2020-07-20

Welcome to Week 18 of the Never-Ending Pandemic

Joaquin Rodrigo's Concierto de Aranjuez for guitar and orchestra is one of my favorite pieces. Here is the great Spanish guitarist Pepe Romero at the Guitar Festival in Belgrade: https://www.youtube.com/watch?v=QPcjtg6FvX8 The second movement has been adapted by a good number of jazz instrumentalist. Gil Evans did a wonderful arrangement for Miles Davis 'Sketches of Spain' LP: https://www.youtube.com/watch?v=38zRx9AYDHQ the adagio movement from the Concerto is the first track but the whole album is worth a listen.

US COVID-19 STATISTICS - **Infection Rate: 1.1%; CFR: 3.7%** (IR unchanged; CFR down 0.1%)

The Washington Post has a devastating article on America's response to the SARS-CoV-2 pandemic, stunning it its breadth of coverage. This is from a country that was ranked top in Johns Hopkins Global Health Security Index last October. Here is a good story about a South Bronx barber who is finally back at work. Arizona continues to suffer from a too early reopening.

The Guardian offers stories of three individuals who have lingering COVID-19 symptoms. China continues to see sporadic outbreaks.

The New York Times has a retrospective story about the European outbreak and readiness. Why we still don't know enough about COVID-19 and pregnancy. How should we seniors evaluate risk?

Kaiser Health News on the need to continue monitoring of children who recover from COVID-10 multi-inflammatory syndrome. Good idea to establish a patient registry for long term follow up!!!! As more younger patients catch COVID-19 tracing becomes more difficult and maybe impossible. I view this as a lack of education about public health measures. Other countries seem to get this job done, why not the US?

I forgot to post this the other day! 😔 Here is a Medscape interview with Tony Fauci that is well worth reading.

Unrelated to COVID-19 but interesting, STAT has a story on how some DNA-sleuths analyzed Civil War artifacts and recreated five genomes of viral vaccines used to suppress smallpox in the 1860s. I am constantly amazed at the tools we have right now. Six questions Congress should ask of COVID-19 vaccine manufacturers, all good questions. Does more testing find more COVID-19 cases? Not always as states where the disease has waned such as New York, more testing will show fewer cases.

It was a surprisingly busy Monday for preprints. Data on the Pfizer mRNA vaccines looks very encouraging. We are still waiting for the Oxford vaccine data which is supposed to be coming out any day now.

MODELING

- From February to April, 2020, Lombardy (Italy) was the area who worldwide registered the highest numbers of SARS-CoV-2 infection. By extensively analyzing 346 whole SARS-CoV-2 genomes, we demonstrated the simultaneous circulation in Lombardy of two major viral

lineages, likely derived from multiple introductions, occurring since the second half of January. Seven single nucleotide polymorphisms (five of them non-synonymous) characterized the SARS-CoV-2 sequences, none of them affecting N-glycosylation sites. These two lineages, and the presence of two well defined clusters inside Lineage 1, revealed that a sustained community transmission was ongoing way before the first COVID-19 case found in Lombardy. [**note: interesting conclusion about virus transmission before the first identified case.**]
https://www.medrxiv.org/content/10.1101/2020.07.19.20152322v1

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission causing coronavirus disease 2019 (COVID-19) may occur through multiple routes. We collected aerosol samples around six patients admitted into mixed acuity wards in April of 2020 to identify the risk of airborne SARS-CoV-2. Measurements were made to characterize the size distribution of aerosol particles, and size-fractionated, aerosol samples were collected to assess the presence of infectious virus in particles sizes of >4.1 µm, 1-4 µm, and <1 µm in the patient environment. Samples were analyzed by real-time reverse-transcriptase polymerase chain reaction (rRT-PCR), cell culture, western blot, and transmission electron microscopy (TEM). SARS-CoV-2 RNA was detected in all six rooms in all particle size fractions (>4.1 µm, 1-4 µm, and <1 µm). Increases in viral RNA during cell culture of the virus from recovered aerosol samples demonstrated the presence of infectious, replicating virions in three <1 µm aerosol samples ($P<0.05$). Viral replication of aerosol was also observed in the 1-4 µm stage but did not reach statistical significance ($0.05<P<0.10$). Western blot and TEM analysis of these samples also showed evidence of viral proteins and intact virions. *The infectious nature of aerosol collected in this study further suggests that airborne transmission of COVID-19 is possible, and that aerosol prevention measures are necessary to effectively stem the spread of SARS-CoV-2*. [**note: some good work by these Nebraska researchers. We still do not fully know the impact of fine aerosol particles. Do they contain enough virus to cause infection?**]
https://www.medrxiv.org/content/10.1101/2020.07.13.20041632v1
- As communities reopen following shelter-in-place orders, they are facing two conflicting objectives. The first is to keep the COVID-19 fatality rate down. The second is to revive the U.S. economy and the livelihood of millions of Americans. In this paper, a team of researchers from the Center on Stochastic Modeling, Optimization, & Statistics (COSMOS) at the University of Texas at Arlington, in collaboration with researchers from University of Texas Southwestern Medical Center and Harvard Medical School, has formulated a computationally-efficient optimization framework, referred to as COSMOS COVID-19 Linear Programming (CC19LP), to study the delicate balance between the expected fatality rate and the level of normalcy in the community. Given the disproportionate fatality characteristics of COVID-19 among those in different age groups or with an underlying medical condition or those living with crowding, the key to the CC19LP framework is a focus on "key contacts" that separate individuals at higher risk from the rest of the population. The philosophy of CC19LP lies in maximizing protection of key contacts, so as to shield high-risk individuals from infection. Given the lack of pharmaceutical solutions, i.e., a vaccine or cure, the CC19LP framework minimizes expected fatalities by optimizing the use of non-pharmaceutical interventions, namely COVID-19 testing; personal protective equipment; and social precautions, such as distancing, hand-washing, and face coverings. *Low-risk individuals that are not key contacts, including most children, are unrestricted and can choose to participate in pre-pandemic normal activities, which eliminates*

*the need for compliance across the entire population*. Consequently, the CC19LP framework demonstrates optimal strategies for protecting high-risk individuals while reopening communities. [**note: I'm still concerned about the potential of children as carriers. There are a lot of caveats in this paper that are not discussed in the abstract. It is worth reading in full.**] https://www.medrxiv.org/content/10.1101/2020.07.16.20152033v1

NEWLY REGISTERED CLINICAL TRIALS

- To conduct an open-label randomized controlled trial on a short course of interferon β-1b and clofazimine combination treatment for patients hospitalized for COVID-19 infection. To assess its safety and clinical efficacy. [**note: there are other interferon β-1b trials but not with this additive. This is an old anti-leprosy drug with a half-life of 70 days and an unpleasant safety profile.**] NCT04465695
- This study is a multi-center, randomized, double-blind, parallel, placebo-controlled, phase Ⅱ clinical trial to evaluate efficacy and safety of Pyramax in mild to moderate COVID-19 patients. [**note: this is a combination drug of pyronaridine and aretsunate used to treat malaria. I don't know why it would be effective against SARS-CoV-2.**] NCT04475107
- The purpose of this study is to evaluate the efficacy and safety of intravenous abatacept administered to hospitalized COVID-19 participants with respiratory compromise. [**note: this is a trial sponsored by BMS. It is a modified antibody drug that interferes with the immune activity of T cells and used in treating rheumatoid arthritis.**] NCT04472494
- The study is designed to evaluate the safety, reactogenicity, tolerability, and immunogenicity of three investigational vaccine groups and one placebo group in healthy volunteers who receive two intramuscular doses of BBV152 vaccine formulations. A total sample size of 1125 healthy volunteers, with 375 and 750 volunteers in phase 1 and 2 studies, respectively. [**note: here is another vaccine this time from India. The company is Bharat Biotech International and the product is an inactivated SARS-CoV-2 viral formulation.**] NCT04471519
- This Phase 2/3 trial evaluates four treatment strategies for non-critically ill hospitalized participants (not requiring ICU admission and/or mechanical ventilation) with SARS CoV-2 infection, in which participants will receive NA-831 or Atazanavir with or without Dexamethasone. [**note: sponsor is NeuroActiva, Inc. I don't know anything about NA-831 other than it is an Alzheimer's drug. Why it should work here is a big question.**] NCT04452565
- The aim of this work is to conduct a randomized, double-blind, placebo-controlled clinical trial to assess the efficacy and safety of cannabidiol (CBD - 300 mg a day) in patients infected with SARS-CoV-2. The specific objectives are to assess whether, in patients with mild and moderate forms of SARS-CoV-2, daily use of CBD 300 mg for fourteen days is capable of: i) decrease viral load; ii) modify inflammatory parameters, such as cytokines, measured from serum; iii) reduce clinical and emotional symptoms through daily clinical evaluation; iv) improve sleep; v) reduce hospitalization and worsen the severity of the disease; v) Monitor the possible adverse effects of CBD use in these patients. [**note: it was only a matter of time that someone registered a cannabis trial! This is from the University of Sao Paolo.**] NCT04467918
- Botox treatment into the upper one third of the face (glabella, forehead lines and/or lateral canthal lines) to analyze mood and self -appearance satisfaction in a Post Covid period on non-

naïve Botox patients [**note: seriously?????? Trial is conducted by DeNova Research**] NCT04439825

CLINICAL TRIAL RESULTS

- Hospital mortality due to COVID-19 in Mexico is high (32%) and as of today, effective treatment options are limited. More effective treatments that shorten hospital stay and reduce mortality are needed. Initial reports for the use of convalescent plasma (CP) therapy for COVID-19 appear promising. We describe a case series of eight patients with impending respiratory failure, who underwent CP therapy. Methods: Six male and two female (ages 31 to 79) patients that were admitted to the intensive-care unit for severe COVID-19 were transfused with two doses of CP (250 mL per dose, anti-SARS-CoV-2 IgG titers > 1:100). Donors were six SARS-CoV-2 infected males who remained asymptomatic for > 7 days and were negative for two nasopharyngeal RT-PCR tests. Clinical characteristics, inflammatory and cellular injury markers, chest X-ray findings and viral loads were analyzed before and after CP administration. Viral load association to disease severity was further analyzed on a separate cohort of asymptomatic vs hospitalized patients with COVID-19. Results: Eight patients with respiratory failure were successfully discharged with a median length of stay of 22.5 (IQR 18.25-29.00). After CP therapy, we observed a reduction of C-reactive protein (CRP) (median, 22.80 mg/dL vs. 1.63 mg/dL), and of procalcitonin (median, 0.27 ng/mL vs. 0.13 ng/mL). High-Sensitivity Cardiac Troponin I (hs-cTnI), Brain Natriuretic Peptide (BNP) and Lactate Dehydrogenase (LDH) were lower, and a mild reduction of pulmonary infiltrates by chest X-ray was observed. Lastly, a reduction of viral load was after CP therapy was found. (log, median [IQR], 1.2 [0.70-2.20] vs. 0.25 [0.00-1.78]). We observed no adverse effects. Conclusions: CP could potentially be an effective therapeutic option for patients with severe COVID-19. Clinical benefit needs to be studied further through randomized controlled trials. [**note: yes, it is a small number of patients (8) but these Mexican doctors were able to treat all of them successfully using convalescent serum. There are a number of trials going on right now and with both mAbs and convalescent serum that will provide conclusive answers.**]
  https://www.medrxiv.org/content/10.1101/2020.07.14.20144469v1
- Haloperidol, a widely used antipsychotic, has been suggested as potential effective treatment for Covid-19 on the grounds of its in-vitro antiviral effects against SARS-CoV-2. Methods: We examined the association between haloperidol use and respiratory failure at AP-HP Greater Paris University hospitals. Data were obtained regarding all adult patients hospitalized with Covid-19 since the beginning of the epidemic. Study baseline was defined as the date of hospital admission. The primary endpoint was a composite of intubation or death and the secondary endpoint was discharge home among survivors in time-to-event analyses. We compared outcomes between patients who were exposed to haloperidol and those who were not, using a multivariable Cox regression model with inverse probability weighting according to the propensity score. Results: Of the 13,279 hospitalized adult patients with positive Covid-19 RT-PCR test, 667 patients (5.0%) were excluded because of missing data. Of the remaining 12,612 patients, 104 (0.8%) were exposed to haloperidol. Over a mean follow-up of 20.8 days, the primary endpoint of respiratory failure respectively occurred in 27 patients (26.0%) exposed to haloperidol and 1,700 patients (13.6%) who were not. Among survivors, the secondary endpoint of discharge home occurred in 26 patients (32.1%) who received haloperidol and 6,110 patients

(55.3%) who did not. In the main analysis, there were no significant associations between haloperidol use and the primary (HR, 1.09; 95% CI, 0.60 to 1.97, p=0.772) and secondary (HR, 0.88; 95% CI, 0.50 to 1.53, p=0.643) endpoints. Results were similar in multiple sensitivity analyses. Conclusion: In this observational study involving patients with Covid-19 who had been admitted to the hospital, haloperidol use was not associated with risk of intubation or death, or with time to hospital discharge home. These results suggest that haloperidol is unlikely to have a clinical efficacy for Covid-19. [**note: it looks like there is no need for a haloperidol clinical trial (I've not seen one that is registered).**]
https://www.medrxiv.org/content/10.1101/2020.07.15.20150490v1

DRUG DEVELOPMENT

- There are few effective therapeutic options for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Early evidence has suggested that IL-6R blockers may confer benefit, particularly in severe coronavirus disease 2019 (Covid-19). We leveraged large-scale human genetic data to investigate whether IL6-R blockade may confer therapeutic benefit in Covid-19. A genetic instrument consisting of seven genetic variants in or close to *IL6R* was recently shown to be linked to altered levels of c-reactive protein (CRP), fibrinogen, circulating IL-6 and soluble IL-6R, concordant to known effects of pharmacological IL-6R blockade. We investigated the effect of these *IL6R* variants on risk of hospitalization for Covid-19 and other SARS-CoV-2-related outcomes using data from The Covid-19 Host Genetics Initiative. The *IL6R* variants were strongly associated with serum CRP levels in UK Biobank. Meta-analysis of scaled estimates revealed a lower risk of rheumatoid arthritis (OR 0.93 per 0.1 SD lower CRP, 95% CI, 0.90-0.96, $P = 9.5 \times 10^{-7}$), recapitulating this established indication for IL-6R blockers (e.g. tocilizumab and sarilumab). The IL-6R instrument was associated with lower risk of hospitalization for Covid-19 (OR 0.88 per 0.1 SD lower CRP, 95% CI, 0.78-0.99, P = 0.03). We found a consistent association when using a population-based control group (i.e. all non-cases; OR 0.91 per 0.1 SD lower CRP, 95% CI, 0.87-0.96, $P = 4.9 \times 10^{-4}$). Evaluation of further SARS-CoV-2-related outcomes suggested association with risk of SARS-CoV-2 infection, with no evidence of association with Covid-19 complicated by death or requiring respiratory support. We performed several sensitivity analyses to evaluate the robustness of our findings. Our results serve as genetic evidence for the potential efficacy of IL-6R blockade in Covid-19. Ongoing large-scale RCTs of IL-6R blockers will be instrumental in identifying the settings, including stage of disease, in which these agents may be effective. [**note: this is from an Oxford group who look to identify some of the genetics that can be linked to patients that can benefit from IL-6 blockers such as tocilizumab.]** https://www.medrxiv.org/content/10.1101/2020.07.17.20155242v1
- There are currently no specific vaccine or drugs proven to be effective against COVID-19. Traditional Chinese herbal medicine has been integrated into the official therapeutic protocol against COVID-19 in China. Qing Fei Pai Du Tang (QFPDT) is a Chinese multi-herbal formula newly developed and specifically optimized for the treatment of COVID-19. Therapeutic administration of QFPDT resulted in an improved cure rate in mild to critically-ill patients. However, the immunological mechanism for the efficacy of QFPDT has been poorly understood. Furthermore, the feasibility of prophylactic use in uninfected individuals remain unconfirmed. We thus examined whether the administration of QFPDT at a dose lower than recommended for therapeutic use alters hematological and/or immunological measures in healthy individuals. We

found that QFPDT elevates the plasma levels of IL-1β, IL-18, TNF-α, and IL-8, which are key mediators of acute inflammatory responses to ssRNA viruses. No apparent adverse effects were observed during the trial. Our finding suggests that the pharmacological action of QFPDT is associated with the upregulation of a subset of proinflammatory cytokines despite its clinical benefits for COVID-19 patients. We should therefore be careful in its prophylactic use in uninfected individuals until we have a better understanding of the immunopharmacological action of QFPDT through further clinical studies with larger cohorts. [**note: here is a cautionary note about using a traditional Chinese medicine. Too often these remedies are inadequately studied for safety and efficacy.**]
https://www.medrxiv.org/content/10.1101/2020.07.13.20146175v1

- An effective vaccine is needed to halt the spread of the SARS-CoV-2 pandemic. Recently, we reported safety, tolerability and antibody response data from an ongoing placebo-controlled, observer-blinded phase 1/2 COVID-19 vaccine trial with BNT162b1, a lipid nanoparticle (LNP) formulated nucleoside-modified messenger RNA encoding the receptor binding domain (RBD) of the SARS-CoV-2 spike protein. Here we present antibody and T cell responses after BNT162b1 vaccination from a second, non-randomized open-label phase 1/2 trial in healthy adults, 18-55 years of age. Two doses of 1 to 50 µg of BNT162b1 elicited robust CD4+ and CD8+ T cell responses and strong antibody responses, with RBD-binding IgG concentrations clearly above those in a COVID-19 convalescent human serum panel (HCS). Day 43 SARS-CoV-2 serum neutralising geometric mean titers were 0.7-fold (1 µg) to 3.5-fold (50 µg) those of HCS. Immune sera broadly neutralised pseudoviruses with diverse SARS-CoV-2 spike variants. Most participants had $T_H1$ skewed T cell immune responses with RBD-specific CD8+ and CD4+ T cell expansion. Interferon (IFN)γ was produced by a high fraction of RBD-specific CD8+ and CD4+ T cells. The robust RBD-specific antibody, T-cell and favourable cytokine responses induced by the BNT162b1 mRNA vaccine suggest multiple beneficial mechanisms with potential to protect against COVID-19. [**note: this is important data from the BioNTech/Pfizer vaccine group! It looks like this will be a solid candidate vaccine.**]
https://www.medrxiv.org/content/10.1101/2020.07.17.20140533v1
- Background: New means of treating COVID-19 are urgently needed. Genetic validation of drugs can foreshadow trial results, and help prioritize investigations. We assessed whether common drugs, suggested as possible treatments for COVID-19 (tocilizumab, anakinra and statins) with established genetic proxies, are effective in COVID-19. We also included dexamethasone as a positive control exposure because the RECOVERY trial suggested benefit in severe COVID-19. Methods: We assessed, using Mendelian randomization, whether genetic proxies of tocilizumab, anakinra, statins and dexamethasone use affected risk of very severe (cases=536, non-cases=329391) or hospitalized (cases=3199, non-cases=897488) COVID-19 using a recent genome-wide association study. Results: Using rs2228145 (IL6R) to proxy effects of tocilizumab use, no association with very severe COVID-19 was found, but possibly an inverse association with hospitalized COVID-19 (odds ratio (OR) 0.83 per standardized effect of higher soluble interleukin-6r, 95% confidence interval 0.67 to 1.02). Using rs12916 (HMGCR) to proxy effects of statins use, an inverse association with very severe COVID-19 was found (OR 0.30 per standardized effect, 95% CI 0.10 to 0.89). Using rs6743376 and rs1542176 to proxy effects of anakinra use, no associations with COVID-19 were found. Dexamethasone, instrumented by cortisol, was possibly inversely associated with very severe COVID-19 (OR 0.20 per standardized

effect 95% CI 0.04 to 1.04). Conclusion: Our study provides some genetic validation for the use of both tocilizumab and statins in COVID-19, but not anakinra, whilst being consistent with the findings from the RECOVERY trial about dexamethasone. Investigation of the underlying mechanisms might facilitate re-purposing and development of effective treatments. [**note: this is an interesting paper about whether there are genetic proxies that might demonstrate whether certain drugs should be used to treat COVID-19. The statin finding is a bit strange as it is not clear what the mechanism for this class of drugs is. There are one or two trials going on.**] https://www.medrxiv.org/content/10.1101/2020.07.09.20149450v1

- Pro-inflammatory immune responses are necessary for effective pathogen clearance, but cause severe tissue damage if not shut down in a timely manner. Excessive complement and IFN-γ-associated responses are known drivers of immunopathogenesis and are among the most highly induced immune programs in hyper-inflammatory SARS-CoV2 lung infection. The molecular mechanisms that govern orderly shutdown and retraction of these responses remain poorly understood. Here, we show that complement triggers contraction of IFN-γ producing CD4+ T helper (Th) 1 cell responses by inducing expression of the vitamin D (VitD) receptor (VDR) and CYP27B1, the enzyme that activates VitD, permitting T cells to both activate and respond to VitD. VitD then initiates the transition from pro-inflammatory IFN-γ+ Th1 cells to suppressive IL-10+ Th1 cells. This process is primed by dynamic changes in the epigenetic landscape of CD4+ T cells, generating super-enhancers and recruiting c-JUN and BACH2, a key immunoregulatory transcription factor. Accordingly, cells in psoriatic skin treated with VitD increased BACH2 expression, and BACH2 haplo-insufficient CD4+ T cells were defective in IL-10 production. As proof-of-concept, we show that CD4+ T cells in the bronchoalveolar lavage fluid (BALF) of patients with COVID-19 are Th1-skewed and that VDR is among the top regulators of genes induced by SARS-CoV2. Importantly, genes normally down-regulated by VitD were de-repressed in CD4+ BALF T cells of COVID-19, indicating that the VitD-driven shutdown program is impaired in this setting. The active metabolite of VitD, alfacalcidol, and cortico-steroids were among the top predicted pharmaceuticals that could normalize SARS-CoV2 induced genes. These data indicate that adjunct therapy with VitD in the context of other immunomodulatory drugs may be a beneficial strategy to dampen hyper-inflammation in severe COVID-19. [**note: this comes from a large group of researchers, including many from NIH, and is the first proof of concept for the role of Vitamin D. There are some clinical trials registered to look at this. Whether ongoing Vitamin D supplementation in non-SARS-CoV-2 individuals is useful remains to be determined]** https://www.biorxiv.org/content/10.1101/2020.07.18.210161v1
- Vaccine and antiviral development against SARS-CoV-2 infection or COVID-19 disease currently lacks a validated small animal model. Here, we show that transgenic mice expressing human angiotensin converting enzyme 2 (hACE2) by the human cytokeratin 18 promoter (K18 hACE2) represent a susceptible rodent model. K18 hACE2-transgenic mice succumbed to SARS-CoV-2 infection by day 6, with virus detected in lung airway epithelium and brain. K18 ACE2-transgenic mice produced a modest TH1/2/17 cytokine storm in the lung and spleen that peaked by day 2, and an extended chemokine storm that was detected in both lungs and brain. This chemokine storm was also detected in the brain at day 4. K18 hACE2-transgenic mice are, therefore, highly susceptible to SARS-CoV-2 infection and represent a suitable animal model for the study of viral pathogenesis, and for identification and characterization of vaccines (prophylactic) and antivirals (therapeutics) for SARS-CoV-2 infection and associated severe COVID-19 disease. [**note:**

**another transgenic mouse model for studying SARS-CoV-2.**]
https://www.biorxiv.org/content/10.1101/2020.07.18.210179v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Characterizing the humoral immune response to SARS-CoV-2 and developing accurate serologic assays are needed for diagnostic purposes and estimating population-level seroprevalence. METHODS We measured the kinetics of early antibody responses to the receptor-binding domain (RBD) of the spike (S) protein of SARS-CoV-2 in a cohort of 259 symptomatic North American patients infected with SARS-CoV-2 (up to 75 days after symptom onset) compared to antibody levels in 1548 individuals whose blood samples were obtained prior to the pandemic. RESULTS Between 14-28 days from onset of symptoms, IgG, IgA, or IgM antibody responses to RBD were all accurate in identifying recently infected individuals, with 100% specificity and a sensitivity of 97%, 91%, and 81% respectively. Although the estimated median time to becoming seropositive was similar across isotypes, IgA and IgM antibodies against RBD were short-lived with most individuals estimated to become seronegative again by 51 and 47 days after symptom onset, respectively. IgG antibodies against RBD lasted longer and persisted through 75 days post-symptoms. IgG antibodies to SARS-CoV-2 RBD were highly correlated with neutralizing antibodies targeting the S protein. No cross-reactivity of the SARS-CoV-2 RBD-targeted antibodies was observed with several known circulating coronaviruses, HKU1, OC 229 E, OC43, and NL63. CONCLUSIONS Among symptomatic SARS-CoV-2 cases, RBD-targeted antibodies can be indicative of previous and recent infection. IgG antibodies are correlated with neutralizing antibodies and are possibly a correlate of protective immunity. [**note: data on antibody persistence from a Boston group. They did not find any cross reactivity with commonly circulating coronaviruses. I hope someone is aggregating the data from all these studies as it will be informative.**] https://www.medrxiv.org/content/10.1101/2020.07.18.20155374v1

DIAGNOSTIC DEVELOPMENT

- Nothing today.

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2020-07-21

It is always a fun time when greats of the guitar get together to just play. From the Crossroads Festival of 2010 here are BB King, Eric Clapton, Robert Cray and Jimmie Vaughan playing 'The Thrill is Gone': https://www.youtube.com/watch?v=Nu4tjTyqbho I have a fond memory of seeing Clapton live with Jack Bruce and Ginger Baker when they made up The Cream back in 1969.

US COVID-19 STATISTICS - **Infection Rate: 1.2%; CFR: 3.6%** (IR up 0.1%; CFR down 0.1%)

Derek Thompson on how long COVID-19 immunity might last.

The Lancet has articles on two recombinant adenovirus COVID vaccines: phase 2 trial from China & the Oxford group. HERE is an accompanying editorial and a Washington Post story. Coupled with yesterday's preprint on the Pfizer results this is good news for the first step towards a vaccine.

The New York Times has a report on Synairgen's inhaled beta-Interferon showing quite a treatment effect. All we have is a company press release on this and it is not clear why they are reporting interim results on what was supposed to be a much larger clinical trial. Did the DSMB stop the trial? There are some strange statements about some findings not being statistically significant. I'll wait for the peer review of this one. A cautionary tale about the cost of a temporary hospital in Queens that is hardly used.

The Washington Post offers up crowdsourcing as a way to live in a pandemic. Fact checking the contretemps between President Trump and Dr. Fauci. One of the last 'Rosie the Riviters' moves on to making COVID-19 masks.

The Guardian has this story of an interesting German experiment to see how a virus can spread in a Leipzig concert venue. Concert goers need proof of a negative SARS-CoV-2 test to participate.

A BMJ piece synopsizes critiques of the Gilead remdesivir trial.

A JAMA editorial suggests that COVID-19 associated inflammatory syndromes in children should not affect decisions to reopen schools. I think this is probably correct given the very small numbers of children who experience this clinically.

STAT has a story on how chronic fatigue syndrome may hold keys to understanding post-COVID-19 syndrome. It will be interesting to see what the numbers of people are that have lingering symptoms.

MODELING

- Background: Covid-19 has been shown to be having a disproportionate impact on the health of individuals from different ethnic groups and those employed in certain occupations, whilst the indirect impacts of Covid-19, including the closure of schools and business and the move to home working, fall disproportionately on the young and on women. These factors may in turn impact upon sleep health. Research on sleep deprivation during the pandemic crisis to date has been limited. The present study aimed to explore the levels and social determinants of self-reported sleep loss among the general population during the Covid-19 pandemic in the UK, with a particular focus on ethnic and gender disparities. Methods: Newly available national representative survey data from Understanding Society COVID19 Study collected during April 2020 were analysed. These data were linked to Wave 9 of Understanding Society conducted in 2018/19, providing information about the respondents prior to the outbreak of the pandemic. Cross-sectional analysis provided prevalence estimates, whilst analysis of the linked longitudinal data provided incidence estimates. The analytical sample included 15,360 respondents aged 16 and above; among these, 12,206 reported no problem of sleep loss before the epidemic. Results: Prevalence and incidence rates of perceived sleep loss were 24.7% and 20.2% respectively. Women (at the level of 31.8% and 27.0%) and individuals from Black, Asian, and minority ethnic (BAME) communities (at the level of 32.0% and 24.6%) were more vulnerable to sleep deprivation due to the pandemic. Multivariate regression analysis shows that being female, the presence of young children in the household, perceived financial difficulties and being a Covid-19-related key worker were all predictive of sleep loss. Once these covariates were controlled for the bivariate relationship between ethnicity and sleep loss was reversed,

reflecting the complex interaction between the coronavirus epidemic and ethnicity. Conclusions: The pandemic has widened the disparity of sleep deprivation across different groups, with women with young children, key workers and people of BAME heritage all experiencing difficulty in sleeping, which in turn may negatively affect mental and physical health and well-being. [**note: not 'Sleepless in Seattle' but this study does look at sleep loss in the UK during the early stage of the lockdown.**] https://www.medrxiv.org/content/10.1101/2020.07.19.20157255v1

- As the COVID-19 pandemic has caused major societal unrest, modelers have worked to project future trends of COVID-19 and predict upcoming challenges and impacts of policy action. These models, alone or in aggregate, are influential for decision-makers at every level. Therefore, the method and documentation of COVID-19 models must be highly transparent to ensure that projections and consequential policies put forth have sound epistemological grounds. We evaluated 29 COVID-19 models receiving high attention levels within the scientific community and/or informing government responses. We evaluated these models against 27 transparency criteria. We found high levels of transparency in model documentation aspects such as reporting uncertainty analysis; however, about half of the models do not share code and a quarter do not report equations. These discrepancies underscore the need for transparency and reproducibility to be at the forefront of researchers' priorities, especially during a global health crisis when stakes are critically high. [**note: here is an evaluation of 29 COVID-19 models using transparency criteria. This is important in evaluation of models.**] https://www.medrxiv.org/content/10.1101/2020.07.18.20156851v1
- Background There are different patterns in the COVID-19 outbreak in the general population and amongst nursing home patients. Different age-groups are also impacted differently. However, it remains unclear whether the time from symptom onset to diagnosis and hospitalization or the length of stay in the hospital is different for different age groups, gender, residence place or whether it is time dependent. Methods Sciensano, the Belgian Scientific Institute of Public Health, collected information on hospitalized patients with COVID-19 hospital admissions from 114 participating hospitals in Belgium. Between March 14, 2020 and June 12, 2020, a total of 14,618 COVID-19 patients were registered. The time of symptom onset, time of COVID-19 diagnosis, time of hospitalization, time of recovery or death, and length of stay in intensive care are recorded. The distributions of these different event times for different age groups are estimated accounting for interval censoring and right truncation in the observed data. Results The truncated and interval-censored Weibull regression model is the best model for the time between symptom onset and diagnosis/hospitalization best, whereas the length of stay in hospital is best described by a truncated and interval-censored lognormal regression model. Conclusions The time between symptom onset and hospitalization and between symptom onset and diagnosis are very similar, with median length between symptom onset and hospitalization ranging between 3 and 10.4 days, depending on the age of the patient and whether or not the patient lives in a nursing home. Patients coming from a nursing home facility have a slightly prolonged time between symptom onset and hospitalization (i.e., 2 days). The longest delay time is observed in the age group 20-60 years old. The time from symptom onset to diagnosis follows the same trend, but on average is one day longer as compared to the time to hospitalization. The median length of stay in hospital varies between 3 and 10.4 days, with the length of stay increasing with age. However, a difference is observed between patients that recover and patients that die. While the hospital length of stay for patients that recover

increases with age, we observe the longest time between hospitalization and death in the age group 20-60. And, while the hospital length of stay for patients that recover is shorter for patients living in a nursing home, the time from hospitalization to death is longer for these patients. But, over the course of the first wave, the length of stay has decreased, with a decrease in median length of stay of around 2 days. [**note: this is a useful study of the Belgian experience related to symptom onset, hospitalization and outcome.**]
https://www.medrxiv.org/content/10.1101/2020.07.18.20156307v1

- Severe acute respiratory syndrome virus (SARS-CoV-2) has infected millions of people worldwide. Our goal was to identify risk factors associated with admission and disease severity in patients with SARS-CoV-2. Design: This was an observational, retrospective study based on real-world data for 7,995 patients with SARS-CoV-2 from a clinical data repository. Setting: Yale New Haven Health (YNHH) is a five-hospital academic health system serving a diverse patient population with community and teaching facilities in both urban and suburban areas. Populations: The study included adult patients who had SARS-CoV-2 testing at YNHH between March 1 and April 30, 2020. Main outcome and performance measures: Primary outcomes were admission and in-hospital mortality for patients with SARS-CoV-2 infection as determined by RT-PCR testing. We also assessed features associated with the need for respiratory support. Results: Of the 28605 patients tested for SARS-CoV-2, 7995 patients (27.9%) had an infection (median age 52.3 years) and 2154 (26.9%) of these had an associated admission (median age 66.2 years). Of admitted patients, 1633 (75.8%) had a discharge disposition at the end of the study period. Of these, 192 (11.8%) required invasive mechanical ventilation and 227 (13.5%) expired. Increased age and male sex were positively associated with admission and in-hospital mortality (median age 81.9 years), while comorbidities had a much weaker association with the risk of admission or mortality. Black race (OR 1.43, 95%CI 1.14-1.78) and Hispanic ethnicity (OR 1.81, 95%CI 1.50-2.18) were identified as risk factors for admission, but, among discharged patients, age-adjusted in-hospital mortality was not significantly different among racial and ethnic groups. Conclusions: This observational study identified, among people testing positive for SARS-CoV-2 infection, older age and male sex as the most strongly associated risks for admission and in-hospital mortality in patients with SARS-CoV-2 infection. While minority racial and ethnic groups had increased burden of disease and risk of admission, age-adjusted in-hospital mortality for discharged patients was not significantly different among racial and ethnic groups. Ongoing studies will be needed to continue to evaluate these risks, particularly in the setting of evolving treatment guidelines. [**note: another large hospital outcomes observational study, this time from the Yale New Haven system.**]
https://www.medrxiv.org/content/10.1101/2020.07.19.20157305v1
- Community-level seroprevalence surveys are needed to determine the proportion of the population with previous SARS-CoV-2 infection, a necessary component of COVID-19 disease surveillance. In May, 2020, we conducted a cross-sectional seroprevalence study of IgG antibodies for nucleocapsid of SARS-CoV-2 among the residents of Blaine County, Idaho, a ski resort community with high COVID-19 attack rates in late March and Early April (2.9% for ages 18 and older). Participants were selected from volunteers who registered via a secure web link, using prestratification weighting to the population distribution by age and gender within each ZIP Code. Participants completed a survey reporting their demographics and symptoms; 88% of volunteers who were invited to participate completed data collection survey and had 10 ml of

blood drawn. Serology was completed via the Abbott Architect SARS-CoV-2 IgG immunoassay. Primary analyses estimated seroprevalence and 95% credible intervals (CI) using a hierarchical Bayesian framework to account for diagnostic uncertainty. Stratified models were run by age, sex, ZIP Code, ethnicity, employment status, and a priori participant-reported COVID-19 status. Sensitivity analyses to estimate seroprevalence included base models with post-stratification for ethnicity, age, and sex, with or without adjustment for multi-participant households. IgG antibodies to the virus that causes COVID-19 were found among 22.7% (95% CI: 20.1%, 25.5%) of residents of Blaine County. Higher levels of antibodies were found among residents of the City of Ketchum 34.8% (95% CI 29.3%, 40.5%), compared to Hailey 16.8% (95%CI 13.7%, 20.3%) and Sun Valley 19.4% (95% 11.8%, 28.4%). People who self-identified as not believing they had COVID-19 had the lowest prevalence 4.8% (95% CI 2.3%, 8.2%). The range of seroprevalence after correction for potential selection bias was 21.9% to 24.2%. This study suggests more than 80% of SARS-CoV-2 infections were not reported. Although Blaine County had high levels of SARS-CoV-2 infection, the community is not yet near the herd immunity threshold. [**note: here is a serology study of ski resort community in Idaho. They estimate that 80% of the SARS-CoV-2 infections were not reported but that even with high levels of antibody positive patients they may not be at the herd immunity threshold.**]
https://www.medrxiv.org/content/10.1101/2020.07.19.20157198v1

NEWLY REGISTERED CLINICAL TRIALS

- Did not check

CLINICAL TRIAL RESULTS

- Coronavirus disease 2019 (COVID-19) is associated with severe pneumonia, respiratory failure and death. We aim to evaluate the efficacy of adjunctive corticosteroids in the management of COVID-19. Methods: This is a retrospective cohort study of hospitalized adults (≥18 years) who were diagnosed with COVID-19 and were given treatment. Treatment included hydroxycholoroquine and lopinavir-ritonavir. Corticosteroids were included as adjunctive therapy in mid-April, 2020. We compared composite outcomes of clinical progression and invasive mechanical ventilation (MV) or death between group that received treatment only (Group A) versus group that received adjunctive corticosteroids (Group B). Entropy balancing was used to generate stabilized weight for covariates between treatment groups. Unweighted Kaplan-Meir curves, weighted and adjusted Cox regression analysis were used to estimate effect of adjunctive corticosteroids on composite outcomes. Subgroup analysis was performed on those with pneumonia. Results: Of 1046 patients with COVID-19, 57 received treatment alone (Group A) and 35 received adjunctive corticosteroids in addition to treatment (Group B). Median day of illness at treatment initiation was 5 day. There were 44 patients with pneumonia; 68.9% of them were not requiring supplemental oxygen at treatment initiation. Overall, 17 (18.5%) of 92 patients had clinical progression including 13 (22.8%) of 57 patients in Group A versus 4 (11.4%) of 35 patients in Group B (p=0.172). Unweighted Kaplan-Meier estimates showed no significant difference in the proportion of patients who had clinical progression or invasive MV or death between the 2 treatment groups. However in those with pneumonia, there were lower proportions of patients in Group B with clinical progression (11.1% , 95% CI 0.0 - 22.2 versus 58.8%, 95% CI 27.3 - 76.7, log rank p<0.001 ); and invasive MV or death (11.3%, 95% CI 0.0 - 22.5

versus 41.2%, 95% CI 12.4. - 60.5, log rank p=0.016). In weighted and adjusted cox regression analysis, patients in Group B were less likely to have clinical progression, (adjusted HR [aHR] 0.08, 95% CI 0.01-0.99, p=0.049) but there was no statistical significant difference in risk of requiring invasive MV or death (aHR 0.22, 95%CI 0.02 - 2.54, p=0.22). In subgroup with pneumonia, patients in Group B were significantly at lower risk of clinical progression (aHR 0.15, 95% CI 0.06 - 0.39, p<0.001) and requiring invasive MV compared to Group A (aHR 0.30, 0.10-0.87, p=0.029). Conclusions: Use of adjunctive corticosteroids is associated with lower risk of clinical progression and invasive MV or death, especially in those with pneumonia. Concurrent use of antivirals and corticosteroids should be considered in the management of COVID-19 related pneumonia. [**note: this is a Singapore study of adjunct corticosteroids. It was done when HCQ and lopinavir/ritonavir were still being clinically used. Patients given corticosteroids had better clinical outcomes.**]
https://www.medrxiv.org/content/10.1101/2020.07.18.20157008v1

DRUG DEVELOPMENT

- Therapeutics targeting replication of SARS coronavirus 2 (SARS-CoV-2) are urgently needed. Coronaviruses rely on host membranes for entry, establishment of replication centers and egress. Compounds targeting cellular membrane biology and lipid biosynthetic pathways have previously shown promise as antivirals and are actively being pursued as treatments for other conditions. Here, we tested small molecule inhibitors that target membrane dynamics or lipid metabolism. Included were inhibitors of the PI3 kinase VPS34, which functions in autophagy, endocytosis and other processes; Orlistat, an inhibitor of lipases and fatty acid synthetase, is approved by the FDA as a treatment for obesity; and Triacsin C which inhibits long chain fatty acyl-CoA synthetases. VPS34 inhibitors, Orlistat and Triacsin C inhibited virus growth in Vero E6 cells and in the human airway epithelial cell line Calu-3, acting at a post-entry step in the virus replication cycle. Of these the VPS34 inhibitors exhibit the most potent activity. [**note: a couple of more compounds that have *in vitro* inhibitory activity. I doubt these will reach the clinical trial stage.**] https://www.biorxiv.org/content/10.1101/2020.07.18.210211v1
- The search for successful therapies of infections with the coronavirus SARS-CoV-2 is ongoing. We tested inhibition of host cell nucleotide synthesis as a promising strategy to decrease the replication of SARS-CoV-2-RNA, thus diminishing the formation of virus progeny. Methotrexate (MTX) is an established drug for cancer therapy and to induce immunosuppression. The drug inhibits dihydrofolate reductase and other enzymes required for the synthesis of nucleotides. Strikingly, the replication of SARS-CoV-2 was inhibited by MTX in therapeutic concentrations around 1 microM, leading to more than 1000-fold reductions in virus progeny in Vero C1008 (Vero E6) as well as Calu-3 cells. Virus replication was more sensitive to equivalent concentrations of MTX than of the established antiviral agent remdesivir. MTX strongly diminished the synthesis of viral structural proteins and the amount of released virus RNA. Virus replication and protein synthesis were rescued by folinic acid (leucovorin) and also by inosine, indicating that purine depletion is the principal mechanism that allows MTX to reduce virus RNA synthesis. The combination of MTX with remdesivir led to synergistic impairment of virus replication, even at 300 nM MTX. The use of MTX in treating SARS-CoV-2 infections still awaits further evaluation regarding toxicity and efficacy in infected organisms, rather than cultured cells. Within the frame of these caveats, however, our results raise the perspective of a two-fold

benefit from re-purposing MTX for treating COVID-19. Firstly, its previously known ability to reduce aberrant inflammatory responses might dampen respiratory distress. In addition, its direct antiviral activity described here would limit the dissemination of the virus. [n**ote methotrexate has been around for a long time. There are two registered trials, one in Brazil and one in Egypt looking at the use of this. Mechanistically the approach makes some sense.]** https://www.biorxiv.org/content/10.1101/2020.07.18.210013v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Knowledge of the host immune response after natural SARS-CoV-2 infection is essential for informing directions of vaccination and epidemiological control strategies against COVID-19. In this study, thirty-four COVID-19 patients were enrolled with 244 serial blood specimens (38.1% after hospital discharge) collected to explore the chronological evolution of neutralizing (NAb), total (TAb), IgM, IgG and IgA antibody in parallel. IgG titers reached a peak later (approximately 35 days postonset) than those of Nab, Ab, IgM and IgA (20~25 days postonset). After peaking, IgM levels declined with an estimated average half-life of 10.36 days, which was more rapid than those of IgA (51.25 days) and IgG (177.39 days). Based on these half-life data, we estimate that the median times for IgM, IgA and IgG to become seronegative are 4.59 (IQR 4.12-5.03), 7.78 (IQR 6.71-9.16) and 42.72 (IQR 33.75-47.96) months post disease onset. The relative contribution of IgM to NAb was higher than that of IgG (standardized β regression coefficient: 0.53 vs 0.48), so the rapid decline in NAb may be attributed to the rapid decay of IgM in acute phase. However, the relative contribution of IgG to NAb increased and that of IgM further decreased after 6 weeks postonset. It's assumed that the decline rate of NAb might slow down to the same level as that of IgG over time. This study suggests that SARS-CoV-2 infection induces robust neutralizing and binding antibody responses in patients and that humoral immunity against SARS-CoV-2 acquired by infection may persist for a relatively long time. [**note: more data on antibody level evolution in COVID-19 patients, this time from China. Humoral immunity may persist for a relatively long time which is a good thing.**] https://www.medrxiv.org/content/10.1101/2020.07.18.20156810v1
- Background: To investigate the significance of IgM and IgG in the progress of COVID-19. Method: A multicenter cross-sectional study conducted in suspected and confirmed patients from four hospitals of China and a cohort study to identify the change pattern and significance in the process of COVID-19 disease. Results: A total of 571 patients were enrolled in the cross-sectional study, including 235 confirmed SARS-CoV-2 infection with 91.9% patients IgG positive and 92.3% IgM positive. 30 patients diagnosed with SARS-CoV-2 infection were enrolled in the cohort study for flowing-up in 20 days. The peak of IgM and IgG reached in 10th and 20 th day separately after symptom onset. The relationship between clinical classification and serological antibodies were analysed. The positive rate of COVID-19 IgG and IgM increased along with the clinical classification and the delay of treatment time. Conclusion: We demonstrated the kinetics of IgM and IgG SARS-CoV-2 antibody in COVID-19 patients, which may contribute to explain the results of IgM and IgG SARS-CoV-2 antibody test and predict the prognosis of COVID-19. [**note: more antibody progression data from China.**] https://www.medrxiv.org/content/10.1101/2020.07.20.20157446v1

DIAGNOSTIC DEVELOPMENT

- We describe the optimization of a simplified sample preparation method which permits rapid and direct detection of SARS-CoV-2 RNA within saliva using reverse-transcription loop-mediated isothermal amplification (RT-LAMP). Treatment of saliva samples prior to RT-LAMP by dilution 1:1 in MucolyseTM, followed by dilution (within the range of 1 in 5 to 1 in 40) in 10% (w/v) Chelex 100 Resin and a 98oC heat step for 2 minutes enabled detection of SARS-CoV-2 RNA in all positive saliva samples tested, with no amplification detected in pooled negative saliva. The time to positivity for which SARS-CoV-2 RNA was detected in these positive saliva samples was proportional to the real-time reverse-transcriptase PCR cycle threshold (CT), with SARS-CoV-2 RNA detected in as little as 05:43 (CT 21.08), 07:59 (CT 24.47) and 08:35 (CT 25.27) minutes, respectively. The highest CT where direct RT-LAMP detected SARS-CoV-2 RNA was 31.39 corresponding to a 1 in 40 dilution of a positive saliva sample (1:1 in MucolyseTM) with a starting CT of 25.27. When RT-LAMP was performed on pools of SARS-CoV-2 negative saliva samples spiked with whole inactivated SARS-CoV-2 virus, RNA was detected at dilutions spanning 1 in 5 to 1 in 160 representing CTs spanning 22.49-26.43. Here we describe a simple but critical rapid sample preparation method which can be used up front of RT-LAMP to permit direct detection of SARS-CoV-2 within saliva samples. Saliva is a sample which can be collected non-invasively without the use of highly skilled staff and critically can be obtained from both healthcare and home settings. Critically, this approach overcomes both the requirement and validation of different swabs and the global bottleneck in obtaining RNA extraction robots and reagents to enable molecular testing by PCR. Such testing opens the possibility of public health approaches for effective intervention to control the COVID-19 pandemic through regular SARS-CoV-2 testing at a population scale, combined with isolation and contact tracing for positive cases. [**note: from the UK, further refinement of saliva collection for SARS-CoV-2 testing.**] https://www.medrxiv.org/content/10.1101/2020.07.16.20155168v1

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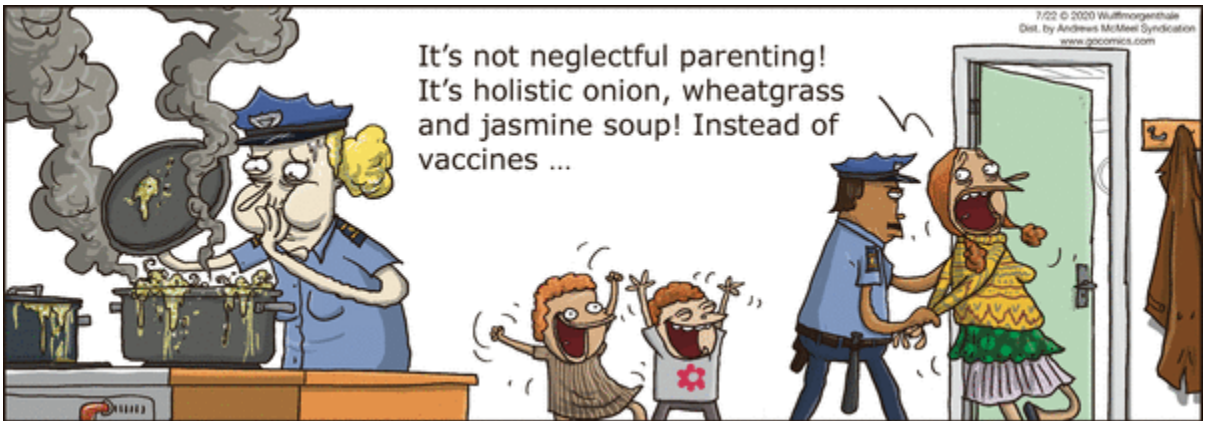
2020-07-22

Let us spend the rest of this week with some nice pandemic inspired videos. We begin with a great version of 'The Longest Time' the Billy Joel song but with COVID-19 associated lyrics. The singers come from a bunch of different choral organizations in Canada and the US: https://www.youtube.com/watch?v=LpAKcQufacc the greatest part of this is the guy getting his haircut by his lockdown partner. Speaking of which, *I need to get Ms. Goldhammer to trim my locks*.

US COVID-19 STATISTICS - **Infection Rate: 1.2%; CFR: 3.6%** (IR no change; CFR no change)

WUMO is back!!!




Oh dear, states don't seem to be reporting important COVID-19 statistics according to The Washington Post. Here is a link to the report from the organization Resolve to Save Lives. There is also a good story on the JAMA CDC study that is detailed below. Here is how Uruguay has avoided the worst of COVID-19. The time for quarantine if COVID-19 is suspected drops down to 10 days based on current knowledge.

The New York Times has an op-ed by Tom Frieden and Cyrus Shahpar on a plan to gather data even without the federal governments help. I hope this is not a Quixotic quest.

Sewage testing shows that Yosemite visitors may have had coronavirus according to The Guardian. I knew this approach would work!!! 😆

JAMA have a large serology study of 10 sites in the United States between March 23 and May 12. In this cross-sectional study of 16 025 residual clinical specimens, estimates of the proportion of persons with detectable SARS-CoV-2 antibodies ranged from 1.0% in the San Francisco Bay area (collected April 23-27) to 6.9% of persons in New York City (collected March 23-April 1). Six to 24 times more infections were estimated per site with seroprevalence than with coronavirus disease 2019 (COVID-19) case report data. An accompanying editorial is well worth reading!!!!

There is an editorial in The New England Journal of Medicine on the UK RECOVERY platform for conducting COVID-19 trials. I have a bit of skepticism about this one. The US has been lagging in terms of getting something similar set up and of course spent a lot of money and effort on a large HCQ preventative trial in health care workers. It's only within the last several weeks that NIH announced a similar effort to the RECOVERY approach. Is this too little and too late? I'm not sure but I don't see much effort to consolidate things in terms of looking at registered trials.

The Lancet have some correspondence discussion about the use of the IL-1 blocker, anakinra, in treating Cytokine storm. I have linked to the primary authors of the original article that has all the relevant links. This is an interesting issue as a lot of the 'published' work to date focuses on the IL-6 blocker, tocilizumab. There may be a role for both treatments as the cytokine storm issue is unraveled.

Medscape has a summary of a commentary on the French HCQ study that sparked all the interest in that drug. That study has major shortcomings and is fully irresponsible. Glad to see scientists stepping up to the plate!

STAT has a summary of yesterday's Congressional hearing about COVID-19 vaccines. Representatives from the five major companies working in this area testified.

Derek Lowe is very prolific today. Here is a commentary on the Pfizer vaccine, Oxford vaccine, and CanSino vaccine. I'm with Derek that the Pfizer/BioNTech vaccine has the leading position right now.

MODELING

- SARS-CoV-2 originated in animals and is now easily transmitted between people. Sporadic detection of natural cases in animals alongside successful experimental infections of pets, such as cats, ferrets and dogs, raises questions about the susceptibility of animals under natural conditions of pet ownership. Here we report a large-scale study to assess SARS-CoV-2 infection in over 500 companion animals living in northern Italy, sampled at a time of frequent human infection. No animals tested PCR positive. However, 3.4% of dogs and 3.9% of cats had measurable SARS-CoV-2 neutralizing antibody titers, with dogs from COVID-19 positive households being significantly more likely to test positive than those from COVID-19 negative households. Understanding risk factors associated with this and their potential to infect other species requires urgent investigation. [**note: owners of dogs and cats will be interested in this Italian study.**] https://www.biorxiv.org/content/10.1101/2020.07.21.214346v1

NEWLY REGISTERED CLINICAL TRIALS

- Did not check.

CLINICAL TRIAL RESULTS

- Background: Superinfections, including invasive pulmonary aspergillosis (IPA), are well-known complications of critically ill patients with severe viral pneumonia. Aim of this study was to evaluate the incidence, risk factors and outcome of IPA in critically ill patients with severe COVID-19 pneumonia. Methods: We prospectively screened 32 critically ill patients with severe COVID-19 pneumonia for a time period of 28 days using a standardized study protocol for oberservation of developement of COVID-19 associated invasive pulmonary aspergillosis (CAPA). We collected laboratory, microbiological, virological and clinical parameters at defined timepoints in combination with galactomannan-antigen-detection from bronchial aspirates. We used logistic regression analyses to assess if COVID-19 was independently associated with IPA and compared it with matched controls. Findings: CAPA was diagnosed at a median of 4 days after ICU admission in 11/32 (34%) of critically ill patients with severe COVID-19 pneumonia as compared to 8% in the control cohort. In the COVID-19 cohort, mean age, APACHE II score and ICU mortality were higher in patients with CAPA than in patients without CAPA (36% versus 9.5%; $p<0.001$). ICU stay (21 versus 17 days; $p=0.340$) and days of mechanical ventilation (20 versus 15 days; $p=0.570$) were not different between both groups. In regression analysis COVID-19 and APACHE II score were independently associated with IPA. Interpretation: CAPA is highly prevalent and associated with a high mortality rate. COVID-19 is independently associated with invasive pulmonary aspergillosis. A standardized screening and diagnostic approach as presented in our study can help to identify affected patients at an early stage. [**note: this is from a single German hospital and points out clearly the need to be on the alert for secondary infections that might accompany COVID-19 pneumonia.**]
https://www.medrxiv.org/content/10.1101/2020.07.21.20158972v1

- The challenge of treating severely ill COVID-19 patients is particularly great due to the need to simultaneously manage oxygenation and the inflammatory state without compromising viral clearance. Currently, there are many tools to aid in oxygen management and in monitoring viral replication. However, predictive biomarkers for monitoring the host immune response across COVID-19 disease stages and specifically, for titrating immunomodulatory therapy are lacking. We utilized a recently cleared platform (MeMed Key) that enables rapid and easy serial measurement of IP-10, a host protein implicated in lung injury due to viral-induced hyperinflammation. A dynamic clinical decision support protocol was employed for managing SARS-CoV-2 positive patients admitted to a COVID-19 dedicated medical center run by Clalit Health Services. This is the first protocol to include real-time measurements of IP-10 as a potential aid for regulating inflammation. Overall, 502 serial real-time IP-10 measurements were performed on 52 patients recruited between 7th April 2020 to 10th May 2020, with 12 patients admitted to the intensive care unit (ICU). IP-10 levels correlated with increased COVID-19 severity score and ICU admission. Within the ICU admitted patients, the number of days with IP-10 measurements >1,000 pg/ml was associated with mortality. Upon administration of corticosteroid immunomodulatory therapy, a significant decrease in IP-10 levels was observed. Real-time IP-10 monitoring represents a new tool to aid in management and therapeutic decisions relating to the inflammatory status of COVID-19 patients. [**note: here is some good work on Israel on a new diagnostic approach to severe COVID-19. There was a decrease in the marker upon corticosteroid therapy.**]
  https://www.medrxiv.org/content/10.1101/2020.07.21.20158782v1

DRUG DEVELOPMENT

- Hyperinflammation mediated by dysregulated monocyte/macrophage function is considered to be the key factor that triggers severe illness in COVID-19. However, no specific targeting molecule has been identified for detecting or treating hyperinflammation related to dysregulated macrophages in severe COVID-19. Herein, we suggest candidate targets for imaging and therapy in severe COVID-19 by analyzing single-cell RNA-sequencing data based on bronchoalveolar lavage fluid of COVID-19 patients. We found that expression of SLC2A3, which can be imaged by [18F]fluorodeoxyglucose, was higher in macrophages from severe COVID-19 patients. Furthermore, by integrating the surface target database and drug-target binding database with RNA-sequencing data of severe COVID-19, we identified CCR1 and FPR1 as surface and druggable targets for drug delivery as well as molecular imaging. Our results provide a resource for candidate targets in the development of specific imaging and therapy for COVID-19-related hyperinflammation. [**note: this is an interesting study but I am not convinced that this is a viable drug target. IL-6 blockers work at an early point to control the immune system.**] https://www.biorxiv.org/content/10.1101/2020.07.20.213082v1
- We investigated the immune events following SARS-COV-2 infection, from the acute inflammatory state up to four weeks post infection, in non-human primates (NHP) with heterogeneous pulmonary pathology. The acute phase was characterized by a rapid migration of CD16+ monocytes from the blood and concomitant increase in CD16+ macrophages in the lungs. We identified two subsets of interstitial macrophages (DR+ CD206-), a transitional CD11c+ CD16+ population that was directly associated with IL-6 levels in plasma, and one long lasting CD11b+ CD16+ population. Strikingly, monocytes were a correlate of viral replication in

bronchial brushes and levels of TARC (CCL17), and worse disease outcomes were associated with high levels of cell infiltration in lungs and CD11b+ CD16+ macrophages accumulation. Importantly, this accumulation was long-lasting and detectable even in animals with mild or no signs of disease. Interestingly, animals with less signs of disease had a high IL-10:IL-6 ratio. Our results unravel cellular mechanisms of COVID-19 and validate NHP as models to test immune therapies. [**note: some more good information on the usefulness of non-human primates for studying SARS-CoV-2.**] https://www.biorxiv.org/content/10.1101/2020.07.21.213777v1

- SARS-CoV-2 is a novel virus that has rapidly spread, causing a global pandemic. In the majority of infected patients, SARS-CoV-2 leads to mild disease; however, in a significant proportion of infections, individuals develop severe symptoms that can lead to permanent lung damage or death. These severe cases are often associated with high levels of pro-inflammatory cytokines and low antiviral responses which can lead to systemic complications. We have evaluated transcriptional and cytokine secretion profiles from infected cell cultures and detected a distinct upregulation of inflammatory cytokines that parallels samples taken from infected patients. Building on these observations, we found a specific activation of NF-κB and a block of IRF3 nuclear translocation in SARS-CoV-2 infected cells. This NF-κB response is mediated by cGAS-STING activation and could be attenuated through STING targeting drugs. Our results show that SARS-CoV-2 curates a cGAS-STING mediated NF-κB driven inflammatory immune response in epithelial cells that likely contributes to inflammatory responses seen in patients and might be a target to suppress severe disease symptoms. [**note: this paper has a very good introduction on how SARS-CoV-2 interacts with the immune system and is worth reading for just that part. It further deciphers how the immune system may be altered by viral infection. cGAS-STING was a new term for me but Wikipedia had the answer!**]
  https://www.biorxiv.org/content/10.1101/2020.07.21.212639v1
- The entry of the coronavirus SARS-CoV-2 into human cells can be inhibited by the approved drugs camostat and nafamostat. Here we elucidate the molecular mechanism of these drugs by combining experiments and simulations. In vitro assays confirm the hypothesis that both drugs act by inhibiting the human protein TMPRSS2. As no experimental structure is available, we provide a model of the TMPRSS2 equilibrium structure and its fluctuations by relaxing an initial homology structure with extensive 280 microseconds of all-atom molecular dynamics (MD) and Markov modeling. We describe the binding mode of both drugs with TMPRSS2 in a Michaelis complex (MC) state preceding the formation of a long-lived covalent inhibitory state. We find that nafamostat to has a higher MC population, which in turn leads to the more frequent formation of the covalent complex and thus higher inhibition efficacy, as confirmed in vitro and consistent with previous virus cell entry assays. Our TMPRSS2-drug structures are made public to guide the design of more potent and specific inhibitors. [**note: I post this only to note that there are trials of both of these drugs. There was some early excitement about camostat but I've not seen any clinical reports.**]
  https://www.biorxiv.org/content/10.1101/2020.07.21.214098v1
- We developed a potent vaccination strategy, based on lentiviral vector (LV), capable of inducing neutralizing antibodies specific to the Spike glycoprotein (S) of SARS-CoV-2, the etiologic agent of CoronaVirus Disease 2019 (COVID-19). Among several LV encoding distinct variants of S, a single one encoding the full-length, membrane anchored S (LV::SFL) triggered high antibody titers in mice, with neutralization activities comparable to patients recovered from COVID-19.

LV::SFL systemic vaccination in mice, in which the expression of the CoV2 receptor hACE2 was induced by transduction of the respiratory tract cells by an adenoviral type 5 (Ad5) vector, despite an intense serum neutralizing activity, only 1 log10 reduction of lung viral loads was observed after SARS-CoV2 challenge. We thus explored the strategy of targeting the immune response to the upper respiratory tract through an intranasal boost administration. Even though, after a prime and target regimen, the systemic neutralizing activity did not increase substantially, up to 5 log10 decrease in lung viral loads was achieved, with the loads in some animals under the limit of detection of a highly sensitive RT-PCR assay. The conferred protection also avoided largely pulmonary inflammation. We confirmed the vaccine efficacy and inhibition of lung inflammation using both integrative and non-integrative LV platforms in golden hamsters, naturally permissive to SARS-CoV2 replication and restituting human COVID-19 physiopathology. Our results provide the proof-of-principle evidence of marked prophylactic effects of an LV-based vaccination strategy against SARS-CoV-2 in two pre-clinical animal models and designate the intranasal LV::SFL-based immunization as a vigorous and promising vaccine approach against COVID-19. [**note: and here we have another vaccine, this one a nasal delivered lentiviral vector based one. It is from a French company, TheraVectys, in collaboration with the Pasteur Institute.**]
https://www.biorxiv.org/content/10.1101/2020.07.21.214049v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- The SARS-CoV-2 infected cases and the caused mortalities have been surging since the COVID-19 pandemic. Viral mutations emerge during the virus circulating in the population, which is shaping the viral infectivity and pathogenicity. Here we extensively analyzed 6698 SARS-CoV-2 whole genome sequences with specific sample collection dates in NCBI database. We found that four mutations, i.e., 5'UTR_c-241-t, NSP3_c-3037-t, NSP12_c-14408-t, and S_a-23403-g, became the dominant variants and each of them represented nearly 100% of all virus sequences since the middle May, 2020. Notably, we found that co-occurrence rates of three significant multi-site co-mutational patterns, i.e., (i) S_a-23403-g, NSP12_c-14408-t, 5'UTR_c-241-t, NSP3_c-3037-t, and ORF3a_c-25563-t; (ii) ORF8_t-28144-c, NSP4_c-8782-t, NSP14_c-18060-t, NSP13_a-17858-g, and NSP13_c-17747-t; and (iii) N_g-28881-a, N_g-28882-a, and N_g-28883-c, reached 66%, 90%, and nearly 100% of recent sequences, respectively. Moreover, we found significant decrease of CpG dinucleotide at positions 241(c)-242(g) in the 5'UTR during the evolution, which was verified as a potential target of human zinc finger antiviral protein (ZAP). The four dominant mutations, three significant multi-site co-mutations, and the potential escape mutation of ZAP-target in 5'UTR region contribute to the rapid evolution of SARS-CoV-2 virus in the population, thus shaping the viral infectivity and pathogenicity. This study provides valuable clues and frameworks to dissect the viral replication and virus-host interactions for designing effective therapeutics. [**note: more on viral mutations and how they may impact infectivity and potential therapeutic design.**] https://www.biorxiv.org/content/10.1101/2020.07.21.213405v1
- To understand humoral dynamics following SARS-CoV-2 infection Design Prospective Cohort Study Setting Great Ormond Street Hospital (Central London Paediatric Hospital) Participants 67 healthcare workers aged >18 years who provided monthly serial serological samples from 29th April 2020 until 30th June 2020. Main outcome measures The change in monthly serial antibody titers to SARS-CoV-2 nucleoprotein (N), spike protein and the receptor binding domain of the

spike protein. Results The mean estimated half-life of the nucleoprotein antibody was 52 days (95% CI 42-65). The spike and RBD antibody had significantly longer mean half-lives of 81 days (95% CI 61-111) and 83 days (95% CI 55-137) respectively. An ACE-2 receptor competition assay demonstrated significant correlation between the spike and RBD antibody titers and ACE2 receptor blocking in-vitro. The time to a negative nucleoprotein antibody test for 50% of the seropositive population was predicted to be 195 days (95% CI 163-236). Conclusions After SARS-CoV-2 infection, the predicted half-life of nucleoprotein antibody was 52 days with 50% of seropositives becoming seronegative to this antibody at 195 days. Widely used serological tests including the Public Health England endorsed assay that depend on the nucleoprotein antibody will therefore underestimate the true prevalence of infection within a year following the majority of infections. [**note: more data on antibody dynamics post-infection. Antibodies against the nucleoprotein disappear quicker than the one against the Spike protein.**]
https://www.medrxiv.org/content/10.1101/2020.07.16.20155663v1

- The high susceptibility of humans to SARS-CoV-2 infection, the cause of COVID-19, reflects the novelty of the virus and limited preexisting B cell immunity. IgG against the SARS-CoV-2 spike (S) protein, which carries the novel receptor binding domain (RBD), is absent or at low levels in unexposed individuals. To better understand the B cell response to SARS-CoV-2 infection, we asked whether virus-reactive memory B cells (MBCs) were present in unexposed subjects and whether MBC generation accompanied virus-specific IgG production in infected subjects. We analyzed sera and PBMCs from non-SARS-CoV-2-exposed healthy donors and COVID-19 convalescent subjects. Serum IgG levels specific for SARS-CoV-2 proteins (S, including the RBD and S2 subunit, and nucleocapsid [N]) and non-SARS-CoV-2 proteins were related to measurements of circulating IgG MBCs. Anti-RBD IgG was absent in unexposed subjects. Most unexposed subjects had anti-S2 IgG and a minority had anti-N IgG, but IgG MBCs with these specificities were not detected, perhaps reflecting low frequencies. Convalescent subjects had high levels of IgG against the RBD, S2, and N, together with large populations of RBD- and S2-reactive IgG MBCs. Notably, IgG titers against the S protein of the human coronavirus OC43 in convalescent subjects were higher than in unexposed subjects and correlated strongly with anti-S2 titers. Our findings indicate cross-reactive B cell responses against the S2 subunit that might enhance broad coronavirus protection. Importantly, our demonstration of MBC induction by SARS-CoV-2 infection suggests that a durable form of B cell immunity is maintained even if circulating antibody levels wane. [**note: this is encouraging if others can confirm as they find durable B cell immunity even as antibody levels wane.**]
https://www.biorxiv.org/content/10.1101/2020.07.20.213298v1
- In a letter to the New England Journal of Medicine, a UCLA group presents their follow up serology study on a group of patients with mild COVID-19. It is a small group of just over 30 patients and they are concerned the humoral immunity may not be long lasting. [**note: until we have a lot more aggregated data, I don't think any conclusion can be drawn.**]
https://www.nejm.org/doi/full/10.1056/NEJMc2025179

DIAGNOSTIC DEVELOPMENT

- The emergence of SARS-CoV-2 has led to the development of new serological assays that could aid in diagnosis and evaluation of seroprevalence to inform an understanding of the burden of COVID-19 disease. Many available tests lack rigorous evaluation and therefore results may be

misleading. Objectives: The aim of this study was to assess the performance of a novel multiplexed immunoassay for simultaneous detection of antibodies against SARS-CoV-2 trimeric spike (S), spike receptor binding domain (RBD), spike N terminal domain and nucleocapsid and a novel pseudo-neutralisation assay. Methods: A multiplexed solid-phase chemiluminescence assay (MesoScaleDiscovery) was evaluated for the simultaneous detection of IgG binding to four SARS-CoV-2 antigens and the quantification of ACE-2 binding inhibition (pseudo-neutralisation assay). Sensitivity was evaluated with a total of 196 COVID-19 serum samples (169 confirmed PCR positive and 27 anti-nucleocapsid IgG positive) from individuals with mild symptomatic or asymptomatic disease. Specificity was evaluated with 194 control serum samples collected from adults prior to December 2019. Results: The specificity and sensitivity of the binding IgG assay was highest for S protein with a specificity of 97.4% and sensitivity of 96.2% for samples taken 14 days and 97.9% for samples taken 21 days following the onset of symptoms. IgG concentration to S and RBD correlated strongly with percentage inhibition measured by the pseudo-neutralisation assay. Conclusion: Excellent sensitivity for IgG detection was obtained over 14 days since onset of symptoms for three SARS-CoV-2 antigens (S, RBD and N) in this multiplexed assay which can also measure antibody functionality. [**note: another multiplex assay with very good sensitivity. This one if from the UK.**]
https://www.biorxiv.org/content/10.1101/2020.07.20.213249v1

- SARS-CoV-2 neutralizing antibodies confer protective immunity against reinfection. We have developed a rapid test for screening SARS-CoV-2 neutralization antibodies using genome-free virus-like particles incorporated with a small luciferase peptide, HiBiT. Their entry into LgBiT-expressing target cells reconstitutes NanoLuc luciferase readily detected by a luminometer. This newly developed HiBiT-tagged Virus-like particle-based Neutralization Test (hiVNT) can readily quantify SARS-CoV-2 neutralizing antibodies within three hours with a high-throughput in a low biosafety setting. Moreover, the neutralizing activity obtained from hiVNT was highly consistent with that measured by the conventional neutralization test using authentic SARS-CoV-2. Furthermore, antibody responses to both viral spike and nucleocapsid proteins correlated with the neutralization activity assessed by hiVNT. Our newly-developed hiVNT could be instrumental to survey individuals for the presence of functional neutralizing antibody against SARS-CoV-2. [**note: yet another new approach to measuring neutralizing antibodies.**]
https://www.medrxiv.org/content/10.1101/2020.07.20.20158410v1

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2020-07-23

Loyal readers will recall the wonderful ABBA performance for the Queen of Sweden that I posted a while back. Here is a 'Momma Mia' cast doing a riff on that song with of course pandemic lyrics. Enjoy and have a good chuckle!!!: https://www.youtube.com/watch?v=FmDcg59Xzek Let us take a moment to remember the great jazz singer Annie Ross who recently passed. Perhaps her greatest fame came as part of the vocal trio: Lambert, Hendricks and Ross. Here is the trio backed by the Count Basie Orchestra singing 'Avenue C': https://www.youtube.com/watch?v=E99TIXB_swg Ross was also known for her solo composition, 'Twisted' . Here is the Lambert, Hendricks and Ross version: https://www.youtube.com/watch?v=JXwMgIlmoaM and one of the great covers by Joni Mitchell: https://www.youtube.com/watch?v=4Vmq-DHQRF4

US COVID-19 STATISTICS - **Infection Rate: 1.2%; CFR: 3.6%** (IR no change; CFR no change)

If the schools in your area are opening, The Washington Post offers 10 things parents can do! Can you get COVID-19 twice? It's difficult to say as the PCR test only looks at the presence of genetic material and not clinical symptoms. There are some people who can test positive for a long period of time and are asymptomatic. We need more data points before arriving at an answer. Colby College in Maine plans to open up in the fall with an ambitious SARS-CoV-2 testing program that will monitor students 2-3 times a week. That may add up to 85,000 tests for the semester at a cost of $2.5 million.

The New York Times answers the vexing question, does the rise in testing drive the rise in COVID-19 cases? Despite what you might hear, the only thing that drives the rise of COVID-19 cases in infection with SARS-CoV-2; testing has nothing to do with this at all! The US Northeast appears to have quelled the SARS-CoV-2 outbreak; let us hope it stays this way. Times reporter, Sarah Kliff, writes about the decision by the US government to purchase COVID-19 vaccine ahead of approval. Opening of schools is way harder than it should be. A convent in Michigan is hit especially hard with 13 nuns perishing from COVID-19.

Regarding vaccine development, The Washington Post reports on how some top managers at biotech company Novavax stand to make a lot of money if the company's vaccine progresses to Phase 2 clinical trials. The payoff is not immediate as the options apparently don't vest for a year. **Editorial Comment:** *I have been against stock options as a method of executive compensation for a lot of years. Along with other executive compensation measures, it focuses management on short term profitability rather than long term. During corporate proxy season, I routinely vote against all such proposals. This may be akin to spitting in the ocean but I feel management should not be rewarded by artificially pumping up stock prices.* This move by the Novavax board was just wrong!

I missed this Medscape interview with Stanford professor, John Ioannidis, that came out on July 15 (do also read the comments to the interview; I found them disturbing). Ioannidis has held a somewhat contrarian view of the pandemic and has been quite outspoken. He is also one of the co-authors of the Stanford Santa Clara County serology study that came out a couple of months ago that apparently showed a much higher level of infection in the county than was reported. That preprint drew immediate criticism from epidemiologists and statisticians from all over the place. The paper was rewritten with a new analysis but there are still lingering questions. As I noted back in April when the initial Twitter storms were unleashed, both the authors of the paper and the critics are missing the big picture. It is obvious to everyone that the level of infection is larger than the number of reported cases and I linked to some work that CDC just came out with the other day. The key issue from the early days of the New York City case explosion was whether the hospital systems would be overburdened. The answer to that question is a resounding yes! This was to be expected from the experience in Lombardy. We are now seeing this repeated in Arizona, Texas, Florida, and parts of Georgia. The Case Fatality Rate (CFR) may eventually bottom out at 0.3% but there are lots of people who need hospitalization to recover. Patients with other clinical symptoms that warrant hospitalization are not being admitted in some areas because of the high incidence of COVID-19. I have no doubt that Professor Ioannidis is correct that the CFR in the US is not 3-4% but one cannot argue against the current statistics of hospital utilization.

Annals of Internal Medicine have a review of age distribution of COVID-19 fatality across nine countries. Data runs through mid-April, so it won't cover the current US outbreaks. "*Selective testing and*

*identifying of older cases considerably warps estimates of the lethality of COVID-19 within populations and comparisons across countries. Removing age distortions and focusing on differences in age-adjusted case fatality will be essential for accurately comparing countries' performance in caring for patients with COVID-19 and for monitoring the epidemic over time.*" There is also a well written editorial on the topic of age related fatality.

The New England Journal of Medicine has a special report on the NIH initiative to rapidly scale up COVID-19 diagnostic testing. The introductory paragraph notes that NIH has been involved in "…multiple wide-ranging collaborative efforts spanning the development of vaccines and diagnostic strategies, the identification and evaluation of safe and effective treatments…" Seriously??????? We are now in late-July and they are now publishing a feel good report on diagnostics? As my readers know, I've been harping on this issue for several months! Maybe 'better late than never' is the new watchword.

JAMA has a research letter from Univ of Washington investigators on the use of sell-collected midnasal swabs for SARS-CoV-2 testing. They found them to be comparable to clinician-collected nasopharngeal swab collection in symptomatic patients. [**note: a link to a preprint of this work was posted some weeks ago**] One of the key issues associated with the number of dispersed clinical trial sites in the US is how to better coordinate trials. This viewpoint discusses how data from individual clinical trials can be pooled. In the absence of a national healthcare system, independent trial sites may be under-enrolled and starting new randomized clinical trial sites is time consuming. [**note: this is a crucial issue and of course one addressed in the paper I wrote way back in April. Maybe it will be fixed by the time the next pandemic arrives.**]

Following up on clinical trials, this STAT piece written by two industry R&D heads looks at the issue from a global perspective. More on this at the COVID R&D alliance. NIH Director, Frances Collins, discusses a 'flurry' of large clinical trials to test new approaches to treating COVID-19.

MODELING

- Nothing today

NEWLY REGISTERED CLINICAL TRIALS

- Too busy reading other preprints to look at the NIH Trail Databse

CLINICAL TRIAL RESULTS

- System-wide molecular characteristics of COVID-19, especially in those patients without comorbidities, have not been fully investigated. We compared extensive molecular profiles of blood samples from 231 COVID-19 patients, ranging from asymptomatic to critically ill, importantly excluding those with any comorbidities. Amongst the major findings, asymptomatic patients were characterized by highly activated anti-virus interferon, T/natural killer (NK) cell activation, and transcriptional upregulation of inflammatory cytokine mRNAs. However, given very abundant RNA binding proteins (RBPs), these cytokine mRNAs could be effectively destabilized hence preserving normal cytokine levels. In contrast, in critically ill patients, cytokine storm due to RBPs inhibition and tryptophan metabolites accumulation contributed to

T/NK cell dysfunction. A machine-learning model was constructed which accurately stratified the COVID-19 severities based on their multi-omics features. Overall, our analysis provides insights into COVID-19 pathogenesis and identifies targets for intervening in treatment. [**note: this is a very extensive look at molecular profiles of 231 patients. Well worth taking a look at.**] https://www.medrxiv.org/content/10.1101/2020.07.17.20155150v1…

- IL-7 promotes a return to normal of lymphocyte count in this Belgian study. Depressed lymphocyte count is one of the pathological hallmarks of severe COVID-19. [**note: The number of patients is small (12) and clearly this warrants further investigation**.] https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2768536
- To analyze the effects of a short course of methyl-prednisolone pulses (MP) during the second week of disease (week-2) on the clinical course of patients with severe coronavirus disease 2019 (COVID-19) pneumonia. DESIGN: Comparative observational study using data collected from routine care. SETTING: Hospital Universitario Cruces, a tertiary level University hospital at Barakaldo, Bizkaia, Spain. PARTICIPANTS: All patients with COVID-19 pneumonia admitted between 1st March and 30th April 2020 to the services of Infectious Diseases and Internal Medicine. INTERVENTIONS: Treatment with week-2-MP (125-250 mg/d for 3 consecutive days with no subsequent tapering) vs. standard of care. MAIN OUTCOMES MEASURES: Time to death and time to death or endotracheal intubation. RESULTS: Two hundred and forty-two patients with confirmed COVID-19 pneumonia and elevated inflammatory markers at admission were included in the study. Sixty-one patients (25%) received week-2-MP. Twenty-two patients (9%) died during the study period. Thirty-one patients (12.8%) suffered death or intubation. The adjusted HR for death was 0.35 (95%CI 0.11 to 1.06, p= 0.064) for patients in the week-2-MP group. The adjusted HR for death or intubation week-2-MP was 0.33 (95%CI 0.13 to 0.84, p=0.020) for patients in the week-2-MP group. These differences were seen in the subcohort of patients with a SaO2/FiO2 at day 7 lower than the median of the whole population: HR 0.31, 95% CI 0.08 to 1.12, p=0.073 and HR 0.34, 95%CI 0.12 to 0.94, p=0.038, respectively, but not in patients with higher SaO2/FiO2. Other predictors of the final outcomes were arterial hypertension, SaO2/FiO2, high-risk CURB65 scores and the use of non-pulse glucocorticoids. Non-pulse glucocorticoids were a predictor of infections (OR 4.72, 95%CI 1.90 to 11.80, p<0.001), while week-2-MP were not (OR 1.04, 95%CI 0.40 to 2.70, p=0.938). CONCLUSIONS: *Week-2-MP are effective in improving the prognosis of patients with COVID-19 pneumonia with features of inflammatory activity and respiratory deterioration entering the second week of disease. The recognition of this high-risk population should prompt early use of MP at this point*. [**note: more data on corticosterioids, this time methylprednisolone form Spain. It's pretty clear that this is front line therapy.**] https://www.medrxiv.org/content/10.1101/2020.07.16.20152868v1
- Use of hydroxychloroquine in hospitalized patients with COVID-19, especially in combination with azithromycin, has raised safety concerns. Here, we report safety data from three outpatient randomized clinical trials. Methods: We conducted three randomized, double-blind, placebo-controlled trials investigating hydroxychloroquine as pre-exposure prophylaxis, post-exposure prophylaxis and early treatment for COVID-19. We excluded individuals with contraindications to hydroxychloroquine. We collected side effects and serious adverse events. We report descriptive analyses of our findings. Results: We enrolled 2,795 participants. The median age of research participants was 40 (IQR 34-49) years, and 59% (1633/2767) reported no

chronic medical conditions. Overall 2,324 (84%) participants reported side effect data, and 638 (27%) reported at least one medication side effect. Side effects were reported in 29% with daily, 36% with twice weekly, 31% with once weekly hydroxychloroquine compared to 19% with placebo. The most common side effects were upset stomach or nausea (25% with daily, 18% with twice weekly, 16% with weekly, vs. 10% for placebo), followed by diarrhea, vomiting, or abdominal pain (23% for daily, 16% twice weekly, 12% weekly, vs. 6% for placebo). Two individuals were hospitalized for atrial arrhythmias, one on placebo and one on twice weekly hydroxychloroquine. No sudden deaths occurred. Conclusion: Data from three outpatient COVID-19 trials demonstrated that gastrointestinal side effects were common but mild with the use of hydroxychloroquine, while serious side effects were rare. No deaths occurred related to hydroxychloroquine. Randomized clinical trials can safely investigate whether hydroxychloroquine is efficacious for COVID-19. [**note: this is just a safety study of HCQ from the Univ of Minnesota that previously published clinical results showing it not to be efficacious. Serious side effects were rare.**]
https://www.medrxiv.org/content/10.1101/2020.07.16.20155531v1

DRUG DEVELOPMENT

- The ongoing COVID-19 pandemic, caused by SARS-CoV-2 infection, has resulted in hundreds of thousands of deaths. Cellular entry of SARS-CoV-2, which is mediated by the viral spike protein and host ACE2 receptor, is an essential target for the development of vaccines, therapeutic antibodies, and drugs. Using a mammalian cell expression system, we generated a recombinant fluorescent protein (Gamillus)-fused SARS-CoV-2 spike trimer (STG) to probe the viral entry process. In ACE2-expressing cells, we found that the STG probe has excellent performance in the live-cell visualization of receptor binding, cellular uptake, and intracellular trafficking of SARS-CoV-2 under virus-free conditions. The new system allows quantitative analyses of the inhibition potentials and detailed influence of COVID-19-convalescent human plasmas, neutralizing antibodies and compounds, providing a versatile tool for high-throughput screening and phenotypic characterization of SARS-CoV-2 entry inhibitors. This approach may also be adapted to develop a viral entry visualization system for other viruses. [**note: this is pretty cool technology to visualize receptor binding and cellular uptake of SARS-CoV-2. It could prove useful.**] https://www.biorxiv.org/content/10.1101/2020.07.22.215236v1
- Hydroxychloroquine, used to treat malaria and some autoimmune disorders, potently inhibits viral infection of SARS coronavirus (SARS-CoV-1) and SARS-CoV-2 in cell-culture studies. However, human clinical trials of hydroxychloroquine failed to establish its usefulness as treatment for COVID-19. This compound is known to interfere with endosomal acidification necessary to the proteolytic activity of cathepsins. Following receptor binding and endocytosis, cathepsin L can cleave the SARS-CoV-1 and SARS-CoV-2 spike (S) proteins, thereby activating membrane fusion for cell entry. The plasma membrane-associated protease TMPRSS2 can similarly cleave these S proteins and activate viral entry at the cell surface. Here we show that the SARS-CoV-2 entry process is more dependent than that of SARS-CoV-1 on TMPRSS2 expression. This difference can be reversed when the furin-cleavage site of the SARS-CoV-2 S protein is ablated. We also show that hydroxychloroquine efficiently blocks viral entry mediated by cathepsin L, but not by TMPRSS2, and that a combination of hydroxychloroquine and a clinically-tested TMPRSS2 inhibitor prevents SARS-CoV-2 infection more potently than either

drug alone. *These studies identify functional differences between SARS-CoV-1 and -2 entry processes, and provide a mechanistic explanation for the limited in vivo utility of hydroxychloroquine as a treatment for COVID-19*. [**note: HCQ research never stops!**] https://www.biorxiv.org/content/10.1101/2020.07.22.216150v1

- we have developed an infectious cDNA clone of the SARS-CoV-2 USA-WA1/2020 strain based on the use of a bacterial artificial chromosome (BAC). Recombinant (r)SARS-CoV-2 was readily rescued by transfection of the BAC into Vero E6 cells. Importantly, the BAC-derived rSARS-CoV-2 exhibited growth properties and plaque sizes in cultured cells comparable to those of the SARS-CoV-2 natural isolate. Likewise, rSARS-CoV-2 showed similar levels of replication to that of the natural isolate in nasal turbinates and lungs of infected golden Syrian hamsters. This is, to our knowledge, the first BAC based reverse genetics system for the generation of infectious rSARS-CoV-2 that displays similar features in vivo to that of a natural viral isolate. This SARS-CoV-2 BAC-based reverse genetics will facilitate studies addressing several important questions in the biology of SARS-CoV-2, as well as the identification of antivirals and development of vaccines for the treatment of SARS-CoV-2 infection and associated COVID-19 disease. [**note: a bacterial clone of SARS-CoV-2 for research**] https://www.biorxiv.org/content/10.1101/2020.07.22.216358v1
- SARS CoV requires $Ca^{2+}$ ions for host cell entry[4] and based on the similarity between SARS CoV and SARS CoV 2[5] it is highly likely that the same requirements exist for the two viruses. Here, we tested whether FDA-approved calcium channel blocker (CCB) drugs are efficacious to inhibit the spread of SARS CoV 2 in cell culture. Our data shows that amlodipine, felodipine and nifedipine limit the growth of SARS CoV 2 in epithelial kidney (Vero E6) and epithelial lung (Calu-3) cells. We observed some differences in the inhibition efficacy of the drugs in the two different cell lines, but with felodopine and nifedipine having the greatest effect. Overall, our data suggest that CCBs have a high potential to treat SARS CoV 2 infections and their current FDA approval would allow for a fast repurposing of these drugs. [**note: I am reminded of the old Biblical phrase, 'many are invited, but few are chose.' In this case, many compounds work *in vitro* but few in the clinic. It would be useful to do some large observational studies to see how patients on these drugs fare. There is one referenced paper in this preprint that comes from a single Brooklyn hospital pointing to an effect from nifedipine and amlodipine. I took a quick look at the paper and it is pretty messy. Sildenafil is being looked at for the same mechanistic approach. There does appear to be a large observational study looking at ACE/ARB and other cardiovascular drugs.**] https://www.biorxiv.org/content/10.1101/2020.07.21.214577v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- SARS-CoV-2 is the newly emerged virus responsible for the global COVID-19 pandemic. There is an incomplete understanding of the host humoral immune response to SARS-CoV-2 during acute infection. Host factors such as age and sex as well the kinetics and functionality of antibody responses are important factors to consider as vaccine development proceeds. The receptor-binding domain of the CoV spike (RBD-S) protein is important in host cell recognition and infection and antibodies targeting this domain are often neutralizing. In a cross-sectional study of anti-RBD-S antibodies in COVID-19 patients we found equivalent levels in male and female patients and no age-related deficiencies even out to 93 years of age. The anti-RBD-S response was evident as little as 6 days after onset of symptoms and for at least 5 weeks after symptom

onset. Anti-RBD-S IgG, IgM, and IgA responses were simultaneously induced within 10 days after onset, but isotype-specific kinetics differed such that anti-RBD-S IgG was most sustained over a 5-week period. The kinetics and magnitude of neutralizing antibody formation strongly correlated with that seen for anti-RBD-S antibodies*. Our results suggest age- and sex- related disparities in COVID-19 fatalities are not explained by anti-RBD-S responses. The multi-isotype anti-RBD-S response induced by live virus infection could serve as a potential marker by which to monitor vaccine-induced responses*. [**note this is an interesting finding from a Vermont group. Antibody response does not appear to be age or sex related.**]
https://www.medrxiv.org/content/10.1101/2020.07.15.20154443v1

- In December 2019, the world awoke to a new zoonotic strain of coronavirus named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). In the present study, we classified betacoronavirus subgroup B into the SARS-CoV-2, SARS-CoV, and SARS-like CoV clusters and the ORF8 genes of these three clusters into types 1, 2, and 3, respectively. One important result of our study is that the recently reported strain RmYN02 is a recombinant SARS2-like CoV strain that belongs to the SARS-CoV-2 cluster, but has an ORF8 from a SARS-like CoV. *This finding provides substantial proof for long-existing hypotheses regarding the recombination events and biological functions of ORF8. Another important result of our study is that we propose that the Spike protein of SARS-CoV-2 may have two receptors for its infection as gp120 of HIV have CD4 and CCR5. We concluded that the furin protease cleavage site acquired by SARS-CoV-2 may increase the efficiency of viral entry into cells, while the type 2 ORF8 acquired by SARS-CoV may increase its replicative efficiency. These two most critical events may provide the most likely explanation for SARS and COVID-2019 pandemics*. [**note: this is a very interesting finding from this Chinese group. Viral recombination is also a feature of influenza outbreaks.**]
https://www.biorxiv.org/content/10.1101/2020.07.22.213926v1
- Neutralizing antibodies elicited by prior infection or vaccination are likely to be key for future protection of individuals and populations against SARS-CoV-2. Moreover, passively administered antibodies are among the most promising therapeutic and prophylactic anti-SARS-CoV-2 agents. However, the degree to which SARS-CoV-2 will adapt to evade neutralizing antibodies is unclear. Using a recombinant chimeric VSV/SARS-CoV-2 reporter virus, we show that functional SARS-CoV-2 S protein variants with mutations in the receptor binding domain (RBD) and N-terminal domain that confer resistance to monoclonal antibodies or convalescent plasma can be readily selected. Notably, SARS-CoV-2 S variants that resist commonly elicited neutralizing antibodies are now present at low frequencies in circulating SARS-CoV-2 populations. Finally, the emergence of antibody-resistant SARS-CoV-2 variants that might limit the therapeutic usefulness of monoclonal antibodies can be mitigated by the use of antibody combinations that target distinct neutralizing epitopes. [**note: the issue of mutation in the Spike protein continues to be of concern with respect to antibody resistance.**]
https://www.biorxiv.org/content/10.1101/2020.07.21.214759v1

DIAGNOSTIC DEVELOPMENT

- Nothing today

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2020-07-24

Staying with quarantine 'concerts' here is a group of Long Island musicians rocking 'We Are the World': https://www.youtube.com/watch?v=lTK84KEDMW8 local musicians full of energy and spirit, something that all of us need a lot more of. There is this more polished version from Broadway United: https://www.youtube.com/watch?v=BdnteHS9bnY but the theme is still ---- We Are All In This Together!!! Taking time out from COVID-19 thinking – Taylor Swift has a new album!!!! GREAT NEWS!!! Here is a vid from 'Folklore': https://www.youtube.com/watch?v=2s5xdY6MCeI and the Washington Post has the backstory on 'The Last Great American Dynasty.' Enjoy this triple treat of music videos.

US COVID-19 STATISTICS - **Infection Rate: 1.2%; CFR: 3.5%** (IR no change; CFR down 0.1%; **note:** the CFR for this current outbreak is hovering just above 1%)

**CONTEST TIME!!!! First person to correctly tell me what is wrong with this picture from Barcelona wins a nice prize!**

According to the New York Times testing supplies for SARS-CoV-2 are again in short supply!😒 Delays are unacceptable if you want to put in place track and trace! One of the big clinical labs, LabCorp, notes that COVID-19 is spreading faster than testing capacity. A cautionary tale about Olympic rowers who were infected by their physical therapist. California suffers the whiplash of an outbreak following a successful lockdown. This is a sad story of the use of chlorine-dioxide for prophylaxis of COVID-19 in Bolivia (I'll not even mention that someone in the US noted this might be an effective treatment: oops I just did).

Derek Lowe on AI, Machine Learning and the pandemic. Don't look for any solutions here.

Jerome Groopman on the COVID-19 long game in The New Yorker. It is a must read! Three ways of looking at children and COVID-19.

I guess these Brazilian investigators did not include President Bolsonaro in their clinical trial! The COVID-19 Brazil team reports in The New England Journal of Medicine the results of their HCQ ± azithromycin trial. Primary outcome was clinical status at 15 days. I won't make you click on the link to find out that neither treatment arm "…did not improve clinical status at 15 days compared with standard care…." Somebody please put this Zombie drug into a deep sleep.

Kaiser Health News has an interesting article on the use of UV-lights to disinfect various indoor settings.

MODELING

- The occurrence of pneumonia separates severe cases of COVID-19 from the majority of cases with mild disease. However, the factors determining whether or not pneumonia develops remain to be fully uncovered. We therefore explored the associations of several lifestyle factors with signs of pneumonia in COVID-19. Methods Between May and July 2020, we conducted an online survey of adults in Germany who had recently gone through COVID-19, predominantly as outpatients (n=201). Of these, 165 had a PCR-based diagnosis and 36 had a retrospective diagnosis by antibody testing. The survey covered demographic information, eight lifestyle factors, comorbidities and medication use. We defined the main outcome as the presence vs. the absence of signs of pneumonia, represented by dyspnea, the requirement for oxygen therapy or intubation. Results Signs of pneumonia occurred in 39 of the 165 individuals with a PCR-based diagnosis of COVID-19 (23.6%). Among the lifestyle factors examined, only overweight/obesity associated with signs of pneumonia (odds ratio 2.68 (1.29 - 5.59) p=0.008). The observed association remained significant after multivariate adjustment, with BMI as a metric variable, and also after including the antibody-positive individuals into the analysis. Conclusions This exploratory study finds an association of overweight/obesity with signs of pneumonia in COVID-19. This finding suggests that a signal proportional to body fat mass, such as the hormone leptin, impairs the body's ability to clear SARS-CoV-2 before pneumonia develops. This hypothesis concurs with previous work and should be investigated further to possibly reduce the proportion of severe cases of COVID-19. [**note: this is a sort of model from a German team. They looked at a cohort of patients who had gone through COVID-19. Overweight/obesity was a major factor in progression to pneumonia. An on-line survey is not the best sampling method, but the results accord with the general findings from others. It's always important to maintain a healthy weight!**]
  https://www.medrxiv.org/content/10.1101/2020.07.23.20161042v1
- Background New Zealand had 1499 cases of COVID-19 before eliminating transmission of the virus. Extensive contract tracing during the outbreak has resulted in a dataset of epidemiologically linked cases. This data contains useful information about the transmission dynamics of the virus, its dependence on factors such as age, and its response to different control measures. Method We use Monte-Carlo network construction techniques to provide an estimate of the number of secondary cases for every individual infected during the outbreak. We then apply standard statistical techniques to quantify differences between groups of individuals. Findings Children under 10 years old are significantly under-represented in the case

data. Children infected fewer people on average and had a lower secondary attack rate in comparison to adults and the elderly. Imported cases infected fewer people on average and had a lower secondary attack rate than domestically acquired cases. Superspreading is a significant contributor to the epidemic dynamics, with 20% of cases among adults responsible for 65-85% of transmission. Asymptomatic cases infected fewer individuals than clinical cases. Serial intervals are approximately normally distributed (μ=5.0 days, σ=5.7 days). Early isolation and quarantine of cases reduced secondary transmission rates. Interpretation Border controls and strong social distancing measures, particularly when targeted at superspreading, play a significant role in reducing the spread of COVID-19. [**note: this is from New Zealand which still stands as the best example of how to contain and control a SARS-CoV-2 outbreak. Some good lessons can be learned from this paper.**]
https://www.medrxiv.org/content/10.1101/2020.07.21.20159335v1

NEWLY REGISTERED CLINICAL TRIALS

- The purpose of this study is to test whether Fisetin, a senolytic drug, can assist in preventing an increase in the disease's progression and alleviate complications of coronavirus due to an excessive inflammatory reaction. To determine if Fisetin treatment can prevent deterioration of oxygenation status as measured by S/F ratio: SpO2/ FiO2, as well as prevent deterioration in physical function (frailty) and hyper-inflammation, other measures of oxygenation status (progression to supplemental oxygen requirement, assisted breathing/ ventilation), and progression from mild/ moderate to severe/ critical proven COVID-19 (CoV) infection (WHO/NIH Baseline Severity Classification) in non-ICU hospitalized patients and to evaluate the safety and tolerability of Fisetin in this patient population. [**note: this is a Mayo Clinic trial. It is marketed as a dietary supplement in the US as a 'scientific way to slow aging.' I have seen other polyphenol compounds mentioned as potential COVID-19 treatments.**] NCT04476953
- The COVID-19 pandemic is of grave concern due its impact on human health and on the economy. Propolis, a natural resin produced by bees from plant materials, has anti-inflammatory, immunomodulatory, anti-oxidant properties, and various aspects of the SARS-CoV-2 infection mechanism are potential targets for propolis compounds. Propolis components have inhibitory effects on the ACE2, TMPRSS2 and PAK1 signaling pathways; in addition, antiviral activity has been proven in vitro and in vivo. This is a pilot randomized study that aims to assess the impact of using Brazilian green propolis extract against the deleterious effects of the new coronavirus. [**note: you find out something new everyday!! It's used as a varnish ingredient in stringed instruments and maybe was the key secret ingredient in Stradivarius violins. Will it cure COVID-19, who knows?**] NCT04480593
- COVID-19 morbidity and mortality has been associated with Cytokine Release Syndrome (CRS) and Acute Respiratory Distress Syndrome (ARDS). ATI-450 is an oral small molecule MAPKAPK2 (MK2) inhibitor that potently inhibits multiple inflammatory cytokines. The investigator hypothesizes that MK2 pathway blockade during active COVID-19 infection in hospitalized participants will result in improvement in respiratory-failure free survival. [**note: at least we have a real drug trial with this one. It is made by Aclaris Therapeutics and the trial is at Univ of Kansas.**] NCT04481685
- The aim of this study is to evaluate the role of the topical corticosteroids nasal spray (momentasonefuratenasal spray) in improving anosmia in patients recovered from COVID-19

infection. [**note: I don't think this is marketed in the US any longer as there was not an OTC switch when the nasal steroids were found to be safe for such use. I use fluticasone.**] NCT04484493

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for COVID-19, enters type II pneumocytes using angiotensin-converting enzyme 2 (ACE2). It is unclear whether ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) increase, decrease, or have no significant effect on ACE2 expression or activity. Therefore, ACEI and ARB may be harmful, beneficial, or have no impact on Coronavirus Disease 2019 severity and mortality. The Specific Aims of this observational study are: (1) Among SARS-CoV-2-positive outpatients, compare all-cause hospitalization and mortality rates between: 1.1 Current users of a range of doses of ACEI/ARB- vs. non- ACEI/ARB-based regimens, and 1.2 Current users of a range of doses of ACEI- vs. ARB-based regimens, and (2) Among those hospitalized for COVID-19, compare all-cause mortality between: 2.1 Current users of a range of doses of ACEI/ARB- vs. non- ACEI/ARB-based regimens, and 2.2 Current users of a range of doses of ACEI- vs. ARB-based regimens. [**note: I mentioned this large observational trial yesterday. It is VA trial.**] NCT04467931
- The recent COVID-19 pandemic has affected many aspects of individuals social life and its negative consequences on Canadian public health go far beyond the direct overload of the hospital care system. Self-isolation and financial uncertainty can significantly deteriorate individuals' mental health, which is only going to aggravate with prolonged physical distancing strategies. Adding to this is the personal and public trauma of lost lives and soon there will be an unprecedented epidemic of mental health problems with crushing effects on the public health sector and economy. To meet this huge new demand for an already strained health system, there is a need for innovative new approaches that significantly expand the capacity of care delivery. While it may not be possible in the short term to increase the number of mental healthcare providers or the number of hours they work, improving their time spent efficiently might be the solution. Virtual care and online delivery of psychotherapy, shown to be clinically effective, efficient and cost-effective, might be the perfect solution to address the high demand faced now. The investigators aim to establish the first academic online psychotherapy clinic to manage mental health problems secondary to COVID-19. The goal is to evaluate the feasibility and efficacy of treating COVID-19 related mental health issues in this clinic, offering a 10-week, diagnosis-specific, online psychotherapy program. The investigators will use the Online Psychotherapy Tool (OPTT), a secure cloud-based digital mental health platform, developed by the PI, Dr. Alavi. Potentially, this method of care delivery could increase care capacity by four-folds. The findings from this project have the potential to influence clinical practice and policy and increase accessibility to care during COVID-19 pandemic, without sacrificing the quality of care. [**note: online psychotherapy – I need to be in this trial!!!**] NCT04476667
- The purpose of this study is to evaluate the efficacy of vadadustat for the prevention and treatment of acute respiratory distress syndrome (ARDS) in hospitalized patients with Coronavirus Disease 2019 (COVID-19). [**note: sponsor is Akebia Therapeutics . It's unclear how this drug will help.**] NCT04478071
- Pioglitazone is an approved anti-hyperglycemic medication and is thought to have anti-inflammatory properties. This study seeks to gather safety and tolerability data related to pioglitazone when given to patients who require hospital admission for confirmed positive COVID-19 infections with elevated blood sugar levels as compared to patients who did not

receive pioglitazone during their hospitalization for COVID-19. [**note: this is the GOTCHA trial that I have been long waiting for.😂 No kidding, that is what they have titled this one. I guess it might be of use for those with high blood sugar.**] NCT04473274

CLINICAL TRIAL RESULTS

- Increasing evidence demonstrated that the expression of Angiotensin I-Converting Enzyme type 2 (ACE2), is a necessary step for SARS-CoV-2 infection permissiveness. In the light of the recent data highlighting an association between COVID-19 and diabetes, a detailed analysis aimed at evaluating ACE2 expression pattern distribution in human pancreas is still lacking. Here, we took advantage of INNODIA network EUnPOD biobank collection to thoroughly analyse ACE2, both at mRNA and protein level, in multiple human pancreatic tissues and using several methodologies. We showed that ACE2 is indeed present in human pancreatic islets, where is preferentially expressed by insulin producing β-cells. Of note, pro-inflammatory cytokines increased ACE2 expression in β-cells, thus putatively suggesting an enhancement of β-cells sensitivity to SARS-CoV-2 during inflammatory conditions. Taken together, our data indicate a potential link between SARS-CoV-2 infection and diabetes, through direct β-cell virus tropism [**note: this is more of an observation paper that may explain why diabetics experience adverse clinical symptoms.**] https://www.biorxiv.org/content/10.1101/2020.07.23.208041v1
- Objective: To determine, whether COVID-19 is associated with a vigorous total IgA response and whether IgA autoantibodies are associated with complications of severe illness. Since thrombotic events are frequent in severe COVID-19 and resemble hypercoagulation of antiphospholipid syndrome (APS), our approach focused on antiphospholipid antibodies (aPL). Materials and methods: In this retrospective cohort study we compared clinical data and aPL from 64 patients with COVID-19 from three independent centers (two in Switzerland, one in Liechtenstein). Samples were collected from April 9, 2020 to May 1, 2020. Total IgA and aPL were measured with FDA-approved commercially available clinical diagnostic kits. Results: Clinical records of the 64 patients with COVID-19 were reviewed and divided into a cohort with mild illness (mCOVID, n=26 [41%]), a discovery cohort with severe illness (sdCOVD, n=14 [22%]) and a confirmation cohort with severe illness (scCOVID, n=24 [38%]). Severe illness was significantly associated with increased total IgA (sdCOVID, P=0.01; scCOVID, P<0.001). Total IgG levels were similar in both cohorts. Among aPL, both cohorts with severe illness significantly correlated with elevated anti-Cardiolipin IgA (sdCOVID and scCOVID, P<0.001), anti-Cardiolipin IgM (sdCOVID, P=0.003; scCOVID, P<0.001), and anti-Beta2 Glycoprotein-1 IgA (sdCOVID and scCOVID, P<0.001). Systemic lupus erythematosus was excluded from all patients as a potential confounder of APS. Conclusions: Higher total IgA and IgA-aPL were consistently associated with severe illness. These novel data strongly suggest that a vigorous antiviral IgA-response triggered in the bronchial mucosa induces systemic autoimmunity. [**note: this is a small patient sample study from Switzerland pointing to another complication in serious COVID-19.**] https://www.medrxiv.org/content/10.1101/2020.07.21.20159244v1
- Microvascular lesions are common in patients with severe COVID-19. Radiologic-pathologic correlation in one case suggests a combination of microvascular hemorrhagic and ischemic lesions that may reflect an underlying hypoxic mechanism of injury, which requires validation in larger studies. OBJECTIVE: To determine the incidence, distribution, and clinical and histopathologic correlates of microvascular lesions in patients with severe COVID-19. DESIGN:

Observational, retrospective cohort study: March to May 2020. SETTING: Single academic medical center. PARTICIPANTS: Consecutive patients (16) admitted to the intensive care unit with severe COVID-19, undergoing brain MRI for evaluation of coma or focal neurologic deficits. EXPOSURES: Not applicable. MAIN OUTCOME AND MEASURES: Hypointense microvascular lesions identified by a prototype ultrafast high-resolution susceptibility-weighted imaging (SWI) MRI sequence, counted by two neuroradiologists and categorized by neuroanatomic location. Clinical and laboratory data (most recent measurements before brain MRI). Brain autopsy and cerebrospinal fluid PCR for SARS-CoV 2 in one patient who died from severe COVID-19. RESULTS: Eleven of 16 patients (69%) had punctate and linear SWI lesions in the subcortical and deep white matter, and eight patients (50%) had >10 SWI lesions. In 4/16 patients (25%), lesions involved the corpus callosum. Brain autopsy in one patient revealed that SWI lesions corresponded to widespread microvascular injury, characterized by perivascular and parenchymal petechial hemorrhages and microscopic ischemic lesions. CONCLUSIONS AND RELEVANCE: SWI lesions are common in patients with neurological manifestations of severe COVID-19 (coma and focal neurologic deficits). The distribution of lesions is similar to that seen in patients with hypoxic respiratory failure, sepsis, and disseminated intravascular coagulation. Collectively, these radiologic and histopathologic findings suggest that patients with severe COVID-19 are at risk for multifocal microvascular hemorrhagic and ischemic lesions in the subcortical and deep white matter. [**note: from the Mass General Hospital, cerebral microvascular injury in severe COVID-19.** ]
https://www.medrxiv.org/content/10.1101/2020.07.21.20159376v1

- Introduction Several comorbid conditions, have been identified as risk factors in patients with COVID-19. However, there is a dearth of data describing the impact of COVID-19 infection in patients with end-stage renal disease on hemodialysis (ESRD-HD). Methods This retrospective case series analyzed 362 adult patients consecutively hospitalized with confirmed COVID-19 illness between March 12, 2020 and May 13, 2020, at a teaching hospital in the New York City metropolitan area. Primary outcome was severe pneumonia as defined by the World Health Organization. Secondary outcomes were: 1) the Combined Outcome of Acute respiratory distress syndrome or in-hospital Death (COAD), and 2) the need for High-levels of Oxygen supplementation (HiO2). Results Patients with ESRD-HD had lower odds for poor outcomes including severe pneumonia [Odds Ratio (OR) 0.4, Confidence Interval (CI) (0.2-0.9) p=.04], HiO2 [OR 0.3, CI (0.1-0.8) p=.02] and COAD [OR 0.4, CI (0.2-1.05) p=.06], when compared to patients without ESRD. In contrast, higher odds for severe pneumonia, COAD and HiO2 were seen with advancing age. African-Americans were over-represented in the hospitalized patient cohort, when compared to their representation in the community (35% vs 18%). Hispanics had higher odds for severe-illness and HiO2 when compared to Caucasians. Conclusions Patients with ESRD-HD had a milder course of illness with a lower likelihood of severe pneumonia and a lesser need for aggressive oxygen supplementation when compared to patients not on chronic dialysis. This protective effect, might have a pathophysiologic basis and needs to be further explored. [**note: this is an interesting clinical finding in dialysis patients who had milder course of COVID-19 illness. Bittersweet news for end stage renal disease patients in that they are not as likely to experience high COVID-19 morbidity and mortality.**]
https://www.medrxiv.org/content/10.1101/2020.07.22.20159202v1

DRUG DEVELOPMENT

- Dexamethasone, a widely used corticosteroid, has recently been reported as the first drug to increase the survival chances of patients with severe COVID-19. Therapeutic agents, including dexamethasone, are mostly transported through the body by binding to serum albumin. Herein, we report the first structure of serum albumin in complex with dexamethasone. We show that it binds to Drug Site 7, which is also the binding site for commonly used nonsteroidal anti-inflammatory drugs and testosterone, suggesting potentially problematic binding competition. This study bridges structural findings with our analysis of publicly available clinical data from Wuhan and suggests that an adjustment of dexamethasone regimen should be considered for patients affected by two major COVID-19 risk-factors: low albumin levels and diabetes. [**note: this is an intriguing finding regarding vascular transport of dexamethasone. Certain patients my need to have their meds adjusted to account for this.**] https://www.biorxiv.org/content/10.1101/2020.07.21.212704v1
- While some compounds have been already reported to reduce SARS-CoV-2 infection and a handful of monoclonal antibodies (mAbs) have been described that neutralize SARS-CoV-2, there is an urgent need for the development and standardization of assays which can be used in high through-put screening (HTS) settings to identify new antivirals and/or neutralizing mAbs against SARS-CoV-2. Here, we described a rapid, accurate and highly reproducible plaque reduction microneutralization (PRMNT) assay that can be quickly adapted for the identification and characterization of both neutralizing mAbs and antivirals against SARS-CoV-2. Importantly, our MNA is compatible with HTS settings to interrogate large and/or complex libraries of mAbs and/or antivirals to identify those with neutralizing and/or antiviral activity, respectively, against SARS-CoV-2. [**note: another potentially useful screening tool for antibody and durg development.**] https://www.biorxiv.org/content/10.1101/2020.07.22.216648v1
- Dysregulated IL-1 and IL-6 responses have been implicated in the pathogenesis of severe Coronavirus Disease 2019 (COVID-19). Innovative approaches for evaluating the biological activity of these cytokines in vivo are urgently needed to complement clinical trials of therapeutic targeting of IL-1 and IL-6 in COVID-19. We show that the expression of IL-1 or IL-6 inducible transcriptional signatures (modules) reflects the bioactivity of these cytokines in juvenile idiopathic arthritis (JIA) and rheumatoid arthritis, and discerns the effect of therapeutic cytokine blockade in JIA. In COVID-19, elevated expression of IL-1 and IL-6 response modules, but not these cytokines per se, is a feature of disease both in blood and in affected organs. We propose that IL-1 and IL-6 transcriptional response modules can provide a dynamic readout of the activity of these cytokine pathways in vivo, with potential applications for identifying COVID-19 patients who may benefit from IL-1 or IL-6 blocking therapy, and to aid quantification of the biological effects of these treatments. [**note: these London researchers may have a way of evaluating patients who may benefit from IL-1 or IL-6 blocking therapy.** ] https://www.biorxiv.org/content/10.1101/2020.07.22.202275v1
- The 2019 novel coronavirus disease (COVID-19) is the disease that has been identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), but the prophylactic treatment of SARS-CoV-2 is still under investigation. The effective delivery of eukaryotic expression plasmids to the immune system's inductive cells constitutes an essential requirement for the generation of effective DNA vaccines. Here, we have explored the use of Salmonella typhimurium as vehicles to deliver expression plasmids orally. Attenuated Salmonella phoP harboring eukaryotic expression plasmids that encoded spike protein of SARS-CoV-2 was administered orally to

Wistar rats. Rats were immunized orally with Salmonella that carried a eukaryotic expression plasmid once a week for three consecutive weeks. The efficiency of the vaccination procedure was due to the transfer of the expression plasmid from the bacterial carrier to the mammalian host. Evidence for such an event could be obtained in vivo and in vitro. Our results showed that all immunized animals generated humoral immunity against the SARS-CoV-2 spike protein, indicating that a Salmonella-based vaccine carrying the Spike gene can elicit SARS-CoV-2-specific humoral immune responses in rats, and may be useful for the development of a protective vaccine against SARS-CoV-2 infection. [**note: another interesting approach to an oral SARS-CoV-2 vaccine. I got excited seeing that the authors were from Inner Mongolia but alas it is part of China so my hope of having a citation from Mongolian scientists was dashed. Still, kudos for finding yet another vector for vaccine delivery.**]
https://www.biorxiv.org/content/10.1101/2020.07.23.217174v1

- A safe and durable vaccine is urgently needed to tackle the COVID19 pandemic that has infected >15 million people and caused >620,000 deaths worldwide. As with other respiratory pathogens, the nasal compartment is the first barrier that needs to be breached by the SARS-CoV-2 virus before dissemination to the lung. Despite progress at remarkable speed, current intramuscular vaccines are designed to elicit systemic immunity without conferring mucosal immunity. We report the development of an intranasal subunit vaccine that contains the trimeric or monomeric spike protein and liposomal STING agonist as adjuvant. This vaccine induces systemic neutralizing antibodies, mucosal IgA responses in the lung and nasal compartments, and T-cell responses in the lung of mice. Single-cell RNA- sequencing confirmed the concomitant activation of T and B cell responses in a germinal center-like manner within the nasal-associated lymphoid tissues (NALT), confirming its role as an inductive site that can lead to long-lasting immunity. The ability to elicit immunity in the respiratory tract has can prevent the initial establishment of infection in individuals and prevent disease transmission across humans. [**note: and another vaccine for today, this time an intranasal subunit vaccine. So many vaccines and too little time to test them all.**]
https://www.biorxiv.org/content/10.1101/2020.07.23.212357v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- The aim of this study is to understand adaptive immunity to SARS-CoV-2 through the analysis of B cell epitope and neutralizing activity in coronavirus disease 2019 (COVID-19) patients. We obtained serum from thirteen COVID-19 patients. Most individuals revealed neutralizing activity against SARS-CoV-2 assessed by a pseudotype virus-neutralizing assay. The antibody production against the spike glycoprotein (S protein) or receptor-binding domain (RBD) of SARS-CoV-2 was elevated, with large individual differences, as assessed by ELISA. In the analysis of the predicted the linear B cell epitopes, two regions (671-690 aa. and 1146-1164 aa.), which were located in S1 and S2 but not in the RBD, were highly reactive with the sera from patients. In the further analysis of the B cell epitope within the S protein by utilizing a B cell epitope array, a hot spot in the N-terminal domain of the S protein but not the RBD was observed in individuals with neutralizing activity. Overall, the analysis of antibody production and B cell epitopes of the S protein from patient serum may provide a novel target for the vaccine development against SARS-CoV-2. [**note: the immunology data continues to come in at a quick pace! This is a**

**Japanese study showing humoral immunity through B cell epitope analysis.**]
https://www.biorxiv.org/content/10.1101/2020.07.22.212761v1

- We describe the first cases of natural SARS-CoV-2 infection detected in animals in the United States. In March 2020, four tigers and three lions at the Bronx Zoo developed mild respiratory signs. SARS-CoV-2 RNA was detected by rRT-PCR in respiratory secretions and/or feces from all seven affected animals; viral RNA and/or antibodies were detected in their keepers. SARS-CoV-2 was isolated from respiratory secretions or feces from three affected animals; in situ hybridization co-localized viral RNA with cellular damage. Whole genome sequence and haplotype network analyses showed tigers and lions were infected with two different SARS-CoV-2 strains, suggesting independent viral introductions. The source of SARS-CoV-2 infection in the lions is unknown. Epidemiological data and genetic similarities between keeper and tiger viruses indicate human to animal transmission. [**note: YIKES! Even the lions and tigers are not safe from SARS-CoV-2. Animals were likely infected in March when New York was the epicenter of the infection. Symptoms were usually of short duration and not all tigers were infected.**]
https://www.biorxiv.org/content/10.1101/2020.07.22.213959v1
- Long-term antibody responses and neutralizing activities following SARS-CoV-2 infections have not yet been elucidated. We quantified immunoglobulin M (IgM) and G (IgG) antibodies recognizing the SARS-CoV-2 receptor-binding domain (RBD) of the spike (S) or the nucleocapsid (N) protein, and neutralizing antibodies during a period of six months following COVID-19 disease onset in 349 symptomatic COVID-19 patients, which were among the first world-wide being infected. The positivity rate and magnitude of IgM-S and IgG-N responses increased rapidly. High levels of IgM-S/N and IgG-S/N at 2-3 weeks after disease onset were associated with virus control and IgG-S titers correlated closely with the capacity to neutralize SARS-CoV-2. While specific IgM-S/N became undetectable 12 weeks after disease onset in most patients, IgG-S/N titers showed an intermediate contraction phase, but stabilized at relatively high levels over the six months observation period. At late time points the positivity rates for binding and neutralizing SARS-CoV-2-specific antibodies was still over 70%. Taken together, our data indicate sustained humoral immunity in recovered patients who suffer from symptomatic COVID-19, suggesting prolonged immunity. [**note: here is some encouraging data from China on sustained humoral immunity in recovered COVID-19 patients.**]
https://www.medrxiv.org/content/10.1101/2020.07.21.20159178v1

DIAGNOSTIC DEVELOPMENT

- Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 has caused a global pandemics. To facilitate the detection of SARS-CoV-2 infection, various RT-LAMP assays using 19 sets of primers had been developed, but never been compared. We performed comparative evaluation of the 19 sets of primers using 4 RNA standards and 29 clinical samples from COVID-19 patients. Six of 15 sets of primers were firstly identified to have faster amplification when tested with four RNA standards, and were further subjected to parallel comparison with the remaining four primer sets using 29 clinical samples. Among these 10 primer sets, Set-4 had the highest positive detection rate of SARS-CoV-2 (82.8%), followed by Set-10, Set-11, Set-13 and Set-14 (75.9%), and Set-14 showed the fastest amplification speed (< 8.5 minutes), followed by Set-17 (< 12.5 minutes). Based on the overall detection performance, Set-4, Set-10, Set-11, Set-13, Set-14 and Set-17 that target Nsp3, S, S, E, N and N gene regions of SARS-CoV-2, respectively, are

determined to be better than the other primer sets. Two RT-LAMP assays with the Set-14 primers in combination with any one of four other primer sets (Set-4, Set-10, Set-11, and Set-13) are recommended to be used in the COVID-19 surveillance. [**note: from China a comparison of 19 sets of primers in a RT-LAMP assay.**]
https://www.medrxiv.org/content/10.1101/2020.07.22.20159525v1

- Background: Since December 2019, the outbreak of coronavirus disease (COVID-19) has been occurred by novel coronavirus (SARS-CoV-2). The rapid and sensitive immunoassays are urgently demanded for detecting specific antibodies as assistant diagnosis for primary screening of asymptomatic individuals, close contacts,suspected or recovered patients of COIVD-19 during the pandemic period. Methods: The recombinant receptor binding domain of SARS-CoV-2 spike protein (S-RBD) was used as the antigen to detect specific IgM and the mixture of recombinant nucleocapsid phosphoprotein (NP) and S-RBD were used to detect specific IgG by the newly designed quantum-dot lateral flow immunoassay strip (QD-LFIA), respectively. Results: A rapid and sensitive QD-LFIA based portable fluorescence smart-phone system was developed for detecting specific IgM/IgG to SARS-CoV-2 from 100 serum samples of COVID-19 patients and 450 plasma samples from healthy blood donors. Among 100 COVID-19 patients diagnosed with NAT previously, 3 were severe, 35 mild and 62 recovered cases. By using QD-LFIA, 78 (78%) and 99 (99%) samples from 100 COVID-19 patients serum were detected positive for anti-SARS-CoV-2 IgM or IgG, respectively, but only one sample (0.22%) was cross-reactive with S-RBD from 450 healthy blood donor plasmas that were collected from different areas of China. Conclusion: An ultrasensitive and specific QD-LFIA based portable fluorescence smart-phone system was developed fo r detection of specific IgM and IgG to SARS-CoV-2 infection, which could be used for investigating the prevalence or assistant diagnosis of COVID-19 in humans. [**note: WOW, is this way cool technology. I'm unsure why they needed to do this inside a biosafety hood. Presumably testing sera does not create aerosols.**]
https://www.medrxiv.org/content/10.1101/2020.07.21.20159392v1

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2020-07-25

It's Saturday I think; I am beginning to lose track of the days as they all run together. What a better way to celebrate the pandemic than a song from the iconic show Saturday Night Live! Here is a song done by Pete Davidson and Adam Sandler, 'Stuck in the House':
https://www.youtube.com/watch?v=3VubWlYr9Ek

US COVID-19 STATISTICS - **Infection Rate: 1.2%; CFR: 3.5%** (IR no change; CFR no change%; **note:** the CFR for this current outbreak is hovering just above 1%)

I can't give prizes away!!! I offered what I thought was an easy question about a Barcelona youth gathering and other than one answer about not being in Barcelona, nobody seemed to notice *no physical distancing or mask wearing.* They wonder why there is a new outbreak in Catalonia.

YIKES; THIS IS NOT GOOD! According to the Washington Post, FDA reports at least 75 brands of hand sanitizer are contaminated with methanol which can cause blindness and other not so nice things. There is a good reason to DIY hand sanitizer. You know exactly what is going into it. Fortunately, I have enough aloe vera gel and isopropanol to make enough to get me through the pandemic. Parents are

getting furious at how badly the US has botched school reopenings. On our neighborhood listserve, I have seen about a dozen requests for nannies and child care providers from families who have school age children with no school to go to in the fall (our county is only doing remote learning). I'm sure wealthy families will band together and higher teachers for 'one room school homes.' How Governor DeWine and Ohio lost their collective nerve over the mask mandate only to have to reinstate it. A cautionary tale if there ever was one. Here is a feel good story about a black owned nursing home in Baltimore that has had ZERO COVID-19 cases.

CDC issued guidelines to prepare K-12 school administrators for a safe return to school this fall. Robert Redfield, the CDC director, noted that schools in COVID-19 hot spots will have a difficult decision to make. St. Andrew's Episcopal School, the Maryland private academy that Trump's 14-year-old son Barron Trump attends, told families this week they should prepare for an all-distance or hybrid-learning model in the fall.

Sarah Zhang looks at the vaccine landscape in The Atlantic.

JAMA have an intriguing report from The Netherlands on four young males (age range 21-32) with no history of major chronic disease. All required mechanical ventilation upon getting COVID-19. In this case series of 4 young male patients with severe COVID-19, rare putative loss-of-function variants of X-chromosomal *TLR7* were identified that were associated with impaired type I and II IFN responses. These preliminary findings provide insights into the pathogenesis of COVID-19. We need more of this type of genetic analysis to get at the bottom of why some individuals progress to severe COVID-19. HERE is an accompanying editorial.

The Lancet has this review of particle sizes of infectious aerosols. It is perhaps the most thorough review of the topic and well worth downloading and reading! There is a good viewpoint article on the need for sustainable biobanking networks for COVID-19 and other diseases of epidemic potential. [**note: I've seen so many papers using data from the UK Biobank. It just makes sense to set up more of these.**] I have linked to a paper on serology testing of UK healthcare workers in the diagnostics section below. There is a commentary on this issue suggesting a need to do serology testing but proceeding with care. Readers might also want to look at this World Bank paper on how testing can help contain COVID-19 and revive the economy.

STAT have a commentary on the ethical conundrum of the risk healthcare workers face in treating COVID-19 patients.

Science have a perspective on how mathematical models can guide pandemic response.

Derek Lowe on intellectual property concerns about the Moderna mRNA vaccine.

This blog post and a link to a two page paper is why I think some economists should leave public health issues to the experts and focus on what they know best. I have corresponded with the authors before on a number of issues and while they are well meaning, they seem to lose the big picture.

No rest for the weary newsletter curator today. Lots of modeling papers for a change along with some interesting clinical data.

MODELING

- We screened three separate cohorts of healthcare workers for SARS-CoV-2 via nasopharyngeal swab PCR. A seroprevalence analysis using multiple assays was performed in a subgroup. The asymptomatic health care worker cohorts had a combined positivity rate of 29/5776 (0.50%, 95%CI 0.32-0.75) compared to the symptomatic cohort rate of 54/1597 (3.4%) (ratio of symptomatic to asymptomatic 6.8:1). Sequencing demonstrated several variants. The seroprevalence (n=996) was 1.4-3.4% depending on assay. Protein microarray analysis showed differing SARS-CoV-2 protein reactivities and helped define likely true positives vs. suspected false positives. Routine screening of asymptomatic health care workers helps identify a significant proportion of infections. [**note: this is an observational screening study of asymptomatic healthcare workers in Canada. Infections can be found in these individuals pointing to a conundrum of perhaps inadvertent viral spreading from asymptomatic people.**] https://www.medrxiv.org/content/10.1101/2020.07.21.20159053v1
- Background: There has been very little focus on the individual risk of acquiring COVID-19 related to choir practice. Methods: We report the case of a high transmission rate of SARS-CoV-2 linked to an indoor choir rehearsal in France in March 2020 at the beginning of the COVID-19 pandemic. Results: A total of 27 participants, including 25 male singers, a conductor and an accompanist attended a choir practice on March 12, 2020. The practice was indoor and took place in a non-ventilated space of 45 m2. The mean age of the participants was 66.9 (range 35-86) years. 70% of the participants (19 of 27) were diagnosed with COVID-19 from 1 to 12 days after the rehearsal with a median of 5.1 days. 36% of the cases needed a hospitalization (7/19), and 21% (4/19) were admitted to an ICU. The index cases were possibly multiple. Discussion: The choir practice was planned in March 2020 at a period when the number of new cases of COVID-19 began to grow exponentially in France because SARS-CoV-2 was actively circulating. The secondary rate attack (70%) was much higher than it is described within households (10-20%) and among close contacts made outside households (0-5%). Singing might have contributed to enhance SARS-CoV-2 person-to-person transmission through emission of droplets and aerosolization in a closed non ventilated space with a relative high number of individuals. Conclusions: Indoor choir practice should be suspended during SARS-CoV-2 outbreaks. Further studies are necessary to test the spread of the virus by the act of singing. As the benefits of the barrier measures and social distancing are known to be effective in terms of a reduction in the incidence of the COVID-19, experts recommendations concerning the resuming of choir practice are necessary. [**note: another example of SARS-CoV-2 infection following a choir rehearsal, this time from France. 70% of the participants were infected. No choral rehearsals for this singer.** 😡 ] https://www.medrxiv.org/content/10.1101/2020.07.19.20145326v1
- ISARIC (International Severe Acute Respiratory and emerging Infections Consortium) partnerships and outbreak preparedness initiatives enabled the rapid launch of standardised clinical data collection on COVID-19 in Jan 2020. Extensive global uptake of this resource has resulted in a large, standardised collection of comprehensive clinical data from hundreds of sites across dozens of countries. Data are analysed regularly and reported publicly to inform patient care and public health response. This report is a part of a series and includes the results of data analysis on 8 June 2020. We thank all of the data contributors for their ongoing support. As of 8JUN20, data have been entered for 67,130 patients from 488 sites across 37 countries. For this

report, we show data for 42,656 patients with confirmed disease who were enrolled >14 days prior. This update includes about 2,400 new cases from France, and we thank these collaborators for this significant addition to the dataset. Some highlights from this report The median time from onset of symptoms to hospital admission is 5 days, but a proportion of patients take longer to get to the hospital (average 14.6 days, standard deviation 8.1). COVID-19 patients tend to require prolonged hospitalisation; of the 88% with a known outcome, the median length of admission to death or discharge is 8 days and the mean 11.5. 17% of patients were admitted to ICU/HDU, about 40% of these on the very day of hospital admission. Antibiotics were given to 83% of patients, antivirals to 9%, steroids to 15%, which becomes 93%, 50% and 27%, respectively for those admitted to ICU/HDU. Attention has been called on overuse of antibiotics and need to adhere to antibiotic stewardship principles. 67% of patients received some degree of oxygen supplementation: of these 23.4% received NIV and 15% IMV. This relatively high proportion of oxygen use will have implications for oxygen surge planning in healthcare facilities. Some centres may need to plan to boost capacity to deliver oxygen therapy if this is not readily available. WHO provides operational advice on surge strategy here https://apps.who.int/iris/bitstream/handle/10665/331746/WHO-2019-nCoV-Oxygen_sources-2020.1-eng.pdf [**note: This is a new resource to me. It will be interesting to see how much data gets uploaded.**] https://www.medrxiv.org/content/10.1101/2020.07.17.20155218v1

- In the fight against the COVID-19 pandemic, lockdowns have succeeded in limiting contagions in many countries, at however heavy societal costs: more targeted non-pharmaceutical interventions are desirable to contain or mitigate potential resurgences. Contact tracing, by identifying and quarantining people who have been in prolonged contact with an infectious individual, has the potential to stop the spread where and when it occurs, with thus limited impact. The limitations of manual contact tracing (MCT), due to delays and imperfect recall of contacts, might be compensated by digital contact tracing (DCT) based on smartphone apps, whose impact however depends on the app adoption. *To assess the efficiency of such interventions in realistic settings, we use here datasets describing contacts between individuals in several contexts, with high spatial and temporal resolution, to feed numerical simulations of a compartmental model for COVID-19. We find that the obtained reduction of epidemic size has a robust behavior: this benefit is linear in the fraction of contacts recalled during MCT, and quadratic in the app adoption, with no threshold effect. The combination of tracing strategies can yield important benefits, and the cost (number of quarantines) vs. benefit curve has a typical parabolic shape, independent on the type of tracing, with a high benefit and low cost if app adoption and MCT efficiency are high enough. Our numerical results are qualitatively confirmed by analytical results on simplified models. These results may inform the inclusion of MCT and DCT within COVID-19 response plans.* [**note: this is from a group of European researchers and looks at manual and digital contact tracing. Using both in combination can result in improved efficiencies.**] https://www.medrxiv.org/content/10.1101/2020.07.24.20159947v1
- Contact tracing is commonly recommended to control outbreaks of COVID-19, but its effectiveness is unclear. This systematic review aimed to examine contact tracing effectiveness in the context of COVID-19. Methods: Following PRISMA guidelines, MEDLINE, Embase, Global Health, and All EBM Reviews were searched using a range of terms related to contact tracing for COVID-19. Articles were included if they reported on the ability of contact tracing to slow or stop the spread of COVID-19 or on characteristics of effective tracing efforts. Two investigators

screened all studies. Results: A total of 33 articles were found. All were observational or modelling studies, so the quality of the evidence was low. Overall, 15 out of 15 observational studies (100%) and 16 out of 18 (89%) modelling studies reported that contact tracing (alone or in combination with other interventions) was associated with better control of COVID-19. Under assumptions of prompt and thorough tracing with no further transmission, modelling studies found that contact tracing could stop an outbreak (e.g. by reducing the reproduction number from 2.2 to 0.57) or reduce infections (e.g. by 24%-71% with a mobile tracing app). Under assumptions of slower, less efficient tracing, modelling studies suggested that tracing could slow, but not stop COVID-19. Conclusions: Observational and modelling studies suggest that contact tracing is associated with better control of COVID-19. Its effectiveness likely depends on a number of factors, including how many and how fast contacts are traced and quarantined, and how effective quarantines are at preventing further transmission. A cautious interpretation suggests that to stop the spread of COVID-19, public health practitioners have 2-3 days from the time a new case develops symptoms to isolate the case and quarantine at least 80% of its contacts, and that once isolated, cases and contacts should infect zero new cases. Less efficient tracing may slow, but not stop, the spread of COVID-19. Inefficient tracing (with delays of 4-5+ days or less than 60% of contacts quarantined without further transmission) may not contribute meaningfully to control of COVID-19. [**note: no big surprises from this systematic review of contact tracing. You either do it robustly or just forget about it and let nature take its course.**] https://www.medrxiv.org/content/10.1101/2020.07.23.20160234v1

- Thousands of school systems have been struggling with the decisions about how to safely and effectively deliver education during the fall semester of 2020, amid the COVID19 pandemic. The objective of this study is to evaluate the public health impact of reopening schools on the spread of COVID19. An agent-based simulation model was adapted and used to project the number of infections and deaths under multiple school reopening dates and scenarios, including different cohorts receiving in-person instruction on alternating days, only younger children returning to in-person instruction, regular schedule (all students receiving in-person instruction), and school closure (all students receiving online instruction). The study period was February 18th-November 24th, 2020 and the state of Georgia was used as a case study. Across all scenarios, the number of COVID19-related deaths ranged from approximately 17 to 22 thousand during the study period, and on the peak day, the number of new infections ranged from 43 to 68 thousand. An alternating school day schedule performed: (i) almost as well as keeping schools closed, with the infection attack rate ranging from 38.5% to 39.8% compared to that of 37.7% under school closure; (ii) slightly better than only allowing children 10 years or younger to return to in-person instruction. Delaying the reopening of schools had a minimal impact on reducing infections and deaths under most scenarios. [**note: this school reopening evaluation is from Georgia Tech. There is something weird about the paper and I cannot figure out what it is and don't want to spend any more time on it.**] https://www.medrxiv.org/content/10.1101/2020.07.22.20160036v1
- We consider testing strategies for active SARS-CoV-2 infection for a large university community population, which we define. Components of such a strategy include individuals tested because they self-select or are recommended for testing by a health care provider for their own health care; individuals tested because they belong to a high-risk group where testing serves to disrupt transmission; and, finally, individuals randomly selected for testing from the university

community population as part of a proactive community testing, or surveillance, program. The proactive community testing program is predicated on a mobile device application that asks individuals to self-monitor COVID-like symptoms daily. The goals of this report are (i) to provide a framework for estimating prevalence of SARS-CoV-2 infection in the university community wherein proactive community testing is a major component of the overall strategy, (ii) to address the issue of how many tests should be performed as part of the proactive community testing program, and (iii) to consider how effective proactive community testing will be for purposes of detection of new disease clusters. We argue that a comprehensive prevalence estimate informed by all testing done of the university community is a good metric to obtain a global picture of campus SARS-CoV-2 infection rates at a particular point in time and to monitor the dynamics of infection over time, for example, estimating the population-level reproductive number, R0). Importantly, the prevalence metric can be useful to campus leadership for decision making. One example involves comparing campus prevalence to that in the broader off-campus community. We also show that under some reasonable assumptions, we can obtain valid statements about the comprehensive prevalence by only testing symptomatic persons in the proactive community testing component. The number of tests performed for individual-level and high-risk group-level needs will depend on the disease dynamics, individual needs, and testing availability. For purposes of this report, we assume that, for these groups of individuals, inferential precision --- that is, the accuracy with which we can estimate the true prevalence from testing a random sample of individuals --- does not drive decisions on the number of tests. On the other hand, for proactive community testing, the desired level of inferential precision {in a fixed period of time can be used to justify the number of tests to perform {in that period. For example, our results show that, if we establish a goal of ruling out with 98\% confidence a background prevalence of 2\% {in a given week, and the actual prevalence is 1\% among those eligible for proactive community testing, we would need to test 835 randomly-selected symptomatics (i.e., those presenting with COVID-like symptoms) per week via the proactive community testing program in a campus of 80k individuals. In addition to justifying decisions about the number of tests to perform, inferential precision can formalize the intuition that testing of symptomatic individuals should be prioritized over testing asymptomatic individuals in the proactive community testing program. [**note: from Univ of Texas at Austin a model for testing at a large university. I'll leave this one to all the university presidents to read.**] https://www.medrxiv.org/content/10.1101/2020.07.23.20160788v1

- This paper assesses the age specificity of the infection fatality rate (IFR) for COVID-19. Our benchmark meta-regression synthesizes the age-specific IFRs from four recent large-scale seroprevalence studies conducted in Belgium, Geneva, Spain, and Sweden. The estimated IFR is close to zero for children and younger adults but rises exponentially with age, reaching about 0.3 percent for ages 50-59, 1 percent for ages 60-69, 4 percent for ages 70-79, and 24 percent for ages 80 and above. We compare those predictions to the age-specific IFRs computed using recent seroprevalence studies of six U.S. geographical areas, three countries that have engaged in comprehensive tracking and tracing of COVID-19 infections, and three small-scale seroprevalence studies. We also review more than 30 other seroprevalence studies whose design was not well-suited for estimating age-specific IFRs. *Our findings indicate that COVID-19 is not just dangerous for the elderly and infirm but also for healthy middle-aged adults, for whom the fatality rate is roughly 50 times greater than the risk of dying in an automobile accident.*

*Consequently, the overall IFR for a given location is intrinsically linked to the age-specific pattern of infections. In a scenario where the U.S. infection rate reaches nearly 30%, our analysis indicates that protecting vulnerable age groups could prevent over 200,000 deaths*. [**note: this model uses seroprevalence studies to imput age-specific IFRs. Note the risk of healthy middle-aged adults. It is not just the old and infirm who are at risk.**]
https://www.medrxiv.org/content/10.1101/2020.07.23.20160895v1

- Abstract Importance Several parameters driving the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remain unclear, including age-specific differences in infectivity and susceptibility, and the contribution of inapparent infections to transmission. Robust estimates of key time-to-event distributions remain scarce as well. Objective Illustrate SARS-CoV-2 transmission patterns and risk factors, and estimate key time-to-event distributions. Design, Setting, and Participants Individual-based data on 1,178 SARS-CoV-2 infected individuals and their 15,648 contacts identified by contact tracing monitoring over the period from January 13-April 02, 2020 were extracted from the notifiable infectious diseases reporting system in Hunan Province, China. Demographic characteristics, severity classification, exposure and travel history, and key clinical timelines were retrieved. Exposures Confirmed SARS-CoV-2 infection by positive polymerase chain reaction test result of respiratory samples, and exposure to SARS-CoV-2 infected individuals via household, relative, social, and other types of contacts. Main Outcomes and Measures The relative contribution of pre-symptomatic and asymptomatic transmission, key time-to-event parameters, and the effect of biological, demographic, and behavioral factors on SARS-CoV-2 infectivity and susceptibility were quantified. Results Among SARS-CoV-2 infected individuals, the estimated mean serial interval was 5.5 days (95%CI -5.0, 19.9) and the mean generation time was 5.5 days (95%CI 1.7, 11.6). Infectiousness was estimated to peak 1.8 days before symptom onset, with 95% of transmission events occurring between -7.6 days and 7.3 days from the date of symptom onset. The proportion of pre-symptomatic transmission was estimated at 62.5%, while a lower bound for the proportion of asymptomatic transmission was 3.5%. Infectiousness of SARS-CoV-2 was not significantly different between working-age adults (15-59 years old) and other age groups (0-14 years old: p-value=0.16; 60 years and over: p-value=0.33), whilst susceptibility to SARS-CoV-2 infection was estimated to increase with age (p-value=0.03). In addition, transmission risk was higher for household contacts (p-value<0.001), but decreased in later generations of a cluster (second generation: OR=0.13, p-value<0.001; generations 3-4: OR=0.05, p-value<0.001, relative to generation 1) and for those exposed to infectors with a larger number of contacts (p-value=0.04). Conclusions and Relevance These findings support the contribution of children to transmission and the importance of pre-symptomatic transmission, in turn highlighting the importance of large-scale testing, contact tracing activities, and the use of personnel protective equipment during the COVID-19 pandemic. [**note: good data from Hunan province in China on infectivity and susceptibility. Transmission risk was higher in household contacts supporting the contribution of children to this. I guess if one sends their kids to school the should build a separate '[tiny house](#)' for them to live in while the pandemic continues. ]**
https://www.medrxiv.org/content/10.1101/2020.07.23.20160317v1
- As severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spreads, the susceptible subpopulation declines causing the rate at which new infections occur to slow down. Variation in individual susceptibility or exposure to infection exacerbates this effect. Individuals that are

more susceptible or more exposed tend to be infected and removed from the susceptible subpopulation earlier. This selective depletion of susceptibles intensifies the deceleration in incidence. Eventually, susceptible numbers become low enough to prevent epidemic growth or, in other words, the herd immunity threshold is reached. Here we fit epidemiological models with inbuilt distributions of susceptibility or exposure to SARS-CoV-2 outbreaks to estimate basic reproduction numbers (R_0) alongside coefficients of individual variation (CV) and the effects of containment strategies. Herd immunity thresholds are then calculated as 1-(1⁄R_0 )^(1⁄((1+〖CV〗^2 ) )) or 1-(1⁄R_0 )^(1⁄((1+〖2CV〗^2 ) )), depending on whether variation is on susceptibility or exposure. Our inferences result in herd immunity thresholds around 10-20%, considerably lower than the minimum coverage needed to interrupt transmission by random vaccination, which for R_0 higher than 2.5 is estimated above 60%. We emphasize that the classical formula, 1-1⁄R_0 , remains applicable to describe herd immunity thresholds for random vaccination, but not for immunity induced by infection which is naturally selective. These findings have profound consequences for the governance of the current pandemic given that some populations may be close to achieving herd immunity despite being under more or less strict social distancing measures. [**note: this is the lowest value for herd immunity that I have seen. I guess we can use New York City as a test case here since serology testing show some areas to have had much higher levels of infection.**]
https://www.medrxiv.org/content/10.1101/2020.07.23.20160762v1

- There is limited information on the effect of age on the transmission of SARS-CoV-2 infection in different settings. We undertook a review of published data/studies on detection of SARS-CoV-2 infection in contacts of COVID-19 cases, as well as serological studies, and studies of infections in the school setting to examine those issues. Those sources suggest significantly lower susceptibility to infection for children aged under 10 years compared to adults, for elevated susceptibility to infection in adults aged over 60y, and for the risk of SARS-CoV-2 infection associated with sleeping close to an infected individual. Those sources also suggest that younger adults (particularly those aged under 35y) often have high rates of SARS-CoV-2 infection in the community. Additionally, there is evidence of robust spread of SARS-CoV-2 in high schools, and more limited spread in primary schools. Some countries with relatively large class sizes in primary schools (e.g. Chile and Israel) reported sizeable outbreaks in some of those schools, though the amount of transmission occurring in these schools (vs. outside) is not clear from current reports. Nonetheless, these reports suggest that classroom crowding and other factors related to social distancing in classrooms/schools may play a role in the spread of SARS-CoV-2 in primary schools. Those findings should have implications for school openings in different age groups of children, and they suggest the need to better protect adults over the age of 60 during the community spread of SARS-CoV-2. [**note: another useful paper for school board members to read while they are deciding what to do about opening. Israel opened the schools only to see viral outbreaks.**] https://www.medrxiv.org/content/10.1101/2020.07.19.20157362v1

NEWLY REGISTERED CLINICAL TRIALS

- Did not read today.

CLINICAL TRIAL RESULTS

- This virus can cause a disease that ranges in spectrum from asymptomatic to severe respiratory disease with multiorgan failure, and the most severe cases are associated with some comorbidities and patient age. However, there are patients who do not have those risk factors who still develop serious disease. In this study, we identified the presence of other respiratory viruses in positive cases of COVID-19 in Mexico to determine if any coinfections were correlated with more severe manifestations of COVID-19. We analysed 103 confirmed cases of COVID-19 using RT-qPCR for the detection of 16 other respiratory viruses.Of the cases analysed, 14 (13.6%) were cases of coinfection, and 92% of them never required hospitalization, even when comorbidities and advanced age were involved. There were not significant differences between the presence of comorbidities and the mean ages of the groups. These results suggest that coinfection is not related to more severe COVID-19 and that, depending on the virus involved, it could even lead to a better prognosis. We believe that our findings may lay the groundwork for new studies aimed at determining the biological mechanism by which this phenomenon occurs and for proposing corresponding strategies to limit the progression to severe cases of COVID-19. [**note: this is quite intriguing. These Mexican researchers found a small subgroup who were coinfected with another respiratory virus and did not progress to severe COVID-19. One patient coinfected with influenza A required hospitalization and later died. This could just be coincident or perhaps an already mounted immune response. Further data is needed from other regions.**] https://www.medrxiv.org/content/10.1101/2020.07.22.20159400v1
- Samples for diagnostic tests for SARS-CoV-2 can be obtained from the upper (nasopharyngeal/oropharyngeal swabs) or lower respiratory tract (sputum or tracheal aspirate or broncho-alveolar lavage - BAL). Data from different testing sites indicates different rates of positivity. Reverse-transcriptase polymerase chain reaction (RT-PCR) allows for semi-quantitative estimates of viral load as time to crossing threshold (Ct) is inversely related to viral load. Objectives The objective of our study was to evaluate SARS-CoV2 RNA loads between paired nasopharyngeal (NP) and deep lung (endotracheal aspirate or BAL) samples from critically ill patients. Methods SARS-CoV-2 RT-PCR results were retrospectively reviewed for 51 critically ill patients from 5 intensive care units in 3 hospitals ; Addenbrookes Hospital Cambridge (3 units), Royal Papworth Cambridge (1 unit), and Royal Sunderland Hospital (1 unit). At the times when paired NP and deep lung samples were obtained, one patient had been on oxygen only, 6 patients on non-invasive ventilation, 18 patients on ECMO, and 26 patients mechanically ventilated. Results Results collected showed significant gradient between NP and deep lung viral loads. Median Ct value was 29 for NP samples and 24 for deep lung samples. Of 51 paired samples, 16 were negative (below limit of detection) on NP swabs but positive (above limit of detection) on deep lung sample, whilst 2 were negative on deep sample but positive on NP (both patients were on ECMO). Conclusions It has been suggested that whilst SARS-CoV1 tends to replicate in the lower respiratory tract, SARS-CoV2 replicates more vigorously in the upper respiratory tract. These data challenge that assumption. These data suggest that viral migration to, and proliferation in, the lower respiratory tract may be a key factor in the progression to critical illness and the development of severe acute respiratory syndrome (SARS). *Factors which promote this migration should be examined for association with severe COVID-19. From a practical point of view, patients with suspected severe COVID-19 should have virological samples obtained from the lower respiratory tract where-ever possible, as upper respiratory samples have a significant negative rate.* [**note: this study shows a differential gradient in paired**

**nasopharngyl testing versus deep lung samples. They looked at 51 severely ill patients and found this could be a manifestation of severe COVID-19. It would be nice to understand the mechanism of migration if that can ever be found.**]
https://www.medrxiv.org/content/10.1101/2020.07.19.20156869v1

- Objectives: There is a lack of clarity regarding the role of angiotensin receptor blockers (ARB) or angiotensin converting enzyme inhibitors (ACEi) in interfering with the SARS-COV-2 binding on human cells and the resulting change in disease severity. We sought to assess the risk of hospitalization for COVID-19 and serious complications in current users of ARB or ACEi compared to users of dihydropyridine calcium channel blockers (dhpCCB). Design: Cohort study Setting: The analysis used de-identified, patient-level data from HealthVerity, linking longitudinal data from US medical and pharmacy claims, which contain information on inpatient or outpatient diagnoses, procedures and medication dispensing. Participants: We identified patients aged 40+ and free of chronic kidney disease (CKD) who were newly diagnosed COVID-19, between March 1, 2020 and May 30, 2020, and adherent to ACEi, ARB, or dhpCCB therapy. Interventions: Current use of an ACEi, ARB, or dhpCCB. Main outcome measures: We compared the 30-day risk of hospitalization for COVID-19 and serious complications. Results: Of 24,708 patients identified, 7,571 were current users of an ARB, 8,484 of an ACEi, and 8,653 of a dhpCCB. The unadjusted 30-day risk of hospitalization for COVID-19 was 2.66% among ARB users, and 2.90% among ACEi users and 3.68% in dhpCCB users. In the PS-matched cohort, the risk of hospitalization among ARB users was 17% lower as compared to dhpCCB (RR=0.83; 0.68-1.00), and the risk among ACE users was 10% lower as compared to dhpCCB (RR=0.90; 0.76-1.07). When including patients with pre-existing CKD, the protective effect of ARB (RR= 0.74; 0.62-0.88) and ACEi (RR=0.84; 0.71-0.99) was more pronounced. Conclusions: This cohort study showed that neither ARB nor ACEi use increase the risk of severe COVID-19 disease among those infected, and instead suggests that current use of ARB may offer a protective effect. This study found no evidence to support the discontinuation of ARB/ACEi therapy. [**note: this is a large cohort study of ACEi/ARG blockers from a commercially insured database. Findings aresimilar to other studies that the drugs do not increase risk. The interesting finding is this is the first study I've seen that shows ARBs may offer a protective effect against hospitalization! We need more observational datq.**]
https://www.medrxiv.org/content/10.1101/2020.07.22.20159855v1
- To investigate the immune status of people who previously had COVID-19 infections, we recruited patients 2 weeks post-recovery and analyzed circulating cytokines and lymphocyte subsets. We measured levels of total lymphocytes, CD4+ T cells, CD8+ T cells, CD19+ B cells, CD56+ NK cells, and the serum concentrations of interleukin (IL)-1, IL-4, IL-6, IL-8, IL-10, transforming growth factor beta (TGF-β), tumor necrosis factor alpha (TNF-α), and interferon gamma (IFN-γ) by flow cytometry. We found that in most post-recovery patients, levels of total lymphocytes (66.67%), CD3+ T cells (54.55%), CD4+ T cells (54.55%), CD8 + T cells (81.82%), CD19+ B cells (69.70%), and CD56+ NK cells(51.52%) remained lower than normal, whereas most patients showed normal levels of IL-2 (100%), IL-4 (80.88%), IL-6 (79.41%), IL-10 (98.53%), TNF-α (89.71%), IFN-γ (100%) and IL-17 (97.06%). Compared to healthy controls, 2-week post-recovery patients had significantly lower absolute numbers of total lymphocytes, CD3+ T cells, CD4+ T cells, CD8+ T cells, CD19+ B cells, and CD56+ NK cells, along with significantly higher levels of IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ and IL-17. Among post-recovery patients, T cells, particularly

CD4+ T cells, were positively correlated with CD19+ B cell counts. Additionally, CD8+ T cells positively correlated with CD4+ T cells and IL-2 levels, and IL-6 positively correlated with TNF-α and IFN-γ. These correlations were not observed in healthy controls. By ROC curve analysis, post-recovery decreases in lymphocyte subsets and increases in cytokines were identified as independent predictors of rehabilitation efficacy. These findings indicate that the immune system has gradually recovered following COVID-19 infection; however, the sustained hyper-inflammatory response for more than 14 days suggests a need to continue medical observation following discharge from the hospital. *Longitudinal studies of a larger cohort of recovered patients are needed to fully understand the consequences of the infection*. [**note: I have not seen a report such as this one that tracks post-recovery cytokine cascade markers. I agree with the final sentence about the need for larger studies here.**]
https://www.medrxiv.org/content/10.1101/2020.07.22.20160259v1

- Background Given that a substantial proportion of the subgroup of COVID-19 patients that face a severe disease course are younger than 60 years, it is critical to understand the disease-specific characteristics of young COVID-19 patients. Risk factors for a severe disease course for young COVID-19 patients and possibly non-linear influences remain unknown. Methods Data of COVID-19 patients with clinical outcome in a designated hospital in Wuhan, China, collected retrospectively from Jan 24th to Mar 27th, were analyzed. Clinical, demographic, treatment and laboratory data were collected from patients' medical records. Uni- and multivariable analysis using logistic regression and random forest, with the latter allowing the study of non-linear influences, were performed to investigate and exploit the clinical characteristics of a severe disease course. Results A total of 762 young patients (median age 47 years, interquartile ranges [IQR] 38 - 55, range 16 - 60; 55.9% female) were included, as well as 714 elderly patients as a comparison group. Among the young patients, 362 (47.5%) had a severe/critical disease course and the mean age was significantly higher in the severe subgroup than in the mild subgroup (59.3 vs. 56.0, Student's t-test: $p < 0.001$). The uni- and multivariable analysis suggested that several covariates such as elevated levels of ASS, CRP and LDH, and decreased lymphocyte counts are influential on disease severity independent of age. Elevated levels of complement C3 (odds ratio [OR] 15.6, 95% CI 2.41-122.3; p=0.039) are particularly associated with the risk for the development of severity specifically in young patients, where no such influence seems to exist for elderly patients. Additional analysis suggests that the influence of complement C3 in young patients is independent of age, gender, and comorbidities. Variable importance values and partial dependence plots obtained using random forests delivered additional insights, in particular indicating non-linear influences of risk factors on disease severity. Conclusion In young patients with COVID-19, the levels of complement C3 correlated with disease severity and tended to be a good predictor of adverse outcome. [**note: more data from Wuhan, this time on younger patients. Elevated levels of complement C3 are correlated with disease severity.**]
https://www.medrxiv.org/content/10.1101/2020.07.24.20161414v1
- Background Reports of Guillain-Barre Syndrome (GBS) have emerged during the Coronavirus Disease 2019 (COVID-19) pandemic. This epidemiological and cohort study sought to investigate any causative association between COVID-19 infection and GBS. Methods The epidemiology of GBS cases reported via the UK National Immunoglobulin Database were studied from 2016-2019 and compared to cases reported during the COVID-19 pandemic. For the cohort study, members of the British Peripheral Nerve Society reported all cases of GBS during the pandemic. The

clinical features, investigation findings and outcomes of COVID-19 (definite or probable) and non-COVID-19 associated GBS cases were compared. Results The UK GBS incidence from 2016-2019 was 1.65-1.88 per 100,000 people per year. GBS and COVID-19 incidence varied between regions and did not correlate (r = 0.06, 95% CI -0.56 to 0.63, p=0.86). GBS incidence fell between March and May 2020 compared to the same months of 2016-2019. Forty-seven GBS cases were included in the cohort study (13 definite, 12 probable COVID-19 and 22 non-COVID-19). There were no significant differences in the pattern of weakness, time to nadir, neurophysiology, CSF findings or outcome. Intubation was more frequent in the COVID-19+ve cohort (7/13, 54% vs 5/22, 23% in COVID negative) thought to be related directly to COVID-19 pulmonary involvement. Conclusions This study finds no epidemiological or phenotypic clues of SARS-CoV-2 being causative of GBS. GBS incidence has fallen during the pandemic which may be the influence of lockdown measures reducing transmission of GBS inducing pathogens such as Campylobacter jejuni and respiratory viruses. [**note: another bit of good news. There appears to be no increase in Guillain-Barre Syndrome. In fact, GBS incidence has fallen in the UK.**] https://www.medrxiv.org/content/10.1101/2020.07.24.20161471v1

DRUG DEVELOPMENT

- There are currently no approved effective treatments for SARS-CoV-2, the virus responsible for the COVID-19 pandemic. Nanobodies are 12-15 kDa single-domain antibody fragments that are more stable and amenable to large-scale production compared to conventional antibodies. Nanobodies can also be administered in an inhaled form directly to the lungs. We have isolated several nanobodies that bind to the SARS-CoV-2 spike protein receptor binding domain and block spike protein interaction with the angiotensin converting enzyme 2 (ACE2) receptor. The SARS-CoV-2 spike protein is responsible for viral entry into human cells via interaction with ACE2 on the cell surface. The lead therapeutic candidate, NIH-CoVnb-112, binds to the SARS-CoV-2 spike protein receptor binding domain at approximately 5 nM affinity, and blocks spike protein interaction with the human ACE2 receptor at approximately 0.02 micrograms/mL EC50 (1.1 nM). The affinity and blocking potency of NIH-CoVnb-112 are substantially better than previously reported candidate nanobody therapeutics for SARS CoV-2, and bind to a distinct site. Furthermore, NIH-CoVnb-112 blocks interaction between ACE2 and several high affinity variant forms of the spike protein. When multimerized or combined with other nanobodies, the effective affinity and blocking interactions may be even more potent, as has been well described for other nanobody therapeutics. These resulting nanobodies have therapeutic, preventative, and diagnostic potential. [**note: another paper on nanobodies. I have yet to see any clinical trials.**] https://www.biorxiv.org/content/10.1101/2020.07.24.219857v1
- A novel STING agonist CDGSF unilaterally modified with phosphorothioate and fluorine was synthesized. CDGSF displayed better STING activity over dithio CDG. Immunization of SARS-CoV-2 Spike protein with CDGSF as an adjuvant elicited an exceptional high antibody titer and a robust T cell response, which were better than the group using aluminium hydroxide as a adjuvant. These results highlighted the adjuvant potential of STING agonist in SARS-CoV-2 vaccine preparation for the first time. [**note: a potential new adjuvant for SARS-CoV-2 vaccines.**] https://www.biorxiv.org/content/10.1101/2020.07.24.217570v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- The SARS-CoV-2 Spike protein acquired a D614G mutation early in the COVID-19 pandemic that appears to confer on the virus greater infectivity and now globally is the dominant form of the virus. Certain of the current vaccines entering phase 3 trials are based on the early D614 form of Spike with the goal of eliciting protective neutralizing antibodies. To determine whether D614G mediates neutralization-escape that could compromise vaccine efficacy, sera from Spike-immunized mice, nonhuman primates and humans were evaluated for neutralization of pseudoviruses bearing either D614 or G614 Spike on their surface. In all cases, G614 Spike pseudovirions were moderately more susceptible to neutralization, indicating this is not an escape mutation that would impede current vaccines. Rather, the gain in infectivity provided by D614G came at the cost of making the virus more vulnerable to neutralizing antibodies. [**note: this is very good news!! The D614G mutation that arose early on looks like not to be an escape mutation and in fact may be more vulnerable to neutralizing antibodies.**] https://www.medrxiv.org/content/10.1101/2020.07.22.20159905v1

DIAGNOSTIC DEVELOPMENT

- Health-care workers constitute a high-risk population for acquisition of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Capacity for acute diagnosis via PCR testing was limited for individuals with mild to moderate SARS-CoV-2 infection in the early phase of the COVID-19 pandemic and a substantial proportion of health-care workers with suspected infection were not tested. We aimed to investigate the performance of point-of-care and laboratory serology assays and their utility in late case identification, and to estimate SARS-CoV-2 seroprevalence. We did a prospective multicentre cohort study between April 8 and June 12, 2020, in two phases. Symptomatic health-care workers with mild to moderate symptoms were eligible to participate 14 days after onset of COVID-19 symptoms, as per the Public Health England (PHE) case definition. Health-care workers were recruited to the asymptomatic cohort if they had not developed PHE-defined COVID-19 symptoms since Dec 1, 2019. In phase 1, two point-of-care lateral flow serological assays, the Onsite CTK Biotech COVID-19 split IgG/IgM Rapid Test (CTK Bitotech, Poway, CA, USA) and the Encode SARS-CoV-2 split IgM/IgG One Step Rapid Test Device (Zhuhai Encode Medical Engineering, Zhuhai, China), were evaluated for performance against a laboratory immunoassay (EDI Novel Coronavirus COVID-19 IgG ELISA kit [Epitope Diagnostics, San Diego, CA, USA]) in 300 samples from health-care workers and 100 pre-COVID-19 negative control samples. In phase 2 (n=6440), serosurveillance was done among 1299 (93·4%) of 1391 health-care workers reporting symptoms, and in a subset of asymptomatic health-care workers (405 [8·0%] of 5049). There was variation in test performance between the lateral flow serological assays; however, the Encode assay displayed reasonable IgG sensitivity (127 of 136; 93·4% [95% CI 87·8–96·9]) and specificity (99 of 100; 99·0% [94·6–100·0]) among PCR-proven cases and good agreement (282 of 300; 94·0% [91·3–96·7]) with the laboratory immunoassay. By contrast, the Onsite assay had reduced sensitivity (120 of 136; 88·2% [95% CI 81·6–93·1]) and specificity (94 of 100; 94·0% [87·4–97·8]) and agreement (254 of 300; 84·7% [80·6–88·7]). Five (7%) of 70 PCR-positive cases were negative across all assays. Late changes in lateral flow serological assay bands were recorded in 74 (9·3%) of 800 cassettes (35 [8·8%] of 400 Encode assays; 39 [9·8%] of 400 Onsite assays), but only seven (all Onsite assays) of these changes were concordant with the laboratory immunoassay. In phase 2, seroprevalence among the workforce was estimated to be 10·6% (95% CI 7·6–13·6) in asymptomatic health-care

workers and 44·7% (42·0–47·4) in symptomatic health-care workers. Seroprevalence across the entire workforce was estimated at 18·0% (95% CI 17·0–18·9). *Although a good positive predictive value was observed with both lateral flow serological assays and ELISA, this agreement only occurred if the pre-test probability was modified by a strict clinical case definition. Late development of lateral flow serological assay bands would preclude postal strategies and potentially home testing. Identification of false-negative results among health-care workers across all assays suggest caution in interpretation of IgG results at this stage; for now, testing is perhaps best delivered in a clinical setting, supported by government advice about physical distancing*. [**note: this is a rigorous evaluation of how point of care serological tests can be used to test a defined population. In this case it is healthcare workers and there are caveats about false negatives.**]
https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30315-5/fulltext#seccestitle10

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2020-07-26

For this reflection Sunday let us have a good time with some fine jazz. Here are icons Ron Carter and Hank Jones live in Kobe Japan with a varied supporting cast. Carter has played bass on an amazing 2221 recording sessions and Jones was part of a great musical family that included brothers Elvin (drummer with John Coltrane) and trumpeter Thad (who headed up a great band with Mel Lewis at the Village Vanguard for a lot of years. I heard them one time live and it was memorable). Here is the concert to enjoy and think: https://www.youtube.com/watch?v=93o0IlbWCLw&t=3580s I always find good jazz conducive to meditation.

The New York Times has another story on how senior management of some small vaccine companies are profiting from stock options even if they never commercialize a product. Let's hope the SEC is looking into this. Should you care if your COVID-19 antibodies are disappearing? Probably not.

The Washington Post has a lengthy story about how politics governed Florida's response to the recent outbreak. I am totally baffled why any television station(s) would want to broadcast a propaganda piece about a baseless conspiracy theory that Tony Fauci helped create the coronavirus.

The Guardian has a story on the fragmented and uncoordinated US clinical trial effort. There are some pointed comments from Oxford's Martin Landray who helped set up the UK RECOVERY trial. This accurate observation does not give me any pleasure. Starr county in Texas has one hospital whose capacity is overtaxed and they are forced to set up "death panels' to decide which patients it can save and which ones will be sent home to die.

Jeez Louise, another morning of busy reading. Some good clinical results are slowing emerging including the first paper I've seen on intravenous immunoglobulin.

MODELING

- Cross-reactivity to SARS-CoV-2 from previous exposure to endemic coronaviruses (eHCoV) is gaining increasing attention as a possible driver of both protection against infection and severity of COVID-19 disease. Here, we use a stochastic individual-based model to show that

heterogeneities in individual exposure histories to endemic coronaviruses are able to explain observed age patterns of hospitalisation due to COVID-19 in EU/EEA countries and the UK, provided there is (i) a decrease in cross-protection to SARS-CoV-2 with the number of eHCoV exposures and (ii) an increase in potential disease severity with number of eHCoV exposures or as a result of immune senescence. We also show that variation in health care capacity and testing efforts is compatible with country-specific differences in hospitalisation rates. Our findings call for further research on the role of cross-reactivity to endemic coronaviruses and highlight potential challenges arising from heterogeneous health care capacity and testing. [**note: we need to know more about exposure to endemic coronaviruses and their impact on immunity to SARS-CoV-2**] https://www.medrxiv.org/content/10.1101/2020.07.23.20154369v1

- Background: COVID-19 has heterogeneous manifestations, though one of the most common symptoms is a sudden loss of smell (anosmia or hyposmia). We investigated whether olfactory loss is a reliable predictor of COVID-19. Methods: This preregistered, cross-sectional study used a crowdsourced questionnaire in 23 languages to assess symptoms in individuals self-reporting recent respiratory illness. We quantified changes in chemosensory abilities during the course of the respiratory illness using 0-100 visual analog scales (VAS) for participants reporting a positive (C19+; n=4148) or negative (C19-; n=546) COVID-19 laboratory test outcome. Logistic regression models identified singular and cumulative predictors of COVID-19 status and post-COVID-19 olfactory recovery. Results: Both C19+ and C19- groups exhibited smell loss, but it was significantly larger in C19+ participants (mean±SD, C19+: -82.5±27.2 points; C19-: -59.8±37.7). Smell loss during illness was the best predictor of COVID-19 in both single and cumulative feature models (ROC AUC=0.72), with additional features providing no significant model improvement. VAS ratings of smell loss were more predictive than binary chemosensory yes/no-questions or other cardinal symptoms, such as fever or cough. Olfactory recovery within 40 days was reported for ~50% of participants and was best predicted by time since illness onset. Conclusions: As smell loss is the best predictor of COVID-19, we developed the ODoR-19 tool, a 0-10 scale to screen for recent olfactory loss. Numeric ratings ≤2 indicate high odds of symptomatic COVID-19 (10<OR<4), especially when viral lab tests are impractical or unavailable. [**note: there must be 100 authors on this manuscript. This is useful information on smell loss. I have to get busy to get my COVID-19 Scent Strip into production!!!! I need to look for some venture capital funding.**] https://www.medrxiv.org/content/10.1101/2020.07.22.20157263v1
- Background Transmission of COVID-19 from people without symptoms poses considerable challenges to public health containment measures. The distribution of viral loads in individuals with and without symptoms remains uncertain. Comprehensive cross-sectional screening of all individuals in a given setting provides an unbiased way to assess viral loads independent of symptoms, which informs transmission risks. COVID-19 cases initially peaked in Massachusetts in mid-April 2020 before declining through June, and congregate living facilities were particularly affected during this early surge. We performed a retrospective analysis of data from a large public health-directed outbreak response initiative that involved comprehensive screening within nursing homes and assisted living facilities in Massachusetts to compare nasopharyngeal (NP) viral loads (as measured by RT-PCR cycle threshold (Ct) levels) in residents and staff to inform our ability to detect SARS-CoV-2 in individuals with or without symptoms in the population. Methods Between April 9 and June 9, 2020, we tested NP swabs from 32,480 unique individuals comprising staff and residents of the majority of nursing homes and assisted living

facilities in Massachusetts. Under the direction of the MA Department of Public Health (MDPH), symptomatology at the time of sampling and demographic information was provided by each facility for each individual to facilitate reporting to health officials. NP swabs were collected, RNA extracted, and SARS-CoV-2 testing performed using quantitative reverse-transcriptase polymerase chain reaction (qRT-PCR). Results The nursing home and assisted living facilities resident cohort (N =16,966) was 65% female with a mean age of 82 years (SD 13 yrs). The staff cohort (N = 15,514) was 76% female with a median age of 45 (SD 15 yrs). A total 2654 residents (15.5%) and 624 staff (4.1%) tested positive for SARS-CoV-2. 12.7% of residents and 3.7% of staff without symptoms tested positive for SARS-CoV-2, compared to 53.1% of residents and 18.2% of staff with symptoms. Of the individuals who tested positive, 70.8% of residents and 92.4% of staff lacked symptoms at the time of testing. In aggregate, the distributions of Cts for viral probes used in the qRT-PCR assay were very similar, with a statistically but not meaningfully different mean (ΔCt 0.71 cycles, $p = 0.006$) and a similar range (12-38 cycles), between populations with and without symptoms over the entire time period, across all sub-categories examined (age, race, ethnicity, sex, resident/staff). Importantly, the Ct mean values and range were indistinguishable between the populations by symptom class during the peak of the outbreak in Massachusetts, with a Ct gap appearing only later in the survey period, reaching >3 cycles ($p \leq 0.001$) for facilities sampled during the last two weeks of the study. Conclusions In a large cohort of individuals screened for SARS-CoV-2 by qRT-PCR, we found strikingly similar distributions of viral load in patients with or without symptoms at the time of testing during the local peak of the epidemic; as the epidemic waned, individuals without symptoms at the time of testing had lower viral loads. The size of the study population, including both staff and residents spanning a wide range of ages, provides a comprehensive cross-sectional point prevalence measurement of viral burden in a study spanning 2 months. Because the distributions of viral loads in infected individuals irrespective of symptomatology are very similar, existing testing modalities that have been validated for detection of SARS-CoV-2 RNA in symptomatic patients should perform similarly in individuals without symptoms at the time of testing. [**note: this is a pretty exhaustive testing of nursing and assisted living facilities in Massachusetts at the height of the outbreak. Useful data about infection levels.**]
https://www.medrxiv.org/content/10.1101/2020.07.20.20157792v1

- The zoonotic spillover of the pandemic SARS-coronavirus 2 (SARS-CoV-2) from an animal reservoir, currently presumed to be the Chinese horseshoe bat, into a naive human population has rapidly resulted in a significant global public health emergency. Worldwide circulation of SARS CoV-2 in humans raises the theoretical risk of reverse zoonosis events with wildlife, reintroductions of SARS-CoV-2 into permissive non-domesticated animals, potentially seeding new host reservoir species and geographic regions in which bat SARS-like coronaviruses have not historically been endemic. Here we report that North American deer mice (Peromyscus maniculatus) and some closely related members of the Cricetidae family of rodents possess key amino acid residues within the angiotensin-converting enzyme 2 (ACE2) receptor known to confer SARS-CoV-2 spike protein binding. Peromyscus rodent species are widely distributed across North America and are the primary host reservoirs of several emerging pathogens that repeatedly spill over into humans including Borrelia burgdorferi, the causative agent of Lyme disease, deer tick virus, and Sin Nombre orthohantavirus, the causative agent of hantavirus pulmonary syndrome (HPS). We demonstrate that adult deer mice are susceptible to SARS-CoV-

2 infection following intranasal exposure to a human isolate, resulting in viral replication in the upper and lower respiratory tract with little or no signs of disease. Further, shed infectious virus is detectable in nasal washes, oropharyngeal and rectal swabs, and viral RNA is detectable in feces and occasionally urine. We further show that deer mice are capable of transmitting SARS-CoV-2 to naive deer mice through direct contact. The extent to which these observations may translate to wild deer mouse populations remains unclear, and the risk of reverse zoonosis and/or the potential for the establishment of Peromyscus rodents as a North American reservoir for SARS-CoV-2 is unknown. Nevertheless, efforts to monitor wild, peri-domestic Peromyscus rodent populations are likely warranted as the SARS-CoV-2 pandemic progresses. [**note: I am sure that more animals will show up to be potential reservoirs for SARS-CoV-2. Look and you shall find. It's unclear whether this will represent a transmission vector.**]
https://www.biorxiv.org/content/10.1101/2020.07.25.221291v1

NEWLY REGISTERED CLINICAL TRIALS

- Disulfiram a safe, easily dosed, FDA-approved drug for the treatment of alcohol dependence has been identified to be a potential therapeutic target for SARS-CoV-2 infection. Disulfiram may have both antiviral (inhibiting viral replication via blocking the Mpro protease and zinc ejection) and anti-inflammatory effects (via inhibition of NF-kB-induced and NLRP inflammasome-induced cytokine release) on SARS-CoV-2. We will test disulfiram 2000 mg/day for 3 consecutive days (doses shown to be well tolerated and safe in a recent phase 2b trial) in 60 symptomatic COVID PCR+ individuals in a randomized (1:1) clinical trial evaluating the effect on COVID symptoms severity, SARS-CoV-2 viral load, and biomarkers of inflammation over 31 days. [**note: a big shout out to this research group for the innovative acronym for this trial: DISulfiram for COvid-19 → DISCO. Despite the great name for the trial, it still will not change my mind about selecting a disco-era music selection**.] NCT04485130
- Present study examined the efficacy and safety of one of the recommended Ayurveda drug (Guduchi Ghan Vati) compared with standard care for patients with asymptomatic Covid-19 patients. [**note: this is a trial from India and it was posted today and marked completed. I do not see any results so they must be analyzing the data. The drug is extrraced from the plant genus, Tinospora cordifolia and is a traditional Indian medicine. I cannot find any reference as to the compounds that make up this medicine but this ONE is probably the best.**]
NCT04480398
- The study is a randomized, double-blind, placebo-controlled, dose escalation, multi-center clinical trial (RCT) of SPI-1005 in adult subjects with positive PCR test for novel SARS-CoV-2 (nCoV2) and moderate symptoms of COVID-19 disease. [**note: the compound is ebselen, an organoselenium molecule. The trial sponsor is Sound Pharmaceuticals. The drug is being tested for several medical conditions so why not COVID-19?**] NCT04484025
- Omega-3 Fatty Acids (Omega-3) are long poly unsaturated fatty acids that can be found in plants and fish, its refer to a group composed of three type of fatty acids called: Eicosapentaenoic acid (EPA), Alpha-linoleic acid (ALA), and Docosahexaenoic acid (DHA) . The health promoting effect of n-3FA may be due to immune modulating and anti-inflammatory actions . The anti-inflammatory properties of n-3FA are used for treatment of the inflammatory diseases such as irritable bowel syndrome, rheumatoid arthritis, eczema, and psoriasis . Many studies reported a significant reduction in the risk of cancers in breast, prostate, ovaries with supplementation of

n-3FA (Larsson et al. 2004) .However, high-doses omega-3 supplements such as 1000 mg/day are widely spread in community pharmacies in Jordan . Currently , community pharmacy around the world are facing the challenge of increased demand for care of uninfected people with Covid -19. Accordingly , the current randomized clinical trial was designed to evaluate the effect of daily 300 mg of omega 3-FA supplements on the immune health status of uninfected people with Covid-19 as a part of as a part of preventive health care . Therefore , this RCT aims to assess whether regular daily dose of regular daily dose of omega 3-FA (300 mg) for 2 months supplementation against COVID-19 infection as a part of preventive treatment protocol in uninfected Jordanian peoples. The investigators hypothesize that the regular dose of omega 3-FA (300 mg) /day for 2 months will significantly change immune responses compared with the control group. [**note: why not try this? It is a trial from Amman, Jordan**] NCT04483271

CLINICAL TRIAL RESULTS

- Background Managing discharged COVID-19 (DC) patients with recurrent positive (RP) SARS-CoV-2 RNA test results is challenging. We aimed to comprehensively characterize the viral RNA level and serum antibody responses in RP-DC patients and evaluate their viral transmission risk. Methods A population-based observational cohort study was performed on 479 DC patients discharged from February 1 to May 5, 2020 in Shenzhen, China. We conducted RT-qPCR, antibody assays, neutralisation assays, virus isolation, whole genome sequencing (WGS), and epidemiological investigation of close contacts. Findings Of 479 DC patients, the 93 (19%) RP individuals, including 36 with multiple RP results, were characterised by young age (median age: 34 years, 95% confidence interval [CI]: 29-38 years). The median discharge-to-RP length was 8 days (95% CI: 7-14 days; maximum: 90 days). After readmission, RP-DC patients exhibited mild (28%) or absent (72%) symptoms, with no disease progression. The viral RNA level in RP-DC patients ranged from 1.9-5.7 log10 copies/mL (median: 3.2, 95% CI: 3.1-3.5). At RP detection, the IgM, IgG, IgA, total antibody, and neutralising antibody (NAb) seropositivity rates in RP-DC patients were 38% (18/48), 98% (47/48), 63% (30/48), 100% (48/48), and 91% (39/43), respectively. Regarding antibody levels, there was no significant difference between RP-DC and non-RP-DC patients. The antibody level remained constant in RP-DC patients pre- and post-RP detection. Virus isolation of nine representative specimens returned negative results. WGS of six specimens yielded only genomic fragments. No clinical symptoms were exhibited by 96 close contacts of 23 RP-DC patients; their viral RNA (96/96) and antibody (20/20) test results were negative. After full recovery, 60% of patients (n=162, 78 no longer RP RP-DC and 84 non-RP-DC) had NAb titres of ≥1:32. Interpretation RP may occur in DC patients following intermittent and non-stable excretion of low viral RNA levels. RP-DC patients pose a low risk of transmitting SARS-CoV-2. An NAb titre of ≥1:32 may provide a reference indicator for evaluating humoral responses in COVID-19 vaccine clinical trials. [**note: this is a useful paper from China that looks at discharged patients with recurrent positive SARS-CoV-2 RNA tests. It is still unclear whether viable virus exists in these individuals.**]
  https://www.medrxiv.org/content/10.1101/2020.07.21.20125138v1
- Background Interleukin-6 (IL-6)-mediated hyperinflammation may contribute to the high mortality of coronavirus disease 2019 (Covid-19). Tocilizumab, an IL-6 receptor blocking monoclonal antibody, has been repurposed for Covid-19, but prospective trials and dose-finding studies in Covid-19 are lacking. Methods We conducted a phase 2 trial of low-dose tocilizumab

in hospitalized adult patients with Covid-19, radiographic pulmonary infiltrate, fever, and C-reactive protein (CRP) >= 40 mg/L who did not require mechanical ventilation. Dose cohorts were determined by a trial Operations Committee, stratified by CRP and epidemiologic risk factors. A range of doses from 40 to 200 mg (low-dose tocilizumab) was evaluated, with allowance for one repeat dose at 24-48 hours. The primary objective was to assess the relationship of dose to fever resolution and CRP response. Outcomes were compared with retrospective controls with Covid-19. Correlative studies evaluating host antibody response were performed in parallel. Findings A total of 32 patients received low-dose tocilizumab. This cohort had improved fever resolution (75.0% vs. 34.2%, p = 0.001) and CRP decline (86.2% vs. 14.3%, p < 0.001) in the 24-48 hours following drug administration, as compared to the retrospective controls (N=41). The probabilities of fever resolution or CRP decline did not appear to be dose-related in this small study (p=0.80 and p=0.10, respectively). Within the 28-day follow-up, 5 (15.6%) patients died. For patients who recovered, median time to clinical recovery was 3 days (IQR, 2-5). Clinically presumed and/or cultured bacterial superinfections were reported in 5 (15.6%) patients. Correlative biological studies demonstrated that tocilizumab-treated patients produced anti-SARS-CoV-2 antibodies comparable to controls. Interpretation Low-dose tocilizumab was associated with rapid improvement in clinical and laboratory measures of hyperinflammation in hospitalized patients with Covid-19. Results of this trial and its correlative biological studies provide rationale for a randomized, controlled trial of low-dose tocilizumab in Covid-19. [**note: small numbers again in this trial. As with other tocilizumab trials this one shows efficacy.**]
https://www.medrxiv.org/content/10.1101/2020.07.20.20157503v1

- Background Effective antiviral therapy against the severe acute respiratory syndrome virus 2 (SARS-CoV-2) remains elusive. Convalescent plasma is an anti-viral approach currently under investigation. We aimed to assess the laboratory and clinical parameters of patients with COVID-19 pneumonia treated with convalescent plasma containing high levels of neutralizing anti-SARS-CoV-2 antibodies. [**note: I really hate abstracts that don't tell you the conclusion to the story! You need to read the paper to find out that convalescent sera did help in shortening symptoms and is likely a viable therapeutic approach. Of course it would be nice if someone was organizing a centralized database to aggregate and analyze such trial data but perhaps that is too much to ask.**] https://www.medrxiv.org/content/10.1101/2020.07.20.20156398v1
- Background Current strategies for preventing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections are limited to non-pharmacological interventions. Hydroxychloroquine (HCQ) has been proposed as a postexposure therapy to prevent Coronavirus disease 2019 (Covid-19) but definitive evidence is lacking. Methods We conducted an open-label, cluster-randomized trial including asymptomatic contacts exposed to a PCR-positive Covid-19 case in Catalonia, Spain. Clusters were randomized to receive no specific therapy (control arm) or HCQ 800mg once, followed by 400mg daily for 6 days (intervention arm). The primary outcome was PCR-confirmed symptomatic Covid-19 within 14 days. The secondary outcome was SARS-CoV-2 infection, either symptomatically compatible or a PCR-positive result regardless of symptoms. Adverse events (AEs) were assessed up to 28 days. Results The analysis included 2,314 healthy contacts of 672 Covid-19 index cases identified between Mar 17 and Apr 28, 2020. A total of 1,198 were randomly allocated to usual care and 1,116 to HCQ therapy. There was no significant difference in the primary outcome of PCR-confirmed, symptomatic Covid-19 disease (6.2% usual

care vs. 5.7% HCQ; risk ratio 0.89 [95% confidence interval 0.54-1.46]), nor evidence of beneficial effects on prevention of SARS-CoV-2 transmission (17.8% usual care vs. 18.7% HCQ). The incidence of AEs was higher in the intervention arm than in the control arm (5.9% usual care vs 51.6% HCQ), but no treatment-related serious AEs were reported. Conclusions *Postexposure therapy with HCQ did not prevent SARS-CoV-2 disease and infection in healthy individuals exposed to a PCR-positive case. Our findings do not support HCQ as postexposure prophylaxis for Covid-19.* [**note: get the stakes out to kill this Zombie drug. I wonder if the big Duke study is even getting enrolled these days.**]
https://www.medrxiv.org/content/10.1101/2020.07.20.20157651v1

- Background: This study is the first of its kind to assess the impact of preemptive therapeutic dose anticoagulation on mortality compared to prophylactic anticoagulation among COVID-19 patients. Its findings provide insight to clinicians regarding the management of COVID-19, particularly with the known prothrombotic state. Research Question: To determine the impact of anticoagulation on in-hospital mortality among COVID-19 positive patients with the a priori hypothesis that there would be a lower risk of in-hospital mortality with use of preemptive therapeutic over prophylactic dose enoxaparin or heparin. Study Design and Methods: Study Design: Retrospective cohort study from April 1 - April 25, 2020. The date of final follow-up was June 12, 2020. Setting: Two large, acute care hospitals in Western Connecticut. Participants: Five hundred and one inpatients were identified after discharge as 18 years or older and positive for SARS-CoV-2. The final sample size included 374 patients after applying exclusion criteria. Demographic variables were collected via hospital billing inquiries, while the clinical variables were abstracted from patients medical records. Exposure: Preemptive enoxaparin or heparin at a therapeutic or prophylactic dose. Main Outcome: In-hospital mortality. Results: When comparing preemptive therapeutic to prophylactic anticoagulation through multi-variable analysis, risk of in-hospital mortality was 2.3 times greater in patients receiving preemptive therapeutic anticoagulation (95% CI = 1.0, 4.9; p = 0.04). Interpretation: An increase in in-hospital mortality was observed with preemptive therapeutic anticoagulation. Thus, in the management of COVID-19 and its complications, we recommend further research and cautious use of preemptive therapeutic over prophylactic anticoagulation. [**note: clearly use of anticoagulants needs to be carefully thought out. In this hospital setting preemptive therapy led to worse outcomes.**] https://www.medrxiv.org/content/10.1101/2020.07.20.20147769v1
- Background. Interventions mitigating progression to mechanical ventilation in COVID-19 would markedly improve outcome and reduce healthcare utilization. We hypothesized that immunomodulation with IVIG would improve oxygenation and reduce length of hospital stay and progression to mechanical ventilation in COVID-19 pneumonia. Methods. Patients with COVID-19 were randomized 1:1 to prospectively receive standard of care (SOC) plus intravenous immunoglobulin (IVIG) 0.5 g/kg/day x 3 days with methylprednisolone 40 mg 30 minutes before infusion versus SOC alone. Results. 16 subjects received IVIG plus SOC and 17 SOC alone. The median age was 51 years for SOC and 58 years for IVIG. APACHE II scores and Charlson comorbidity indices were similar for IVIG and SOC (median 7.5 vs 7 and 2 for both, respectively). Seven SOC versus 2 IVIG subjects required mechanical ventilation (p=0.12, Fisher exact test). Among subjects with A-a gradient of >200 mm Hg at enrollment, the IVIG group showed i) a lower rate of progression to requiring mechanical ventilation (2/14 vs 7/12, p=0.038 Fisher exact test), ii) shorter median hospital length of stay (11 vs 19 days, p=0.01 Mann Whitney U), iii)

shorter median ICU stay (2.5 vs 12.5 days, p=0.006 Mann Whitey U), and iv) greater improvement in PaO2/FiO2 at 7 days (median [range] change from time of enrollment +131 [+35 to +330] vs +44.5 [-115 to +157], p=0.01, Mann Whitney-U test) than SOC. Conclusion. This pilot prospective randomized study comprising largely of Latino patients showed that IVIG significantly improved hypoxia and reduced hospital length of stay and progression to mechanical ventilation in COVID-19 patients with A-a gradient >200 mm Hg. [**note: this is the first paper that I have seen that looks at intravenous immunoglobulin. It looks like this is a viable treatment for COVID-19 pneumonia.**]
https://www.medrxiv.org/content/10.1101/2020.07.20.20157891v1

DRUG DEVELOPMENT

- Infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiological agent of coronavirus disease 2019 (COVID-19), may elicit uncontrolled and damaging inflammatory reactions, due to an excessive immune response and dysregulated production of cytokines and chemokines. Thus, it is critical to identify compounds able to inhibit virus replication and thwart the excessive inflammatory reaction and tissue lesions secondary to SARS-CoV-2 infection. Here, we show that the neuropeptides VIP and PACAP, molecules endowed with immunoregulatory properties, were able to inhibit SARS-CoV-2 RNA synthesis/replication in human monocytes and viral production in lung epithelial cells. VIP and PACAP protected these cells from virus-induced cytopathicity, and reduced the production of proinflammmatory mediators. VIP and PACAP prevented the SARS-CoV-2-induced NF-kB activation, which is critically involved in the production of inflammatory mediators, and promoted CREB activation, a transcription factor with antiapoptotic activity and also a negative regulator of NF-kB, in infected monocytes. By imparing this signaling loop, VIP and PACAP prevented NF-kB-dependent production of proinflammatory cytokines. As a possible host response to control patient inflammation, we identified that VIP levels were elevated in plasma from patients with severe forms of COVID-19, correlating with the inflammatory marker CRP and survival on those patients. Since a synthetic form of VIP is clinically approved in Europe and under two clinical trials for patients with COVID-19, our results provide the scientific evidence to further support clinical investigation of these neuropeptides against COVID-19. [**note: there are a couple of trials with VIP going on!**]
https://www.biorxiv.org/content/10.1101/2020.07.25.220806v1
- The current COVID-19 pandemic has claimed hundreds of thousands of lives and its causative agent, SARS-CoV-2, has infected millions, globally. The highly contagious nature of this respiratory virus has spurred massive global efforts to develop vaccines at record speeds. In addition to enhanced immunogen delivery, adjuvants may greatly impact protective efficacy of a SARS-CoV-2 vaccine. To investigate adjuvant suitability, we formulated protein subunit vaccines consisting of the recombinant S1 domain of SARS-CoV-2 Spike protein alone or in combination with either CoVaccine HTTM or Alhydrogel. CoVaccine HTTM induced high titres of antigen-binding IgG after a single dose, facilitated affinity maturation and class switching to a greater extent than Alhydrogel and elicited potent cell-mediated immunity as well as virus neutralising antibody titres. Data presented here suggests that adjuvantation with CoVaccine HTTM can rapidly induce a comprehensive and protective immune response to SARS-CoV-2. [**note: another possible vaccine adjuvant.]** https://www.biorxiv.org/content/10.1101/2020.07.24.220715v1

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters through the airways and infects the lungs, causing lethal pulmonary damage in vulnerable patients. This virus contains spike proteins on its envelope that binds to human angiotensin-converting enzyme 2 (hACE2) expressed on the surface of airway cells, enabling entry of the virus for causing infection. In severe cases, the virus enters the circulatory system, contributing to multiorgan failure. Soluble form of hACE2 binds to SARS-CoV-2 spike protein and prevents viral entry into target cells. Moreover, soluble recombinant ACE2 ameliorates lung injury but its short half-life limits its therapeutic utility. Here, we engineered synthetic mRNA to encode a soluble form of hACE2 (hsACE2) to prevent viral infection. Novel lipid nanoparticles (LNPs) were used to package mRNA and transfect mammalian cells for enhanced production of secreted proteins. Intravenously administered LNP led to hepatic delivery of the mRNA. This elicited secretion of hsACE2 into the blood circulation within 2 h, and levels of circulating hsACE2 peaked at 6 h and gradually decreased over several days. Since the primary site of entry and pathogenesis for SARS-CoV-2 is the lungs, we instilled LNPs into the lungs and were able to detect hsACE2 in the bronchoalveolar lavage fluid within 24 h and lasted for 48 h. Through co-immunoprecipitation, we found that mRNA-generated hsACE2 was able to bind with the receptor binding domain of the SARS-CoV-2 spike protein. Furthermore, hsACE2 was able to strongly inhibit (over 90%) SARS-CoV-2 pseudovirus infection. Our proof of principle study shows that mRNA-based nanotherapeutics can be potentially deployed for pulmonary and extrapulmonary neutralization of SARS-CoV-2 and open new treatment opportunities for COVID-19. [**note: this is an intriguing approach to therapy how long lived is it? There are some trials going on with soluble recombinant ACE2 but I've not seen any data yet.**]
  https://www.biorxiv.org/content/10.1101/2020.07.24.205583v1
- Perfusion of convalescent plasma (CP) has demonstrated a potential to improve the pneumonia induced by SARS-CoV-2, but procurement and standardization of CP are barriers to its wide usage. Heterologous polyclonal antibodies of animal origin have been used to fight against infectious agents and are a possible alternative to the use of CP in SARS-CoV-2 disease. However, heterologous polyclonal antibodies trigger human natural xenogeneic antibody responses particularly directed against animal-type carbohydrate epitopes, mainly the N-glycolyl form of the neuraminic acid (Neu5Gc) and the Gal alpha1,3-galactose (a-Gal), ultimately forming immune complexes and potentially leading to serum sickness or allergy. To circumvent these drawbacks, we engineered animals lacking the cytidine monophosphate-N-acetylneuraminic acid hydroxylase (CMAH) and alpha1,3-galactosyltransferase (GGTA1) enzymes to produce glyco-humanized polyclonal antibodies (GH-pAb) lacking Neu5Gc and a-Gal epitopes. We also found that these IgG Fc domains fail to interact with human Fc receptors and thereby should confer the safety advantage to avoiding macrophage dependent exacerbated inflammatory responses or elicit antibody-dependent enhancement (ADE), two drawbacks possibly associated with antibody responses against SARS-CoV-2. Therefore, we immunized CMAH/GGTA1 double knockout (DKO) pigs with the SARS-CoV-2 spike receptor binding domain (RBD) domain to elicit neutralizing antibodies. Animals rapidly developed hyperimmune sera with end-titers binding dilutions over one to a million and end-titers neutralizing dilutions of 1:10,000. The IgG fraction purified and formulated following clinical Good Manufacturing Practices, named XAV-19, neutralized Spike/ACE-2 interaction at a concentration < 1microgram/mL and inhibited infection of human cells by SARS-CoV-2 in cytopathic assays. These data and the accumulating safety

advantages of using glyco-humanized swine antibodies in humans warrant clinical assessment of XAV-19 to fight against COVID-19. [**note: this is a new approach to antibody production from Xenothera. I am curious about what the production levels are as this could be an alternative to mammalian cell culture.**] https://www.biorxiv.org/content/10.1101/2020.07.25.217158v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

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DIAGNOSTIC DEVELOPMENT

- In order to elucidate novel aspects of the host response to SARS-CoV-2 we performed RNA sequencing on peripheral blood samples across 77 timepoints from 46 subjects with COVID-19 and compared them to subjects with seasonal coronavirus, influenza, bacterial pneumonia, and healthy controls. Early SARS-CoV-2 infection triggers a conserved transcriptomic response in peripheral blood that is heavily interferon-driven but also marked by indicators of early B-cell activation and antibody production. Interferon responses during SARS-CoV-2 infection demonstrate unique patterns of dysregulated expression compared to other infectious and healthy states. Heterogeneous activation of coagulation and fibrinolytic pathways are present in early COVID-19, as are IL1 and JAK/STAT signaling pathways, that persist into late disease. Classifiers based on differentially expressed genes accurately distinguished SARS-CoV-2 infection from other acute illnesses (auROC 0.95). The transcriptome in peripheral blood reveals unique aspects of the immune response in COVID-19 and provides for novel biomarker-based approaches to diagnosis. [**note: this is only pertinent to clinical diagnostic approaches to disease management but interesting**]
  https://www.medrxiv.org/content/10.1101/2020.07.20.20155507v1
- The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected millions of people worldwide. PCR tests are currently the gold standard for diagnosis of the current coronavirus disease (COVID-19) and serology tests are used to detect seroconversion in infected patients. However, there is a lack of quantitative and ultra-sensitive viral antigen tests for COVID-19. Here we show that Single Molecule Array (Simoa) assays can quantitatively detect SARS-CoV-2 spike, S1 subunit, and nucleocapsid antigens in the plasma of COVID-19 patients. Combined with Simoa anti-SARS-CoV-2 serological assays, we show correlation between production of antibodies and clearance of viral antigens from serial plasma samples from COVID-19 patients. Furthermore, we demonstrate the presence of viral antigens in blood correlates with disease severity in hospitalized COVID-19 patients. These data suggest that SARS-CoV-2 viral antigens in the blood could be a marker for severe COVID-19 cases. [**note: here is another useful clinical diagnostic approach looking at viral antigens in blood.**]
  https://www.medrxiv.org/content/10.1101/2020.07.20.20156372v1