce mortality and improve survival rates. Itolizumab is an anti-CD6 humanized monoclonal antibody with an immunomodulating action on Teffector cells that downregulates T-cell activation, proliferation and subsequent production of various chemokines and cytokines. The efficacy and safety of Itolizumab for the treatment of cytokine release syndrome in patients with moderate to severe acute respiratory distress syndrome (ARDS) due to COVID-19 was evaluated in a multi-centric, open-label, two-arm, controlled, randomized,

phase 2 study. Eligible patients were randomized (2:1) to arm A (best supportive care + Itolizumab) and arm B (best supportive care). The primary outcome of interest was reduction in all-cause mortality 30 days after enrolment. Thirty-six patients were screened, 5 were treated as first dose sentinels and the rest were randomized, whilst 4 patients were considered screen failures. Two patients in the Itolizumab treatment arm discontinued prior to receiving the first dose and were replaced. At the end of 1 month, there were 3 deaths in arm B, and none in arm A (p= 0.0296). At the end of the follow-up period, more patients in Arm A had improved SpO2 without increasing FiO2 (p=0.0296), improved PaO2 (p=0.0296), and reduction in IL-6 (43 pg/ml vs 212 pg/ml; p=0.0296) and tumor necrotic factor-α (9 pg/ml vs 39 pg/ml; p=0.0253) levels. *Itolizumab was generally safe and well tolerated, and transient lymphopenia (11 patients in Arm A) and infusion reactions (7 patients) were the commonly reported treatment related safety events. These encouraging results indicate that larger clinical trials are warranted to establish the role of Itolizumab in controlling immune hyperactivation in COVID-19*. [**note: finally, a clinical trial result! This is from India and looks at itolizumab in moderate to severe ARDS patients. This is an anti-CD6 mAb and was developed by Biocon and the Center for Molecular Immunology in Cuba. The trial size is too small to draw any conclusions.**]
https://www.medrxiv.org/content/10.1101/2020.12.01.20239574v1

DRUG DEVELOPMENT

- *Fast track microfluidic screening of the antibody repertoires of 12 convalescent COVID-19 donors comprising 2.8mio antibodies yielded MTX-COVAB, a human-derived monoclonal antibody with low picomolar neutralization IC50 of SARS-CoV-2. COVAB neutralization potency is on par with the Regeneron cocktail as demonstrated in a comparative neutralization assay. MTX-COVAB shows strong efficacy in vivo and binds to all currently identified clinically relevant variants of SARS-CoV-2. MTX-COVAB completes GMP manufacturing by the end of this year and will be tested in the clinic in March 2021*. [**note: here is another human-derived antibody with potent neutralizing activity against SARS-CoV-2.**]
https://www.biorxiv.org/content/10.1101/2020.12.01.406934v1
- Small molecule inhibitors that reverse disease severity have proven difficult to discover. One of the key approaches that has been widely applied in an effort to speed up the translation of drugs is drug repurposing. A few drugs have shown in vitro activity against Ebola virus and demonstrated activity against SARS-CoV-2 in vivo. Most notably the RNA polymerase targeting remdesivir demonstrated activity in vitro and efficacy in the early stage of the disease in humans. Testing other small molecule drugs that are active against Ebola virus would seem a reasonable strategy to evaluate their potential for SARS-CoV-2. We have previously repurposed pyronaridine, tilorone and quinacrine (from malaria, influenza, and antiprotozoal uses, respectively) as inhibitors of Ebola and Marburg virus in vitro in HeLa cells and of mouse adapted Ebola virus in mouse in vivo. We have now tested these three drugs in various cell lines (VeroE6, Vero76, Caco-2, Calu-3, A549-ACE2, HUH-7 and monocytes) infected with SARS-CoV-2 as well as other viruses (including MHV and HCoV 229E). The compilation of these results indicated considerable variability in antiviral activity observed across cell lines. We found that tilorone and pyronaridine inhibited the virus replication in A549-ACE2 cells with IC50 values of 180 nM and IC50 198 nM, respectively. *We have also tested them in a pseudovirus assay and used microscale thermophoresis to test the binding of these molecules to the spike protein. They*

bind to spike RBD protein with Kd values of 339 nM and 647 nM, respectively. Human Cmax for pyronaridine and quinacrine is greater than the IC50 hence justifying in vivo evaluation. We also provide novel insights into their mechanism which is likely lysosomotropic. [**note: some more potential small molecule drugs for COVID-19 testing. They were tested against Ebola and Marburg viruses. Given the lack of specificity for HCQ which was also thought to be lyosomotropic, I am not optimistic about these drugs. Clinical trials, if they do occur, will certainly answer the question.**]
https://www.biorxiv.org/content/10.1101/2020.12.01.407361v1

- Viral entry via binding of the receptor binding domain (RBD) located within the S1 subunit of the SARS-CoV-2 Spike (S) protein to its target receptor angiotensin converting enzyme (ACE) 2 is a key step in cell infection. The efficient transition of the virus is linked to a unique protein called open reading frame (ORF) 8. As SARS-CoV-2 infections can develop into life threatening lower respiratory syndromes, effective therapy options are urgently needed. Several publications propose vitamin D treatment, although its mode of action against COVID-19 is not fully elucidated. It is speculated that vitamin D's beneficial effects are mediated by up regulating LL-37, a well known antimicrobial peptide with antiviral effects. Methods: Recombinantly expressed SARS-CoV-2 S protein, the extended S1 subunit (S1e), the S2 subunit (S2), the receptor binding domain (RBD), and ORF8 were used for surface plasmon resonance (SPR) studies to investigate LL-37's ability to bind to SARS-CoV-2 proteins and to localize its binding site within the S protein. Binding competition studies were conducted to confirm an inhibitory action of LL-37 on the attachment of SARS-CoV-2 S protein to its entry receptor ACE2. Results: We could show that LL-37 binds to SARS-CoV-2 S protein (LL-37/S-Strep KD = 407 nM, LL-37/S-His KD = 414 nM) with the same affinity, as SARS-CoV-2 binds to hACE2 (hACE2/S-Strep KD = 374 nM, hACE2/S-His KD = 368 nM). The binding is not restricted to the RBD of the S protein, but rather distributed along the entire length of the protein. Interaction between LL-37 and ORF8 was detected with a KD of 294 nM. Further, inhibition of the binding of S-Strep (IC50 = 735 nM), S1e (IC50 = 168 nM), and RBD (IC50 = 126 nM) to hACE2 by LL-37 was demonstrated. Conclusions: *We have revealed a biochemical link between vitamin D, LL-37, and COVID-19 severity. SPR analysis demonstrated that LL-37 binds to SARS-CoV-2 S protein and inhibits binding to its receptor hACE2, and most likely viral entry into the cell. This study supports the prophylactic use of vitamin D to induce LL-37 that protects from SARS-CoV-2 infection, and the therapeutic administration of vitamin D for the treatment of COVID-19 patients. Further, our results provide evidence that the direct use of LL-37 by inhalation and systemic application may reduce the severity of COVID-19.* [**note: perhaps this is how Vitamin D works.**]
https://www.biorxiv.org/content/10.1101/2020.12.02.408153v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Travel-related dissemination of SARS-CoV-2 continues to contribute to the global pandemic. A novel SARS-CoV-2 lineage (B.1.177) reportedly arose in Spain in the summer of 2020, with subsequent spread across Europe linked to travel by infected individuals. Surveillance and monitoring through the use of whole genome sequencing (WGS) offers insights into the global and local movement of pathogens such as SARS-CoV-2 and can detect introductions of novel variants. Methods: We analyzed the genomes of SARS-CoV-2 sequenced for surveillance purposes from specimens received by Public Health Ontario (Sept 6 - Oct 10, 2020), collected

from individuals in eastern Ontario. Taxonomic lineages were identified using pangolin (v2.08) and phylogenetic analysis incorporated publicly available genomes covering the same time period as the study sample. Epidemiological data collected from laboratory requisitions and standard reportable disease case investigation was integrated into the analysis. Results: *Genomic surveillance identified a COVID-19 case with SARS-CoV-2 lineage B.1.177 from an individual in eastern Ontario in late September, 2020. The individual had recently returned from Europe. Genomic analysis with publicly available data indicate the most closely related genomes to this specimen were from Southern Europe. Genomic surveillance did not identify further cases with this lineage. Conclusions: Genomic surveillance allowed for early detection of a novel SARS-CoV-2 lineage in Ontario which was deemed to be travel related. This type of genomic-based surveillance is a key tool to measure the effectiveness of public health measures such as mandatory self-isolation for returned travellers, aimed at preventing onward transmission of newly introduced lineages of SARS-CoV-2*. [**note: the virus just loves to travel on airplanes!! Here is a study from Ontario that shows the Spanish variant from the summer made its way to Canada.**] https://www.medrxiv.org/content/10.1101/2020.11.30.20241265v1

DIAGNOSTIC DEVELOPMENT

- A central problem in the COVID-19 pandemic is that there is not enough testing to prevent infectious spread of SARS-CoV-2, causing surges and lockdowns with human and economic toll. Molecular tests that detect viral RNAs or antigens will be unable to rise to this challenge unless testing capacity increases by at least an order of magnitude while decreasing turnaround times. Here, we evaluate an alternative strategy based on the monitoring of olfactory dysfunction, a symptom identified in 76-83% of SARS-CoV-2 infections -- including those that are otherwise asymptomatic -- when a standardized olfaction test is used. We model how screening for olfactory dysfunction, with reflexive molecular tests, could be beneficial in reducing community spread of SARS-CoV-2 by varying testing frequency and the prevalence, duration, and onset time of olfactory dysfunction. We find that monitoring olfactory dysfunction could reduce spread via regular screening, and could reduce risk when used at point-of-entry for single-day events. In light of these estimated impacts, and because olfactory tests can be mass produced at low cost and self-administered, we suggest that screening for olfactory dysfunction could be a high impact and cost effective method for broad COVID-19 screening and surveillance. [**note: I just knew that a smell company would come out of the pandemic. Too bad it was not mine!!! One of the authors of this paper is a founder of an olfactory test company u-Smell-it LLC and has related pending patents. I wonder if his patents pre-date mine?**] https://www.medrxiv.org/content/10.1101/2020.11.30.20241174v1
- A high volume of testing followed by rapid isolation and quarantine measures is critical to the containment of SARS-CoV-2. RT-PCR of nasopharyngeal swabs (NPS) has been established as sensitive gold standard for the detection of SARS-CoV-2 infection. Yet, additional test strategies are in demand to increase and broaden testing opportunities. As one attractive option, saliva has been discussed as an alternative to NPS as its collection is simple, non-invasive, suited for children and amenable for mass- and home-testing. Methods Here, we report on the outcome of a head-to-head comparison of SARS-CoV-2 detection by RT-PCR in saliva and nasopharyngeal swab (NPS) of 1187 adults and children reporting to outpatient test centers and an emergency unit for an initial SARS-CoV-2 screen. Results In total, 252 individuals were tested SARS-CoV-2

positive in either NPS or saliva. SARS-CoV-2 RT-PCR results in the two specimens showed a high agreement (Overall Percent Agreement = 98.0%). Despite lower viral loads in saliva, we observed sensitive detection of SARS-CoV-2 in saliva up to a threshold of Ct 33 in the corresponding NPS (Positive Percent Agreement = 97.7%). In patients with Ct above 33 in NPS, agreement rate dropped but still reaches notable 55.9%. Conclusion *The comprehensive parallel analysis of NPS and saliva reported here establishes saliva as a reliable specimen for the detection of SARS-CoV-2 that can be readily added to the diagnostic portfolio to increase and facilitate testing.* [**note: here is a large Swiss study on the utility of saliva testing for SARS-CoV-2 compared to the nasopharyngeal swab. Saliva is a reliable specimen (and of course easier to collect).**] https://www.medrxiv.org/content/10.1101/2020.12.01.20241778v1

- SARS-CoV-2 is a respiratory virus but it is also detected in a significant proportion of fecal samples of COVID-19 cases. Recent studies have shown that wastewater surveillance can be a low-cost tool for management of COVID-19 pandemic and tracking COVID-19 outbreaks in communities but most studies have been focusing on sampling from wastewater treatment plants. Institutional level of wastewater surveillance may serve well for early warning purposes since cases can be tracked and immediate action can be executed in the event of positive signal. In this study, a novel Moore swab method was developed and used for wastewater surveillance of COVID-19 at institutional level. Among the 219 swab samples tested, 28 (12.8%) swabs collected from the three campuses and two buildings were positive for SARS-CoV-2. Further individual clinical diagnosis validated the wastewater results and indicated that this method was sensitive enough to detect 1-2 cases in a building. In addition, comparison between grab and Moore swab methods from the hospital sewage line indicated that Moore swab method was more sensitive than the grab sampling method. These results suggest that the Moore swab is a sensitive, practical, and easy to use early warning tool for COVID-19 surveillance especially in low-resource settings and at an early stage of infection in communities. [**note: this is a pretty cool paper from Emory Univ. These investigators revive the 'old' Moore Swab technique that was used in the late 1940s to trace *Salmonella Paratyphi B* in effluent sewage water. They did real time sampling of residence halls on the Emory campus.**] https://www.medrxiv.org/content/10.1101/2020.12.01.20238006v1
- Wastewater-based epidemiology is an emerging tool to monitor COVID-19 infection levels by measuring the concentration of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA in wastewater. There remains a need to improve wastewater RNA extraction methods' sensitivity, speed, and reduce reliance on often expensive commercial reagents to make wastewater-based epidemiology more accessible. *We present a kit-free wastewater RNA extraction method, titled "Sewage, Salt, Silica and SARS-CoV-2" (4S), that employs the abundant and affordable reagents sodium chloride (NaCl), ethanol and silica RNA capture matrices to recover 6-fold more SARS-CoV-2 RNA from wastewater than an existing ultrafiltration-based method. The 4S method concurrently recovered pepper mild mottle virus (PMMoV) and human 18S ribosomal subunit rRNA, both suitable as fecal concentration controls. The SARS-CoV-2 RNA concentrations measured in three sewersheds corresponded to the relative prevalence of COVID-19 infection determined via clinical testing. Lastly, controlled experiments indicate that the 4S method prevented RNA degradation during storage of wastewater samples, was compatible with heat pasteurization, and could be performed in approximately 3 hours. Overall, the 4S method is promising for effective, economical, and accessible wastewater-based epidemiology*

for SARS-CoV-2, providing another tool to fight the global pandemic. [**note: wow, a second new approach to wastewater sampling from Cal Berkeley!]**
https://www.medrxiv.org/content/10.1101/2020.12.01.20242131v1

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2020-12-04

Here is one of our special favorited, The Emerson String Quartet. We have been going to see them for over ten years as they have a five-concert season at the Smithsonian Baird Auditorium. The last live music concert that we attended was about a year ago and this is something we miss dearly. Here they are performing the Schubert String Quintet in C that came out after Schubert's death at a tragically young age. The quartet are joined by David Finckel who was the cellist in the quartet for 34 years before retiring to do more duo recitals with his wife, pianist Wu Han: https://www.youtube.com/watch?v=T0GOv95iDf0 We heard this quintet live several years ago and it is spellbinding.

Just a note, **there will be no Saturday newsletter this week**. I will have an extra special newsletter on Sunday!!!!

The New England Journal of Medicine just posted an on-line communication on the durability of immune response following the Moderna mRNA administration. It is really good news in that the immune response was elevated three months following the second injection!!!

Speaking of mRNA vaccines, Kara Swisher has a great interview with the German duo who came up with the BioNTech vaccine. You can listen to the podcast or read the transcript. The German-Turkish duo are modest about their achievement and engaging speakers.

The Washington Post notes that nursing home workers are burned out. This is not a surprise. The recent surge in COVID-19 cases was preceded by the lowest levels of social distancing. Delta Airlines is launching an effort to improve contact tracing on international flights. This is good!

The New York Times has a very good story on the pandemic outbreak in Queens from last spring. I had a question from a loyal reader yesterday about why saliva testing is not be used more. The Times has an article on just this!!! Orange County CA plans to distribute 500K home use saliva test kits to residents. This is good to see. It looks like herd immunity is not present in New York City. Here is a report on Europe's second wave of COVID-19. Here is another in the ongoing survey of epidemiologists that the Times has done. This time they ask how they are living now and what do they think is next.

The Atlantic has the cautionary story of Iowa where doing nothing seems not to be the best option.

Nature have an important article on how adoptive transfer of purified IgG from convalescent macaques protects naïve recipient rhesus macaques against SARS-CoV-2 challenge in a dose dependent fashion. Depletion of CD8+ T cells in convalescent animals partially abrogated the protective efficacy of natural immunity against SARS-CoV-2 re-challenge, suggesting the importance of cellular immunity in the context of waning or subprotective antibody titers. These data demonstrate that relatively low antibody titers are sufficient for protection against SARS-CoV-2 in rhesus macaques, and that cellular immune responses may also contribute to protection if antibody responses are suboptimal. One of the authors of the paper helped develop the J&J COVID-19 vaccine. If this can be directly correlated to protection

data from human clinical trials, it promises to help shorten vaccine development time. I have long felt that this approach should be pursued and am glad to see this paper! Here is a NY Times article on this finding.

The Lancet have an observational study on risk of mortality in patients taking metformin for diabetes. *Metformin was significantly associated with reduced mortality in women with obesity or type 2 diabetes who were admitted to hospital for COVID-19. Prospective studies are needed to understand mechanism and causality. If findings are reproducible, metformin could be widely distributed for prevention of COVID-19 mortality, because it is safe and inexpensive*. Here is a commentary on the study. It is interesting that the benefit was not observed in males. The authors discuss possible reasons for this. Here is a report from England on the use of a mobile app to identify COVID-19 hotspots. *Our method could help to detect rapid case increases in regions where government testing provision is lower. Self-reported data from mobile applications can provide an agile resource to inform policy makers during a quickly moving pandemic, serving as a complementary resource to more traditional instruments for disease surveillance*.

MODELING

- After yesterday's deluge of papers, there is nothing to report on today.

NEWLY REGISTERED CLINICAL TRIALS

- Alas, you are going to be disappointed that I am not posting anything here.

CLINICAL TRIAL RESULTS

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes Coronavirus disease 2019 (COVID-19) exhibits two major variants based on mutations of its spike protein, i.e., the D614 prototype and G614 variant. Although neurological symptoms have been frequently reported in patients, *it is still unclear whether SARS-CoV-2 impairs neuronal activity or function. Here, we show that expression of both D614 and G614 spike proteins is sufficient to induce phenotypes of impaired neuronal morphology, including defective dendritic spines and shortened dendritic length. Using spike protein-specific monoclonal antibodies, we found that D614 and G614 spike proteins show differential S1/S2 cleavage and cell fusion efficiency. Our findings provide an explanation for higher transmission of the G614 variant and the neurological manifestations observed in COVID-19 patients*. [**note: this paper is from China and looks at both the D614 and G614 variant and their impact on neuronal synapses.**]
  https://www.biorxiv.org/content/10.1101/2020.12.03.409763v1

DRUG DEVELOPMENT

- The development of an effective vaccine against SARS-CoV-2, the etiologic agent of COVID-19, is a global priority. Here, we compared the protective capacity of intranasal and intramuscular delivery of a chimpanzee adenovirus-vectored vaccine encoding a pre-fusion stabilized spike protein (ChAd-SARS-CoV-2-S) in Golden Syrian hamsters. While immunization with ChAd-SARS-CoV-2-S induced robust spike protein specific antibodies capable or neutralizing the virus, antibody levels in serum were higher in hamsters immunized by an intranasal compared to

intramuscular route. Accordingly, ChAd-SARS-CoV-2-S immunized hamsters were protected against a challenge with a high dose of SARS-CoV-2. After challenge, ChAd-SARS-CoV-2-S-immunized hamsters had less weight loss and showed reductions in viral RNA and infectious virus titer in both nasal swabs and lungs, and reduced pathology and inflammatory gene expression in the lungs, compared to ChAd-Control immunized hamsters. Intranasal immunization with ChAd-SARS-CoV-2-S provided superior protection against SARS-CoV-2 infection and inflammation in the upper respiratory tract. These findings support intranasal administration of the ChAd-SARS-CoV-2-S candidate vaccine to prevent SARS-CoV-2 infection, disease, and possibly transmission. [**note: vaccine work continues! This report is from Washington Univ and they have a chimpanzee adenovirus vector that can be delivered intranasaly or by normal injection. It protects in a hamster model.**]
https://www.biorxiv.org/content/10.1101/2020.12.02.408823v1

- Xylitol has been reported to reduce the severity of viral infections. Xylitol has also been demonstrated to reduce the severity of pneumonia, and increase the survivability of animal subjects. Pneumonia and acute respiratory distress syndrome are potentially fatal complications of COVID-19. We tested the effectiveness of xylitol against SARS-CoV-2. Virus titers and LRV of SARS-CoV-2, were incubated with a single concentration of nasal spray. Toxicity was observed in the top dilution (1/10). Virus was seen below that dilution so it did not affect calculations of virus titer or LRV. After a 25-minute contact time, the nasal spray reduced virus from 4.2 to 1.7 log10 CCID50 per 0.1 mL, a statistically significant reduction of 2.5 log10 CCID50. STEM Images obtained at the BIoCryo Laboratory revealed virus contained on the cell wall but none intra-cellular, possibly due to D-xylose (xylitol) production of glycoaminoglycans decoy targets. Xylitol and grapefruit seed extract are not exotic nor expensive rare high technology answers to viral epidemics. The potential in saving lives and the economies of the world by using X-GSE combination therapy should inspire large clinical trials, especially in those nations whereas the healthcare system would be dangerously compromised by the adoption of less effective and significantly more financially demanding therapies. Because there are no risk factors in using the X/GSE combination therapy, and the nasal spray is over the counter available without a prescription, and the spray allows for comfortable long term mask-wearing, adoption of this preventive anti-viral therapy should be encouraged. [**note: here is another paper showing that a xylitol nasal spray may be useful in conjunction with grape seed extract. Do two papers constitute material evidence that this works?**]
https://www.biorxiv.org/content/10.1101/2020.12.02.408575v1
- Recombinant human antibodies are proven potent neutralizers of viruses and can block the interaction of viral surface proteins with their host receptors. To develop neutralizing anti-SARS-CoV-2 antibodies, antibody gene libraries from convalescent COVID-19 patients were constructed and recombinant antibody fragments (scFv) against the receptor binding domain (RBD) of the S1 subunit of the viral spike (S) protein were selected by phage display. The selected antibodies were produced in the scFv-Fc format and 30 showed more than 80% inhibition of spike (S1-S2) binding to cells expressing ACE2, assessed by flow cytometry screening assay. The majority of these inhibiting antibodies are derived from the VH3-66 V-gene. *The antibody STE90-C11 showed an IC50 of 0.56 nM in a plaque-based live SARS-CoV-2 neutralization assay. The crystal structure of STE90-C11 in complex with SARS-CoV-2-RBD was solved at 2.0 A resolution showing that the antibody binds at the same region as ACE2 to RBD. In*

contrast to other published anti-SARS-CoV-2 antibodies, the binding of STE90-C11 is not blocked by known RBD mutations, endowing our antibody with higher intrinsic resistance to those possible escape mutants. [**note: this is from Germany and uses phage display to select a potent neutralizing antibody with intrinsic resistance to possible escape mutants.**]
https://www.biorxiv.org/content/10.1101/2020.12.03.409318v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Human CoV strains discovered during previous SARS outbreaks have been hypothesized to pass from bats to humans using intermediate hosts, e.g. civets for SARS-CoV and camels for MERS-CoV. The discovery of an intermediate host of SARS-CoV-2 and the identification of specific mechanism of its emergence in humans are topics of primary evolutionary importance. In this study we investigate the evolutionary patterns of 11 main genes of SARS-CoV-2. Previous studies suggested that the genome of SARS-CoV-2 is highly similar to the horseshoe bat coronavirus RaTG13 for most of the genes and to some Malayan pangolin coronavirus (CoV) strains for the receptor binding (RB) domain of the spike protein. We provide a detailed list of statistically significant horizontal gene transfer and recombination events (both intergenic and intragenic) inferred for each of 11 main genes of the SARS-Cov-2 genome. Our analysis reveals that two continuous regions of genes S and N of SARS-CoV-2 may result from intragenic recombination between RaTG13 and Guangdong (GD) Pangolin CoVs. Statistically significant gene transfer-recombination events between RaTG13 and GD Pangolin CoV have been identified in region [1215-1425] of gene S and region [534-727] of gene N. *Moreover, some significant recombination events between the ancestors of SARS-CoV-2, RaTG13, GD Pangolin CoV and bat CoV ZC45-ZXC21 coronaviruses have been identified in genes ORF1ab, S, ORF3a, ORF7a, ORF8 and N. Furthermore, topology-based clustering of gene trees inferred for 25 CoV organisms revealed a three-way evolution of coronavirus genes, with gene phylogenies of ORF1ab, S and N forming the first cluster, gene phylogenies of ORF3a, E, M, ORF6, ORF7a, ORF7b and ORF8 forming the second cluster, and phylogeny of gene ORF10 forming the third cluster. The results of our horizontal gene transfer and recombination analysis suggest that SARS-Cov-2 could not only be a chimera resulting from recombination of the bat RaTG13 and Guangdong pangolin coronaviruses but also a close relative of the bat CoV ZC45 and ZXC21 strains. They also indicate that a GD pangolin may be an intermediate host of SARS-CoV-2*. [**note: here is a paper from Montreal that looks at horizontal gene transfer and recombination of SARS-CoV-2 genes. This may shed light on the virus's origin and intermediate hosts.**]
https://www.biorxiv.org/content/10.1101/2020.12.03.410233v1

DIAGNOSTIC DEVELOPMENT

- Nothing new today.

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2020-12-06

For this final reflection Sunday, it is appropriate to remember that we are all one and in this together. What better way to do so than listen to Beethoven's Ninth Symphony? It was his final symphony and the

fourth movement that sets Schiller's poem to music never fails to amaze and thrill me. It is frequently performed to consecrate new symphony hall and opera houses. There is no one great performance of this work, but lots that warrant listening to. First up is the famous Berlin Celebration Concert commemorating the reunification of Germany after the fall of the Berlin wall. The orchestra and chorus are made up from members of multiple orchestras under the baton of Leonard Bernstein and the soloists are June Anderson, Sarah Walker, Klaus Konig and Jan-Hendrik Rootering: https://www.youtube.com/watch?v=Hn0IS-vlwCI The next offering is the Chicago Symphony from 2015 under the direction of Ricardo Muti with soloists: Camilla Nylund, Ekaterina Gubanova, Matthew Polenzani and Eric Owens: https://www.youtube.com/watch?v=rOjHhS5MtvA Of course we have to have one of my YouTube faves, the Frankfurt Radio Symphony conducted by Andrés Orozco-Estrada with soloists: Camilla Nylund, Gerhild Romberger, Michael König, and Nathan Berg: https://www.youtube.com/watch?v=gT91esZK90I and finally Daniel Barenboim's West-Eastern Divan Orchestra from the Proms concert with Ana Samuil, Waltraud Meier, Michael König and René Pape: https://www.youtube.com/watch?v=sJQ32q2k8Uo Any one of these performances will inspire you this Sunday!!

Today is newsletter #250 and I've put this out daily with three holiday exceptions since the end of March. I seems prudent given the scientific advances and the near approval of two mRNA vaccines to step away. In recent weeks the number of papers on new scientific advances has decreased markedly. (Actually, the real reason is that I am running out of music selections!) I know that some of my readers will be disappointed and maybe others will think 'I glad I won't get these daily emails on COVID-19 anymore.' It has been fun and challenging trying to distill what is important from what is not and to communicate it in a rational manner. I'm going to use the remainder of this note to discuss what has gone right and wrong in the response to the pandemic.

While the Chinese government sought to hide the early evidence of the pandemic nature of SARS-CoV-2, scientists from the country stepped forward and wrote some excellent papers that have furthered our knowledge of the virus. I applaud their efforts at the same time issuing a critique of the government in Beijing.

The criticism of governments extends beyond China. Many countries made missteps that resulted in higher levels of morbidity and mortality than needed to occur. That contempt for public health authorities arose and evolved is a tragedy beyond comprehension. Some of this was brought about by foolish decisions by not urging wearing of masks early enough and in the case of the CDC, foolishly designing a complex diagnostic test for the virus that didn't work properly resulting in month's delay in responding to the pandemic. The National Institutes of Health was slow to react as well. Back in April, I wrote a modest paper on how to conduct clinical trials in a pandemic, but it wasn't until weeks later that the Foundation for the National Institutes of Health announced a similar type of partnership. In contrast, the UK set up their RECOVERY trial system quickly and produced some of the key results that have informed clinicians.

The FDA must accept a significant amount of blame. The Agency was ill-served by a Commissioner who was inept at best in responding to a public health crisis and bowed to political winds when he should have steered a strong course. The over regulation of COVID-19 diagnostic tests delayed a rapid roll out of a massive testing regime that was and is still needed. Exceptions should have been made for university and independent laboratories to scale up testing. The University of Washington clinical lab

deserves a shout out for putting in place a diagnostic testing regime for local hospitals. Much more could have been done in this area had the Agency been more flexible. Experimental Use Authorizations (EUA) should have been more readily granted (they are after all experimental and not a final well examined diagnostic test).

FDA's early issuance of an EUA for hydroxychloroquine was a major blunder and will forever be a black mark on the Agency. This drug should have remained a mere curiosity rather than being established as a standard treatment in the absence of evidence that it worked. Because of the FDA move, many US doctors elevated the use of this drug and a number of US clinical trials were registered. Fortunately, most of these trials were terminated once evidence of harm and lack of effectiveness began to come in. Despite this, there were still groups of scientists who continue to maintain the drug works against SARS-CoV-2 infections.

There has been recent criticism of FDA as the UK gave the first approval to the Pfizer vaccine. It has to be said that the approval system in the UK is much different than in the US. A good examination of the FDA process is in this STAT piece that just appeared. I think the Biologics Center has been transparent about what is required for an EUA and the requirement for a full two months of safety data was warranted in that this is a totally new approach to a vaccine (there was an early experimental mRNA for Zika Virus but it never made it into clinical trials as the disease went away). I don't think FDA has been dragging its feet on this process though I wonder why some of the Advisory Committee member quoted in the STAT article didn't want to move up the scheduled meeting. I think both mRNA vaccines will receive an EUA approval barring any surprises. FDA also needs to be sure the manufacturing processes are well controlled and the proposed shipping procedures will assure product stability. Manufacturing at large volume that is required for the US and other countries will be a much larger effort than the public believes. Producing doses for a 40K clinical trials is easy, producing tens of millions of doses a month (or more) is hard. One thing I still don't understand is why the Pfizer vaccine has to be stored at ultra-cold temperatures and the Moderna one does not. Perhaps the Pfizer manufacturing folks are more conservative.

One of the more disturbing events has been calls by some states and groups for independent review(s) of the FDA EUA decision (here is the latest such request) These groups are just stupid to put it bluntly and are doing a great disservice to the FDA and its citizen reviewers. Do they think that the FDA is not looking out for the best interests of the American republic? Some years ago, when I was working at PhRMA in regulatory affairs, I received a letter from a doctor in Illinois who had a similar feeling. He indicated that he and other like-minded physicians would be happy to review drug application dossiers in their spare time. After all, how hard could this be? We were in the midst of renegotiating the Prescription Drug User Fee Act and I had received data on review activities from the FDA on the drug review process. By my calculation, an average drug review dossier required 10 person years to review (as my friends from the pharma industry know, this is spread out over many employees and not just 10). I informed this doctor of this outlining how the work input was calculated. I never heard from him again. The same thing goes for vaccine review; it is an intensive process and a small outside group is not going to be able to look at data over a weekend and make any kind of informed decision.

One thing that needs to be done for vaccine development going forward is to observe whether there is a direct correlation to immune response from the vaccine and protection from infection. If research can show there is (and there have been some recent research papers on this), this has the promise of

shortening development and maybe only a safety study would need to be done to support licensure. Remember that we let influenza vaccines on the market each year based on strain identification and manufacturing controls. While it was good that Zika Virus disappeared, it is unfortunate that all the new vaccine approaches that were under development did not enter trials. For those who are interested, there is a good Mayo Clinic Proceedings document on this topic. Despite all these comments, the development of a variety of different vaccines for SARS-CoV-2 has to go down as a tremendous scientific and technical achievement.

The biggest disappointment is the complete collapse of the public health infrastructure in the US. I was optimistic back in March when the first lockdown was implemented that we would get a handle on the virus, develop a testing regime, and figure out how to aggressively track and trace the virus. From the early days in pandemic-stricken New York City, it was always about preventing collapse of the hospitals under a deluge of COVID-19 patients. Extraordinary efforts were made in setting up field hospitals and bringing a military hospital ship to help take care of sick patients. Fortunately, these resources were not needed. Unfortunately, the revulsion in wearing masks and social distancing by large numbers of people have contribute to the second wave of this fall which is leading to increasing morbidity and mortality. ICU beds in many parts of the country are now close to full. Many of those occupying these beds will recover as patient care has improved markedly since the gloomy days of March. To paraphrase a famous political statement, "it's all about the hospitals, stupid." We are so far away from being able to track and trace that it is both tragic and filled with black humor.

It is my hope that as we begin a large-scale vaccination program, that steps are taken to create a high-level commission to examine what went right and wrong in the US battle against SARS-CoV-2. It is my firm conviction that very few people will emerge from this retrospective with their reputations intact.

Here are some things I especially found exciting (there are likely many others):

- The rapid use of genetic typing to track SARS-CoV-2 evolution as it moved across the world
- The development of diagnostic testing of sewage to track viral outbreak
- Lots of good do it yourself (DIY) approaches to lots of different things such as mask sterilization, some universities setting up small scale manufacturing of diagnostics test kits and even a COVID-19 vaccine developed by some researchers in the Boston area (I wonder how that project worked and whether they are collecting any clinical data on those who prepared and took the vaccine)
- Interesting statistical models of viral spread and decision-making tools
- A better understanding of viral immunology
- While many of the preprints I read may never be published in a peer reviewed journal, I was impressed by scientists from countries both big and small for all the efforts made trying to unlock mysteries about SARS-CoV-2

Lasciate ogne speranza, voi ch'intrate of course comes from the first part of Dante's 'Divine Comedy' that I read some years ago. An interesting parlor game, once we escape the pandemic, is to decide who belongs in the nine levels of Hell that Dante constructed. There is no shortage of candidates.

No doubt that I have overlooked some points but to paraphrase the title of Bach's great Cantata 82, 'Ich habe genug! (as a special music bonus, here is a wonderful recording of the Cantata with Dietrich Fischer-Dieskau as the soloist)

I'll leave you with one final story to read. Ed Yong has done yeoman's work at The Atlantic covering the COVID- 19 pandemic. In this article he looks at the current state of the healthcare system as we continue to battle through high levels of hospitalizations. I wonder how many healthcare workers will be scarred by their experience. To all of them, I salute you for your selflessness in the face of an invisible enemy. That you put in 36 hour shifts and some of you got sick and some perished from COVID-19 makes you heroes in my view, and I hope all my readers.

Finally, I would like to thank each one of you who have read the newsletters. I hope you all have found these newsletters both useful and entertaining. It was a labor of love and I learned an awful lot reading papers from all over the world. To those of you who have corresponded with me, I thank you. I've made some new friends and hope that we can meet in person some day when this pandemic is over.

I plan on leaving the COVID-19 web site up for the foreseeable future in hopes it proves of some value.