2020-11-16

Welcome to Week 35 of the Pandemic Newsletter

Let's do some opera this week (those of you who don't like the art form can skip ahead). We will start off with Bellini's 'I Puritani' a classic bel canto piece. I've featured Bellini before with the classic aria 'Casta Diva' from Norma. Here is the duet A Te, O Cara with Juan Diego Florez and Nino Machaidze. Both singers throw off the high notes with such ease. Enjoy this: https://www.youtube.com/watch?v=MaLJXYQ1jxE

I received a question from a reader yesterday about how the COVID-19 pandemic compares to the yearly flu. Early on, it was said that COVID-19 would not be much different from the flu. This is incorrect as we have sadly seen. CDC keeps good statistics on the flu seasons. Flu epidemics can start in the late fall and are usually over by early March in the US. We also have vaccines, that while imperfect, do offer protection. There are statistics from the UK for the 1957-58 Asian flu epidemic that showed the case fatality rate to be 0.3%. The worst recent US year from the CDC statistics was 2017-18 where the extrapolated CFR was 0.14%. It's still hard to know what the COVID-19 CFR will eventually be because we have such poor data for the number of infections. If we only go by cases that have shown up with a positive test, it's about 10.9M right now. Deaths are 244K. doing the math, the CFR = 2.2% My estimate has been it will settle down to between 0.3-0.6%. Although there are circulating coronaviruses, SARS-CoV-2 is a totally new one where there has been no previous human exposure which has led to increased morbidity and mortality than anything we have seen in the past decades.

More good news from the vaccine front. Moderna reported out interim results from its late stage trial and the vaccine is 94.5% effective. It will be interesting to see how these numbers hold up and what the real-world experience is. mRNA vaccines have the potential to be a game changer in dealing with infectious viruses because of their ease of construction.

The Washington Post notes that experts urge caution in using COVID-19 risk and tracking tools. More on the Moderna vaccine. New Zealand believes that meat exports are not contaminated with COVID-19. I also find this hard to believe. I am glad that I renewed my drivers license last summer!

The New York Times reports on doctors and nurses retiring early because of the pandemic. My orthopedist is one of them. Saville Row tailors are adapting to the pandemic, though I wonder what the future really is for business attire if the trend to remote work remains. I still have some business suits that have not been warn in several years. Toni Fauci gets it right! It is a problem that the Trump COVID-19 team is not cooperating with the Biden team. Here is another report on the Moderna vaccine.

STAT continues with the excitement about the Moderna vaccine. Here is an opinion piece on a plan for COVID-19 home testing. Base it on reason and not speculation! The two authors had experience in developing home HIV test kits that were never approved.

Nature has an interesting piece on what COVID-19 forecasters can learn from climate models. Methods that are routine in computation-heavy fields could lead to more reliable pandemic predictions.

As is usual for Monday, there is hardly anything worth mentioning on the preprint servers.

MODELING

- Nothing New

NEWLY REGISTERED CLINICAL TRIALS

- You got your wish yesterday!

CLINICAL TRIAL RESULTS

- Nothing New

DRUG DEVELOPMENT

- Nothing New

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Nothing New

DIAGNOSTIC DEVELOPMENT

- Nothing New

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2020-11-17

What do opera singers do in the midst of a pandemic? As members of the Israel Opera show, they sing from home! Here is a funny send up of Libiamo from Verdi's La Traviata. Here is hoping for rapid vaccine deployment so we can go back to live performances ASAP. Enjoy this one: https://www.youtube.com/watch?v=KcLZnkPppbM

Some of my readers have recently asked about what types of vaccines will be available and which ones they should take. I will not recommend any one vaccine as we only have data on large trails from two candidates right now both of which are the new mRNA vaccines by Pfizer/BioNTech and Moderna. Each showed 90% protection in large trials. I was pleasantly surprised at this as I was expecting maybe something about 70%. We should be hearing from AstraZeneca who are partnering with Oxford on their Adenovirus vector vaccine. Johnson & Johnson and Novavax are also in large scale trials but maybe a month behind as is Sanofi. If the subsequent vaccines come in with similar data that would be great as the supply of vaccine would be high enough for the US populace by the middle of 2021. Pfizer have already announced that they will be handling distribution of their vaccine as it requires ultra-cold temperatures. The others will be distributed through Operation Warp Speed but I haven't looked into how the logistics will be handled other than that CVS and Walgreens have already been announced as partners in this effort. It is still unclear who will be first in line to be vaccinated. I am interested in looking at the data for those over 60 as that's the demographic I am in. Recent vaccines have used immune boosting adjuvants in vaccine preparations that help with old folk's lessened immune systems. Of the vaccines under development only Novavax and the Sanofi/GSK vaccines are taking this approach and Novavax animal studies have shown very high antibody levels. Perhaps it is not needed if the various vectored vaccines provide an adjuvant-like boost. Assuming the efficacy data for subsequent vaccines are the same, one should feel comfortable in terms of being protected. One big unknown is whether there are any unique safety issues associated with a particular vaccine. At present none of the trial data indicates that this is the case. We will learn a lot from all these efforts so when the next

pandemic comes, the vaccine industry will be ready with a prompt response. I view this whole effort as amazing given the long time period for traditional vaccine development.

The National Academy of Medicine and the American Public Health Association will host a webinar on COVID-19 vaccine update this Wednesday. More information on this and to register is at: https://www.covid19conversations.org/

The New York Times reports on efforts in some states to give added scrutiny to a COVID-19 vaccine. This is a waste of time and taxpayer money. The FDA review process will be thorough, addressing both safety and efficacy. There is NOTHING these state-based scientists can bring to the table. Here is a longer article on the Moderna vaccine. You can always get updates on vaccine development from the NYT vaccine tracker.

The Washington Post has advice for eating outdoors in cold weather.

The New Yorker's Michael Specter discusses state approvals of COVID-19 vaccines.

Former CDC Director, Tom Frieden, points out that we know the way to beat COVID-19.

Derek Lowe has information on the Moderna vaccine.

STAT look at the vaccine landscape in light of the data from Pfizer and Moderna.

Kaiser Health News have a report on the increase of student enrollment in public health programs. This is a good sign.

MODELING

- The high proportion of transmission events derived from asymptomatic or presymptomatic infections make SARS-CoV-2, the causative agent in COVID-19, difficult to control through the traditional non-pharmaceutical interventions (NPIs) of symptom-based isolation and contact tracing. As a consequence, many US universities are developing asymptomatic surveillance testing labs, to augment existing NPIs and control outbreaks on campus. We built a stochastic branching process model of COVID-19 dynamics at UC Berkeley to advise optimal control strategies in a university environment. Our model combines behavioral interventions in the form of group size limits to deter superspreading, symptom-based isolation, and contact tracing, with asymptomatic surveillance testing. We find that behavioral interventions offer a cost-effective means of epidemic control: group size limits of twelve or fewer greatly reduce superspreading, and rapid isolation of symptomatic infections can halt rising epidemics, depending on the frequency of asymptomatic transmission in the population. *Surveillance testing can overcome uncertainty surrounding asymptomatic infections, with the most effective approaches prioritizing frequent testing with rapid turnaround time to isolation over test sensitivity. Importantly, contact tracing amplifies population-level impacts of all infection isolations, making even delayed interventions effective. Combination of behavior-based NPIs and asymptomatic surveillance also reduces variation in daily case counts to produce more predictable epidemics. Furthermore, targeted, intensive testing of a minority of high transmission risk individuals can effectively control the COVID-19 epidemic for the surrounding population. We offer this blueprint*

and easy-to-implement modeling tool to other academic or professional communities navigating optimal return-to-work strategies for the 2021 year. [**note: I may be wrong but I think this is the first paper I've read with a Nobel Laureate (Jennifer Doudna) as a co-author. This is from Cal Berkeley and offers a control model with asymptomatic testing in a university environment.]** https://www.medrxiv.org/content/10.1101/2020.11.12.20230870v1

- Recent epidemiological studies have investigated the potential effects of childhood immunization history on COVID-19 severity. Specifically, prior exposure to Bacillus Calmette-Guerin (BCG) vaccine, oral poliovirus vaccine (OPV), or measles vaccine have been postulated to reduce COVID-19 severity - putative mechanism is via stimulation of the innate immune system to provide broader protection against non-specific pathogens. While these epidemiological results remain inconclusive, we sought to investigate the potential role of adaptive immunity via cross-reactivity between vaccine preventable diseases (VPDs) with SARS-CoV-2. We implemented a comprehensive exploration of immune homology (including sequence homology, immune epitopes, and glycosylation patterns) between SARS-CoV-2 and all pathogens with FDA-approved vaccines. *Sequence homology did not reveal significant alignments of protein sequences between SARS-CoV-2 with any VPD pathogens, including BCG-related strains. We also could not identify any shared T or B cell epitopes between SARS-CoV-2 and VPD pathogens among either experimentally validated epitopes or predicted immune epitopes. For N-glycosylation (N-glyc), while sites with the same tripeptides could be found between SARS-CoV-2 and certain VPD pathogens, their glycosylation potentials and positions were different. In summary, lack of immune homology between SARS-CoV-2 and VPD pathogens suggests that childhood immunization history (i.e., BCG vaccination or others) does not provide protection from SARS-CoV-2 through adaptive cross-immunity*. [**note: there have been papers arguing that childhood vaccinations offer protection against SARS-CoV-2 through adaptive cross-immunity. This paper argues against this.**] https://www.medrxiv.org/content/10.1101/2020.11.13.20230862v1
- When COVID-19 was detected among passengers on Diamond Princess (DP) cruise ship in the end of January and beginning of February of this year, unfortunately it has become an ideal experimental model for studying the transmission potential of COVID-19 in a closed environment while it is hard to do so in the wider open population. Information collected from such an outbreak is crucial for policy makers to understand and manage the epidemic. To disclose the information such as infection onset time, transmission time, and so on from the available observed incomplete data, we must develop valid statistic models and solid inference methods. Due to the fact that the priority for RT-PCR test for COVID-19 was given to symptomatic and their close contacts and elderly individuals, we have to take this selection bias into considerations in the statistic inference. Based on RT-PCR test data performed on the Diamond Princess cruise, in this paper we propose a novel mixture model where the mixing proportions vary with time to estimate the infection distribution and the total infected individuals after a 14-day of quarantine. Compared with the epidemiologic description of COVID-19 spread in open space, we have found some unique features in the Diamond Princess cruise ship. Our fndings may shed lights on preventing future pandemic outbreaks in cruise ship. [**note: here is a Chinese paper with a model for the outbreak on the Diamond Princess cruise ship.**] https://www.medrxiv.org/content/10.1101/2020.11.14.20230938v1

- The current SARS-CoV-2 pandemic has emphasized the vulnerability of human populations to novel viral pressures, despite the vast array of epidemiological and biomedical tools now available. Notably, modern human genomes contain evolutionary information tracing back tens of thousands of years, which may help identify the viruses that have impacted our ancestors - pointing to which viruses have future pandemic potential. Here, we apply evolutionary analyses to human genomic datasets to recover selection events involving tens of human genes that interact with coronaviruses, including SARS-CoV-2, that started 25,000 years ago. These adaptive events were limited to ancestral East Asian populations, the geographical origin of several modern coronavirus epidemics. An arms race with an ancient corona-like virus may thus have taken place in ancestral East Asian populations. By learning more about our ancient viral foes, our study highlights the promise of evolutionary information to combat the pandemics of the future. [**note: this is an interesting paper that postulates an ancient coronavirus-like epidemic drove adaptation in East Asians several thousand years ago.]**
  https://www.biorxiv.org/content/10.1101/2020.11.16.385401v1
- Human coronaviruses (HCoVs) are mainly associated with respiratory infections. However, there is evidence that highly pathogenic HCoVs, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and Middle East Respiratory Syndrome (MERS-CoV), infect the gastrointestinal (GI) tract and are shed in the fecal matter of the infected individuals. These observations have raised questions regarding the possibility of fecal-oral route as well as foodborne transmission of SARS-CoV-2 and MERS-CoV. Studies regarding the survival of HCoVs on inanimate surfaces demonstrate that these viruses can remain infectious for hours to days, however, to date, there is no data regarding the viral survival on fresh produce, which is usually consumed raw or with minimal heat processing. *To address this knowledge gap, we examined the persistence of HCoV-229E, as a surrogate for highly pathogenic HCoVs, on the surface of commonly consumed fresh produce, including: apples, tomatoes and cucumbers. Herein, we demonstrated that viral infectivity declines within a few hours post-inoculation (p.i) on apples and tomatoes, and no infectious virus was detected at 24h p.i, while the virus persists in infectious form for 72h p.i on cucumbers. The stability of viral RNA was examined by droplet-digital RT-PCR (ddRT-PCR), and it was observed that there is no considerable reduction in viral RNA within 72h p.i.* [**note: here is a paper that looks at the persistence of human coronaviruses on fresh produce. We always wash our fruit and produce prior to eating and I don't view this as a particularly major risk.**]
  https://www.biorxiv.org/content/10.1101/2020.11.16.385468v1
- The University of Arizona utilized wastewater-based epidemiology paired with clinical testing as a surveillance strategy to monitor COVID-19 prevalence in a dormitory community. *Positive SARS-CoV-2 RNA detection in wastewater led to prompt testing of all residents and the identification and isolation of three infected individuals which averted potential disease transmission*. [**note: here is a report from the Univ of Arizona on the implementation of their wastewater surveillance activity.**]
  https://www.medrxiv.org/content/10.1101/2020.11.13.20231340v1

NEWLY REGISTERED CLINICAL TRIALS

- You won't see anything here today.

CLINICAL TRIAL RESULTS

- A disruption of the crosstalk between gut microbiota and the lung (gut-lung axis) has been implicated as a driver of severity during respiratory-related diseases. Lung injury causes systemic inflammation, which disrupts gut barrier integrity, increasing the permeability to gut microbes and their products. This exacerbates inflammation, resulting in positive feedback. *To test the possibility that a disrupted gut contributes to Coronavirus disease 2019 (COVID-19) severity, we used a systems biology approach to analyze plasma from COVID-19 patients with varying disease severity and controls. Severe COVID-19 is associated with a dramatic increase in tight junction permeability and translocation of bacterial and fungal products into blood. This intestinal disruption and microbial translocation correlate strongly with increased systemic inflammation and complement activation, lower gut metabolic function, and higher mortality. Our study highlights a previously unappreciated factor with significant clinical implications, disruption in gut barrier integrity, as a force that contributes to COVID-19 severity*. [**note: this is an interesting finding about disruption in the gut predisposing someone to severe COVID-19.**] https://www.medrxiv.org/content/10.1101/2020.11.13.20231209v1
- The effects of SARS-CoV-2 infection on immune responses during pregnancy have not been systematically evaluated. Objective: To assess the impact of SARS-CoV-2 infection during pregnancy on inflammatory and humoral responses in maternal and fetal samples and compare antibody responses to SARS-CoV-2 among pregnant and non-pregnant women. Design: Immune responses to SARS-CoV-2 were analyzed using samples from pregnant and non-pregnant women who had either tested positive or negative for SARS-CoV-2. We measured, proinflammatory and placental cytokine mRNAs, neonatal Fc receptor (FcRn) receptor expression, and tetanus antibody transfer in maternal and cord blood samples. Additionally, we measured anti-spike (S) IgG, anti-S-receptor binding domain (RBD) IgG, and neutralizing antibody (nAb) responses to SARS-CoV-2 in serum or plasma collected from non-pregnant women, pregnant women, and cord blood. Setting: Johns Hopkins Hospital (JHH) Participants: Pregnant women were recruited through JHH outpatient obstetric clinics and the JHH Labor & Delivery unit. Non-pregnant women were recruited after receiving outpatient SARS-CoV-2 testing within Johns Hopkins Health System, USA. Adult non-pregnant women with positive RT-PCR results for SARS-CoV-2, within the age range of 18-48 years, were included in the study. Exposures: SARS-CoV-2 Main Outcomes and Measures: Participant demographic characteristics, antibody titers, cytokine mRNA expression, and FcRn receptor expression. Results: SARS-COV-2 positive pregnant women expressed more IL1β, but not IL6, in blood samples collected within 14 days versus > 14 days after a confirmed SARS-CoV-2 test, with similar patterns observed in the fetal side of placentas, particularly among asymptomatic pregnant women. *Pregnant women with confirmed SARS-CoV-2 infection also had reduced anti-S-RBD IgG titers and were less likely to have detectable nAb as compared with non-pregnant women. Although SARS-CoV-2 infection did not disrupt FcRn expression in the placenta, maternal transfer of nAb was inhibited by SARS-CoV-2 infection during pregnancy. Conclusions and Relevance: SARS-CoV-2 infection during pregnancy was characterized by placental inflammation and reduced antiviral antibody responses, which may impact the efficacy of COVID-19 therapeutics in pregnancy. The long-term implications of placental inflammation for neonatal health also requires greater consideration*. [**note: here is a study on the effect of SARS-CoV-2 on pregnant women from Johns Hopkins.**] https://www.medrxiv.org/content/10.1101/2020.11.13.20231373v1

DRUG DEVELOPMENT

- Abstract: Previously, we have demonstrated that ACIS KEPTIDE™, a chemically modified peptide, selectively binds to ACE-2 receptor and prevents the entry of SARS-CoV2 virions in vitro in primate kidney Cells. However, it is not known if ACIS KEPTIDE™ attenuates the entry of SARS-CoV2 virus in vivo in lung and kidney tissues, protects health, and prevent death once applied through intranasal route. In our current manuscript, we demonstrated that the intranasal administration of SARS-CoV2 (1*106) strongly induced the expression of ACE-2, promoted the entry of virions into the lung and kidney cells, caused acute histopathological toxicities, and mortality (28%). Interestingly, thirty-minutes of pre-treatment with 50 µg/Kg Body weight ACIS normalized the expression of ACE-2 via receptor internalization, strongly mitigated that viral entry, and prevented mortality suggesting its prospect as a prophylactic therapy in the treatment of COVID-19. On the contrary, the peptide backbone of ACIS was unable to normalize the expression of ACE-2, failed to improve the health vital signs and histopathological abnormalities. *In summary, our results suggest that ACIS is a potential vaccine-alternative, prophylactic agent that prevents entry of SARS-CoV2 in vivo, significantly improves respiratory health and also dramatically prevents acute mortality in K18-hACE2 humanized mice*. [**note: this is a follow up paper on the development of a potential blocking agent for SARS-CoV-2 binding to ACE2.**] https://www.biorxiv.org/content/10.1101/2020.11.13.378257v1
- The Spike protein of SARS-CoV-2 is essential for virus entry into human cells. In fact, most neutralizing antibodies against SARS-CoV-2 are directed against Spike, making it the antigen of choice for use in vaccines and diagnostic tests. In the current pandemic context, global demand for Spike proteins has rapidly increased and could exceed hundreds of grams to kilograms annually. Coronavirus Spikes are large, heavily glycosylated, homo-trimeric complexes, with inherent instability. Their poor manufacturability now threatens the availability of these proteins for vaccines and diagnostic tests. *Here, we outline a scalable, GMP-compliant, chemically defined process for the production of a cell-secreted, stabilized form of the trimeric Spike protein. The process is chemically defined and based on clonal, suspension-CHO cell populations and on protein purification via a two-step, scalable down-stream process. The trimeric conformation was confirmed using electron microscopy and HPLC analysis. Binding to susceptible cells was shown using a virus-inhibition assay. The diagnostic sensitivity and specificity for the detection of serum SARS-CoV-2 specific IgG1 was investigated and found to exceed that of Spike fragments (S1 and RBD). The process described here will enable the production of sufficient, high-quality trimeric Spike protein to meet the global demand for SARS-CoV-2 vaccines and diagnostic tests*. [**note: this is from the Swiss company, ExcellGene.**] https://www.biorxiv.org/content/10.1101/2020.11.15.382044v1
- Herein, we report the discovery of a plant-derived small molecule, 6,8-dihydroxy-9-isobutyl-2,2,4,4-tetramethyl-7-(3-methylbutanoyl)-4,9-dihydro-1H- xanthene-1,3(2H)-dione (rhodomyrtone, RDT), which exhibited potent broad-spectrum antiviral activities against several RNA and DNA viruses, including SARS-CoV-2, respiratory syncytial virus (RSV), herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), varicella-zoster virus (VZV), human cytomegalovirus (HCMV), and Kaposi's sarcoma-associated herpesvirus (KSHV). RDT can significantly suppress viral gene expression and show the low possibility to elicit drug-resistant variants. Mechanistic study implied that RDT inhibited viral infection by disturbing the cellular factors that essential for viral gene expression. Our results suggested that RDT might be a

promising lead compound for the development of broad-spectrum antiviral drugs. [**note: another drug development paper from China. From what I can see in the literature this compound was identified by Dutch scientists back in 2009 as a new antibacterial agent. However, it seems never to have been developed as such. It comes from rose myrtle plants.**] https://www.biorxiv.org/content/10.1101/2020.11.14.382770v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Severe acute respiratory coronavirus 2 (SARS-CoV-2), the agent of the ongoing COVID-19 pandemic, jumped into humans from an unknown animal reservoir in late 2019. In line with other coronaviruses, SARS-CoV-2 has the potential to infect a broad range of hosts. SARS-CoV-2 genomes have now been isolated from cats, dogs, lions, tigers and minks. SARS-CoV-2 seems to transmit particularly well in mink farms with outbreaks reported in Spain, Sweden, the Netherlands, Italy, the USA and Denmark. Genomic data from SARS-CoV-2 isolated from infected minks provides a natural case study of a secondary host jump of the virus, in this case from humans to animals, and occasionally back again. We screened published SARS-CoV-2 genomes isolated from minks for the presence of recurrent mutations common in mink but infrequent in SARS-CoV-2 genomes from human infections. We identify 23 recurrent mutations including three nonsynonymous mutations in the Receptor Binding Domain of the SARS-CoV-2 spike protein that independently emerged at least four times but are only very rarely observed in strains circulating in humans. The repeat emergence of mutations across phylogenetically distinct lineages of the virus isolated from minks points to ongoing adaptation of SARS-CoV-2 to a new host. *The rapid acquisition and spread of SARS-CoV-2 mutations in minks suggests that if a similar phenomenon of host adaptation had occurred upon its jump into humans, those human-specific mutations would likely have reached fixation already before the first SARS-CoV-2 genomes were generated*. [**note: more on mutations of SARS-CoV-2 in minks.**] https://www.biorxiv.org/content/10.1101/2020.11.16.384743v1
- An unaddressed key question in the current coronavirus disease 2019 (COVID-19) pandemic is the duration of immunity for which specific T cell responses against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are an indispensable element. Being situated in Wuhan where the pandemic initiated enables us to conduct the longest analyses of memory T cell responses against SARS-CoV-2 in COVID-19 convalescent individuals (CIs). Magnitude and breadth of SARS-CoV-2 memory CD4 and CD8 T cell responses were heterogeneous between patients but robust responses could be detected up to 9 months post disease onset in most CIs. Loss of memory CD4 and CD8 T cell responses were observed in only 16.13% and 25.81% of CIs, respectively. Thus, the overall magnitude and breadth of memory CD4 and CD8 T cell responses were quite stable and not inversely correlated with the time from disease onset. Interestingly, the only significant decrease in the response was found for memory CD4 T cells in the first 6-month post COVID-19 disease onset. *Longitudinal analyses revealed that the kinetics of SARS-CoV-2 memory CD4 and CD8 T cell responses were quite heterogenous between patients. Loss of memory CD4 T cell responses was observed more frequently in asymptomatic cases than after symptomatic COVID-19. Interestingly, the few CIs in which SARS-CoV-2-specific IgG responses disappeared showed more durable memory CD4 T cell responses than CIs who remained IgG-positive for month. Collectively, we provide the first comprehensive characterization of the long-term memory T cell response in CIs, suggesting that SARS-CoV-2-specific T cell immunity is long-*

lasting in the majority of individuals. [**note: this comes from a research group in Wuhan and is good news on memory T cell response!**]
https://www.biorxiv.org/content/10.1101/2020.11.15.383463v1

- Understanding immune memory to SARS-CoV-2 is critical for improving diagnostics and vaccines, and for assessing the likely future course of the pandemic. We analyzed multiple compartments of circulating immune memory to SARS-CoV-2 in 185 COVID-19 cases, including 41 cases at > 6 months post-infection. Spike IgG was relatively stable over 6+ months. *Spike-specific memory B cells were more abundant at 6 months than at 1 month. SARS-CoV-2-specific CD4+ T cells and CD8+ T cells declined with a half-life of 3-5 months. By studying antibody, memory B cell, CD4+ T cell, and CD8+ T cell memory to SARS-CoV-2 in an integrated manner, we observed that each component of SARS-CoV-2 immune memory exhibited distinct kinetics*. [**note: here is another longevity study on immune system variants from a La Jolla group.**]
https://www.biorxiv.org/content/10.1101/2020.11.15.383323v1

DIAGNOSTIC DEVELOPMENT

- Using the children's toy, ***Shrinky-Dinks©,*** we present an aptamer-based electrochemical (E−AB) assay that recognizes the spike protein of SARS-CoV-2 in saliva for viral infection detection. The low-cost electrodes are implementable at population scale and demonstrate detection down to 0.1 fg mL−1 of the S1 subunit of the spike protein. [**note: OMG!!!!!!!!!!!!!! Shrinky-Dinks!!!!! I remember when my daughters used to create things with these. This gets a big shout out and creativity award from me. DIY for everyone.**]
https://www.medrxiv.org/content/10.1101/2020.11.14.20231811v1

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2020-11-18

After yesterday's pandemic spoof on Verdi's Traviata aria, we will return again to Bellini. I have already covered the famous Casta Diva aria from Norma in a four day September flurry (you can search the Pandemic Music selection document on the website for the links to those). There is a great duet for the two female leads, Mira O Norma. Here we have maybe two of the greatest, Joan Sutherland and Marilyn Horne, from a 1970 television broadcast: https://www.youtube.com/watch?v=GrY66tzzveY Phenomenal singing!!!

I'll continue to keep the *updates on the vaccine front* coming. J&J's chief scientist, Paul Stoffels, noted that they should have 60K people in the trial around the end of the year with an efficacy endpoint possible by the early part of 2021. This is a single dose adenovirus vectored vaccine. Pfizer will seek regulatory review within days. Here is how their vaccine is manufactured and another view. Data on one of the Chinese COVID-19 vaccines has been published. This is the inactivated whole cell vaccine and here is a commentary on this study.

The Washington Post has a very sad story from a South Dakota nurse about COVID-19 deniers. Are there lessons from the 2009 H1N1 flu vaccine program that need to be considered for the coming COVID-19 vaccines? This seems like a no brainer; COVID-19 testing before flying. Airlines should underwrite this ASAP. COVID-19 alert apps are now available in many states. We have downloaded the

one for Maryland onto our Android phones. FDA has just approved a rapid at home COVID-19 test. Here is an analysis of Sweden's COVID-19 strategy.

The New York Times has an op-ed from Emily Oster regarding dealing with people who ignore COVID-19 safety. There is also a piece from Aaron Carroll on the misplaced closing of schools as the first part of a lockdown. For me this is the biggest tragedy in that preparations were not taken by lots of school districts to get this right!! Working women are facing trials and tribulations because of the pandemic. Does remdesivir actual work against COVID-19? I am in the camp with these authors and think that it is not clear. I would put the drug into a broad Treatment IND that would allow Gilead to only recoup costs and not make a profit until a more substantive data package was generated. Immunity to SARS-CoV-2 may last a long time (I linked to the article yesterday); it is the presence of immune cells that we need to focus on.

Here is how Nassau County in New York addressed the first wave of COVID-19.

STAT cover a very important point; the interoperability of electronic health data systems. Excuse me while I pick myself up from the floor after a paroxysm of laughter. This has been a huge issue for the past 20 years and we had some dedicated efforts on this when I was working at PhRMA. Maybe the pandemic will accelerate the need to solve this problem, but I am doubtful.

Medscape have a commentary about whether low-risk supplements should be advised for patients with COVID-19. Here is a commentary on SARS-CoV-2 diagnostics.

MODELING

- Quantitatively describing the time course of the SARS-CoV-2 infection within an infected individual is important for understanding the current global pandemic and possible ways to combat it. *Here we integrate the best current knowledge about the abundance of potential SARS-CoV-2 host cells and typical concentrations of virions in bodily fluids to estimate the total number and mass of SARS-CoV-2 virions in an infected person. We estimate that each infected person carries 10^9-10^{11} virions during peak infection, with a total mass of about 1 µg-0.1 mg, which curiously implies that all SARS-CoV-2 virions currently in the world have a mass of only 0.1-1 kg. Knowledge of the absolute number of virions in an infected individual can put into perspective parameters of the immune system response, minimal infectious doses and limits of detection in testing*. [**note: here is an extrapolation of viral burden in infected individuals.**] https://www.medrxiv.org/content/10.1101/2020.11.16.20232009v1
- Behavioral and life style factors plausibly play a role in likelihood of being hospitalized for COVID-19. Genetic vulnerability to hospitalization after SARS-CoV2 infection may partially relate to comorbid behavioral risk factors, especially the use of combustible psychoactive substances. Paralleling the COVID-19 crisis has been increasingly permissive laws for recreational cannabis use. Cannabis Use Disorder (CUD) is a psychiatric disorder that is heritable and genetically correlated with respiratory disease, independent of tobacco smoking. By leveraging genome-wide association summary statistics of CUD and COVID-19, we find that at least 1/3rd of the genetic vulnerability to COVID-19 overlaps with genomic liability to CUD (rg=.34, p=0.0003). Genetic causality as a potential mechanism of risk could not be excluded. The association between CUD and COVID-19 remained when accounting for genetics of trying marijuana, tobacco smoking (ever smoking regularly, cigarettes per day, smoking cessation, age of smoking

initiation), BMI, fasting glucose, forced expiration volume, education attainment, and Townsend deprivation index. *Heavy problematic cannabis use may increase chances of hospitalization due to COVID-19 respiratory complications. Curbing excessive cannabis use may be an essential strategy in COVID-19 mitigation*. [**note: here is a cautionary warning to heavy users of cannabis.**] https://www.medrxiv.org/content/10.1101/2020.11.15.20229971v1

NEWLY REGISTERED CLINICAL TRIALS

- Look elsewhere!

CLINICAL TRIAL RESULTS

- Importance: Patients with COVID-19 may exhibit 25-hydroxyvitamin D deficiency, but the beneficial effects of vitamin D3 supplementation in this disease remain to be proven by randomized controlled trials. Objective: To investigate the efficacy and safety of vitamin D3 supplementation in patients with severe COVID-19. Design, Setting, and Participants: This is a multicenter, double-blind, randomized, placebo-controlled trial conducted in two centers (a quaternary hospital and a field hospital) in Sao Paulo, Brazil. The trial included 240 hospitalized patients with severe COVID-19. The study was conducted from June 2, 2020 to October 7, 2020. Interventions: Patients were randomly allocated (1:1 ratio) to receive either a single oral dose of 200,000 IU of vitamin D3 or placebo. Main Outcomes and Measures: The primary outcome was hospital length of stay, defined as hospital discharge from the date of randomization or death. Secondary outcomes were mortality, admission to ICU, mechanical ventilation requirement, and serum levels of 25-hydroxyvitamin D, creatinine, calcium, C-reactive protein, and D-dimer. Results: Of 240 randomized patients (mean age, 56 years; 56% men), 232 (96.7%) were included in the primary analysis. Log-rank test showed that hospital length of stay was comparable between the vitamin D3 supplementation and placebo groups (7.0 days [95% CI, 6.1 to 7.9] and 7.0 days [95% CI, 6.2 to 7.8 days]; hazard ratio, 1.12 [95% CI, 0.9 to 1.5]; P = .379; respectively). The rate of mortality (7.0% vs 5.1%; P = .590), admission to ICU (15.8% vs 21.2%; P = .314), and mechanical ventilation requirement (7.0% vs 14.4%; P = .090) did not significantly differ between groups. Vitamin D3 supplementation significantly increased serum 25-hydroxyvitamin D levels compared to placebo (difference, 24.0 ng/mL [95% CI, 21.0% to 26.9%]; P = .001). No adverse events were observed. Conclusions and Relevance: *Among hospitalized patients with severe COVID-19, vitamin D3 supplementation was safe and increased 25-hydroxyvitamin D levels, but did not reduce hospital length of stay or any other relevant outcomes vs placebo. This trial does not support the use of vitamin D3 supplementation as an adjuvant treatment of patients with COVID-19*. [**note: this is the first vitamin D study that I've seen results on. It only covers treatment of hospitalized patients and not those who are taking the vitamin prophylactically. It doesn't work as a direct treatment for COVID-19.**] https://www.medrxiv.org/content/10.1101/2020.11.16.20232397v1

DRUG DEVELOPMENT

- The development of preventive corona virus disease (COVID)-19 vaccines is an urgent need, especially for the aging population that is most affected by the ongoing pandemic. The Janssen Ad26.COV2.S vaccine candidate is currently the only one evaluated as a single dose vaccination regimen in Phase 3 clinical studies. While the advantages of single dose vaccines, especially for

use during a pandemic, are obvious, multiple doses may potentially improve magnitude and durability of immune responses. Here we assessed the immunogenicity of one- and two-dose Ad26.COV2.S vaccine regimens in adult and aged non-human primates (NHP). A second vaccine dose, administered 8 weeks post the first immunization, induced a significant increase in antigen-specific binding and neutralizing antibody responses in both adult and aged animals as compared to a single dose. In addition, in one-dose regimens neutralizing antibody responses were maintained for at least 14 weeks, providing an early indication of durable immune responses elicited by Ad26.COV2.S. *Similar to what we showed previously in adult animals, Ad26.COV2.S vaccination of aged NHP induced a CD8+ T cell response and a Th1 skewed CD4+ T cell response. These data support the initiation of a two-dose Ad26.COV2.S regimen in a Phase 3 clinical trial in adults and elderly*. [**note: here is more data on the Johnson & Johnson vaccine, suggesting that two doses may improve protection. The company has announced they will initiate a parallel trial with a second dose 57 days later.**]
https://www.biorxiv.org/content/10.1101/2020.11.17.368258v1

- Combating the COVID-19 pandemic requires potent and low-cost therapeutics. We identified a novel series of single-domain antibodies (i.e., nanobody), Nanosota-1, from a camelid nanobody phage display library. Structural data showed that Nanosota-1 bound to the oft-hidden receptor-binding domain (RBD) of SARS-CoV-2 spike protein, blocking out viral receptor ACE2. The lead drug possessing an Fc tag (Nanosota-1C-Fc) bound to SARS-CoV-2 RBD with a Kd of 15.7picomolar (~3000 times more tightly than ACE2 did) and inhibited SARS-CoV-2 infection with an ND50 of 0.16microgram/milliliter (~6000 times more potently than ACE2 did). Administered at a single dose, Nanosota-1C-Fc demonstrated preventive and therapeutic efficacy in hamsters subjected to SARS-CoV-2 infection. *Unlike conventional antibody drugs, Nanosota-1C-Fc was produced at high yields in bacteria and had exceptional thermostability. Pharmacokinetic analysis of Nanosota-1C-Fc documented a greater than 10-day in vivo half-life efficacy and high tissue bioavailability. Nanosota-1C-Fc is a potentially effective and realistic solution to the COVID-19 pandemic*. [**note: here is another nanobody paper. I would like to see some human clinical data on these products.**]
https://www.biorxiv.org/content/10.1101/2020.11.17.386532v1
- The Coronavirus disease 2019 (COVID-19) has created an acute worldwide demand for sustained broadband pathogen suppression in households, hospitals, and public spaces. The latest surges in infections have surpassed 125,000 daily new cases in the US, the highest rates of the pandemic. *In response, we have created a rapid-acting, self-sterilizing copper configuration capable of killing SARS-CoV-2 and other microbes in seconds. This highly active conformation destroys pathogens faster than any conventional copper configuration. The material maintains its antimicrobial efficacy over consecutive periods of use and is shelf stable. We have performed rigorous testing in accordance with guidelines from U.S. governing authorities and believe that the material could offer broad spectrum, non-selective defense against most microbes via integration into masks and other protective equipment*. [**note: this is a pretty interesting finding about a form of copper that can deactivate the virus quickly. The company is Kuprion.**]
https://www.biorxiv.org/content/10.1101/2020.11.16.384040v1
- Following the emergence of SARS-CoV-2, the search for an effective and rapidly available treatment was initiated worldwide based on repurposing of available drugs. Previous reports described the antiviral activity of certain tyrosine kinase inhibitors (TKIs) targeting the Abelson

kinase 2 against pathogenic coronaviruses. Imatinib, one of them, has more than twenty years of safe utilization for the treatment of hematological malignancies. In this context, Imatinib was rapidly evaluated in clinical trials against Covid-19. Here, we present the pre-clinical evaluation of Imatinib in multiple models. *Our results indicated that Imatinib and another TKI, the Masitinib, exhibit an antiviral activity in VeroE6 cells. However, Imatinib was inactive in a reconstructed bronchial human airway epithelium model. In vivo, Imatinib therapy failed to impair SARS-CoV-2 replication in a golden Syrian hamster model despite high concentrations in plasma and in the lung. Overall, these results do not support the use of Imatinib and similar TKIs as antivirals in the treatment of Covid-19*. [**note: perhaps tyrosine kinase inhibitors are not a good therapeutic approach.**] https://www.biorxiv.org/content/10.1101/2020.11.17.386904v1

- To evaluate immunization strategies, we made nanoparticles displaying the receptor-binding domain (RBD) of only SARS-CoV-2 (homotypic nanoparticles) or co-displaying the SARS-CoV-2 RBD along with RBDs from animal betacoronaviruses that represent threats to humans (mosaic nanoparticles; 4-8 distinct RBDs). Mice immunized with RBD-nanoparticles, but not soluble antigen, elicited cross-reactive antibody binding and neutralization responses, confirming increased immunogenicity from multimerization. Mosaic-RBD-nanoparticles elicited antibodies with superior cross-reactive recognition of heterologous RBDs compared to sera from immunizations with homotypic SARS-CoV-2-RBD-nanoparticles or antibodies from COVID-19 convalescent human plasmas. Moreover, sera from mosaic-RBD-immunized mice neutralized heterologous pseudotyped coronaviruses equivalently or better after priming than sera from homotypic SARS-CoV-2-RBD-nanoparticle immunizations, demonstrating no loss of immunogenicity against any particular RBD resulting from co-display. *Thus, a single immunization with mosaic-RBD-nanoparticles provides a potential strategy to simultaneously protect against SARS-CoV-2 and emerging zoonotic coronaviruses.* [**note: this is from Cal Tech and uses a different approach to elicit neutralizing antibodies.**] https://www.biorxiv.org/content/10.1101/2020.11.17.387092v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Bat coronavirus (CoV) RaTG13 shares the highest genome sequence identity with SARS-CoV-2 among all known coronaviruses, and also uses human angiotensin converting enzyme 2 (hACE2) for virus entry. Thus, SARS-CoV-2 is thought to have originated from bat. However, whether SARS-CoV-2 emerged from bats directly or through an intermediate host remains elusive. Here, we found that Rhinolophus affinis bat ACE2 (RaACE2) is an entry receptor for both SARS-CoV-2 and RaTG13, although RaACE2 binding to the receptor binding domain (RBD) of SARS-CoV-2 is markedly weaker than that of hACE2. We further evaluated the receptor activities of ACE2s from additional 16 diverse animal species for RaTG13, SARS-CoV, and SARS-CoV-2 in terms of S protein binding, membrane fusion, and pseudovirus entry. We found that the RaTG13 spike (S) protein is significantly less fusogenic than SARS-CoV and SARS-CoV-2, and seven out of sixteen different ACE2s function as entry receptors for all three viruses, indicating that all three viruses might have broad host rages. Of note, RaTG13 S pseudovirions can use mouse, but not pangolin ACE2, for virus entry, whereas SARS-CoV-2 S pseudovirions can use pangolin, but limited for mouse, ACE2s enter cells. Mutagenesis analysis revealed that residues 484 and 498 in RaTG13 and SARS-CoV-2 S proteins play critical roles in recognition of mouse and human ACE2. Finally, two polymorphous *Rhinolophous sinicus bat ACE2s showed different susceptibilities to virus*

entry by RaTG13 and SARS-CoV-2 S pseudovirions, *suggesting possible coevolution. Our results offer better understanding of the mechanism of coronavirus entry, host range, and virus-host coevolution*. [**note: here is more evolutionary information on SARS-CoV-2]**
https://www.biorxiv.org/content/10.1101/2020.11.16.385849v1

- Memory B cells play a fundamental role in host defenses against viruses, but to date, their role have been relatively unsettled in the context of SARS-CoV-2. We report here a longitudinal single-cell and repertoire profiling of the B cell response up to 6 months in mild and severe COVID-19 patients. Distinct SARS-CoV-2 Spike-specific activated B cell clones fueled an early antibody-secreting cell burst as well as a durable synchronous germinal center response. While highly mutated memory B cells, including preexisting cross-reactive seasonal Betacoronavirus-specific clones, were recruited early in the response, neutralizing SARS-CoV-2 RBD-specific clones accumulated with time and largely contributed to the late remarkably stable memory B-cell pool. *Highlighting germinal center maturation, these cells displayed clear accumulation of somatic mutations in their variable region genes over time. Overall, these findings demonstrate that an antigen-driven activation persisted and matured up to 6 months after SARS-CoV-2 infection and may provide long-term protection*. [**note: here is another study on memory B cells and persistence, this time from French investigators.**
https://www.biorxiv.org/content/10.1101/2020.11.17.385252v1

DIAGNOSTIC DEVELOPMENT

- Nothing new today.

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2020-11-19

Mad scenes in opera have a storied history. Most were written as star vehicles for sopranos. Perhaps the best known one comes from Donizetti's frequently staged opera, Lucia di Lammermoor, based on the Walter Scott novel 'The Bride of the Lammermoor.' There are some good clips of this one! Here is Lisette Oropesa in a Madrid performance: https://www.youtube.com/watch?v=VtUcTREkLFo Natalie Dessay from the Met in NYC: https://www.youtube.com/watch?v=C1LC6BRJQiQ Diana Damrau brandishing a pistol in a totally bizarre production from Germany: https://www.youtube.com/watch?v=cFR9Lho1a8A the great Joan Sutherland in an Australian performance: https://www.youtube.com/watch?v=U3_8wz_xNI0 and finally, Laura Claycomb from the Houston Grand Opera: https://www.youtube.com/watch?v=cefNIpc1wGM Enjoy the madness!!!!! I want to see an enterprising composer do a mad scene incorporating a COVID-19 theme!!

On the vaccine front, The Lancet has a report on the Phase 2 study of the AstraZeneca/Oxford adenovirus vectored vaccine. Good news: *ChAdOx1 nCoV-19 appears to be better tolerated in older adults than in younger adults and has similar immunogenicity across all age groups after a boost dose. Further assessment of the efficacy of this vaccine is warranted in all age groups and individuals with comorbidities*. I expect this will be the next one to be deployed widely.

The Washington Post reports on the poor outcome of this Ohio wedding where masks were not worn. The number of infectious people in the US is disturbing. Here is more on the Pfizer vaccine and it looks like they are getting ready to request an EUA from FDA. Here is another in the continuing 'voices from the pandemic series', this time it is a county health director discussing the issues she faces in doing her job. This is an awfully sad story to read; I thought we would do better as a nation. ☹ Is hand sanitizer the perfect holiday gift? Wait time for COVID-19 testing is becoming very long. If you are traveling, this tips from flight attendants may be helpful.

The New York Times notes that scrubbing surfaces may not be all that helpful for an airborne virus. The WHO thinks that there is a slowing of viral infections in Europe. UNICEF warns of a lost generation and thinks school closings are ineffective. States that imposed few restrictions now have the worst outbreaks.

STAT reports on the grim story of hospital staffing shortages. Here is one person's experience in the Moderna vaccine clinical trial.

The Annals of Internal Medicine have a report on mask wearing from Denmark that is a bit confounding. *The recommendation to wear surgical masks to supplement other public health measures did not reduce the SARS-CoV-2 infection rate among wearers by more than 50% in a community with modest infection rates, some degree of social distancing, and uncommon general mask use. The data were compatible with lesser degrees of self-protection*. This is contrary to other studies and here is an editorial that discusses the limitations of the Danish study and a second one. Mask wearing is a prudent practice, full stop.

MODELING

- Granular estimates of infection are important for understanding population-level immunity. We examined seroprevalence of anti-SARS-CoV-2 antibodies in Pune city in India and its implication for protective immunity. Methods Seroprevalence was estimated during July 20-August 5, 2020 from 1659 randomly selected individuals recruited from five administrative Pune sub-wards (combined population 366,984). Prevalence of anti-SARS-CoV-2 spike protein antibodies were estimated and along with correlates of virus neutralisation. Findings Seropositivity was extensive (51.3%; 95%CI 39.9-62.4) but varied widely in the five localities tested, ranging from 35.8% to 66.4%. Seropositivity was higher in crowded living conditions in the slums (OR 1.91), and was lower in those 65 years or older (OR 0.59). The infection-fatality ratio was estimated at 0.28%. Post survey, COVID-19 incidence was lower in areas noted to have higher seroprevalence. Substantial virus-neutralising activity was observed in seropositive individuals, but with considerable heterogeneity in the immune response and possible age-dependent diversity in the antibody repertoire. Interpretation *Despite crowded living conditions having facilitated widespread transmission, the variability in seroprevalence in localities that are in geographical proximity indicates a heterogenous spread of infection. Declining infection rates in areas with high seropositivity suggest population-level protection and is supported by substantial neutralising activity in asymptomatically infected individuals. The heterogeneity in antibody levels and neutralisation capacity indicates the existence of immunological sub-groups of*

functional interest. [**note: here is a serology study from a metro area in India.** }
https://www.medrxiv.org/content/10.1101/2020.11.17.20228155v1

- Many healthcare facilities report SARS-CoV-2 outbreaks but analysis of transmission during the first wave is complicated by the high prevalence of infection and limited viral genetic diversity. Furthermore, there is limited evidence on the contribution of different vectors for nosocomial infection or on the effectiveness of interventions. Detailed epidemiological and viral nanopore sequence data were analysed from 574 consecutive patients with a PCR positive SARS-CoV-2 test between March 13th and March 31st, when the pandemic first impacted on a large, multisite healthcare institution in London. During this time the first major preventative interventions were introduced including progressive community social distancing (CSD) policies leading to mandatory national lockdown, exclusion of hospital visitors, and introduction of universal surgical facemask-use by healthcare-workers (HCW). Incidence of nosocomial cases, community SARS-CoV-2 cases, and infection in a cohort of 228 HCWs followed the same dynamic course, decreasing subsequent to CSD and prior to introduction of the main hospital-based interventions. We investigated clusters involving nosocomial cases based on overlapping ward-stays during the 14-day incubation period and SARS-CoV-2 genome sequence similarity. Our method placed 80 (89%) of all 90 probable and definite nosocomial cases into 14 clusters containing a median of 4 patients (min 2, max 19) No genetic support was found for the majority of epidemiological clusters (31/44 70%) and genomics revealed multiple contemporaneous outbreaks within single epidemiological clusters. *We included a measure of hospital enrichment compared to community cases to increase confidence in our clusters, which were 1-14 fold enriched. Applying genomics, we could provide a robust estimate of the incubation period for nosocomial transmission, with a median lower bound and upper bound of 6 and 9 days respectively. Six (43%) clusters spanned multiple wards, with evidence of cryptic transmission, and community-onset cases could not be identified in more than half the clusters, particularly on the elective hospital site, implicating HCW as vectors of transmission. Taken together these findings suggest that CSD had the dominant impact on reducing nosocomial transmission by reducing HCWs infection*. [**note: this is from the UK using early pandemic data. Community social distancing appeared to be the best controlling factor.**]
https://www.medrxiv.org/content/10.1101/2020.11.17.20232827v1
- We ascertained IgG levels across a single US metropolitan site, Chicago, over the 2020 summer, a period when restrictions on activities had been lifted. Methods: We utilized a self-sampled dried blood spot assay to quantitatively monitor antibodies to the receptor binding domain (RBD) of the spike glycoprotein of SARS-CoV-2 in 1545 participants, with return of blood spot cards either by mail or in-person drop-off. Results: Seroprevalence was 19.8%, with no significant difference between method of contact, or between essential and non-essential workers. Only a small number (1.2%) of participants reported having had a diagnosis of COVID-19 based on virus detection, consistent with a 16-fold greater exposure to SARS-CoV-2 measured by serology than detected by viral testing. *Only a modest correlation was observed between having antibodies to SARS-CoV-2 nucleocapsid compared to RBD, with many only having detectable anti-RBD antibodies. From a subset of those who participated in repeat testing, three-quarters of seropositive individuals retained detectable antibodies for at least 120 days. One seropositive individual experienced a strong boost in IgG levels following a symptomatic illness, suggestive of potential re-exposure. Conclusions: These data underscore the*

importance of a self-collected, quantitative assay with adequate sensitivity to detect antibodies at the lower levels among non-hospitalized persons with community-acquired exposure to COVID-19. [**note: here is a small serology study from Chicago using self-sampled dried blood spots.**] https://www.medrxiv.org/content/10.1101/2020.11.17.20233452v1

- This study reports a comprehensive empirical investigation of the nature and correlates of anti-mask attitudes during the COVID-19 pandemic. Accumulating evidence underscores the importance of facemasks, as worn by the general public, in limiting the spread of infection. Accordingly, mask-wearing has become increasingly mandatory in public places such as stores and on public transit. Although the public has been generally adherent to mask-wearing, a small but vocal group of individuals refuse to wear masks. Anti-mask protest rallies have occurred in many places throughout the world, sometimes erupting violently. Few empirical studies have examined the relationship between anti-mask attitudes and mask non-adherence and little is known about how such attitudes relate to one another or other factors (e.g., non-adherence to social distancing, anti-vaccination attitudes). To investigate these issues, the present study surveyed 2,078 adults from the US and Canada. Consistent with other surveys, we found that most (84%) people wore masks because of COVID-19. The 16% who did not wear masks scored higher on most measures of negative attitudes towards masks. *Network analyses indicated that negative attitudes about masks formed an intercorrelated network, with the central nodes in the network being (a) beliefs that masks are ineffective in preventing COVID-19, and (b) psychological reactance (PR; i.e., an aversion to being forced to wear masks). These central nodes served as links, connecting the network of anti-masks attitudes to negative attitudes toward SARSCoV2 vaccination, beliefs that the threat of COVID-19 has been exaggerated, disregard for social distancing, and political conservatism. Findings regarding PR are important because, theoretically, PR is likely to strengthen other anti-masks attitudes (e.g., beliefs that masks are ineffective) because people with strong PR react with anger and counter-arguments when their beliefs are challenged, thereby leading to a strengthening of their anti-mask beliefs. Implications for improving mask adherence are discussed*. [**note: here is a Canadian paper on resistance to wearing masks.]**
  https://www.medrxiv.org/content/10.1101/2020.11.17.20233585v1
- Large-scale wastewater surveillance has the ability to greatly augment the tracking of infection dynamics especially in communities where the prevalence rates far exceed the testing capacity. However, current methods for viral detection in wastewater are severely lacking in terms of scaling up for high throughput. In the present study, we employed an automated magnetic-bead based concentration approach for viral detection in sewage that can effectively be scaled up for processing 24 samples in a single 40-minute run. The method compared favorably to conventionally used methods for viral wastewater concentrations with a limit of detection of 8.809 viral gene copies/ml from input sample volumes as low as 10ml and can enable the processing of over 100 wastewater samples in a day. *Using the high throughput pipeline, samples from the influent stream of the primary wastewater treatment plant of San Diego county (serving 2.3 million residents) were processed for a period of 13 weeks. Wastewater estimates of SARS-CoV-2 viral genome copies in raw untreated wastewater correlated strongly with clinically reported cases by the county, and enabled prediction of cases up to 3 weeks in advance. Taken together, the results show that the high-throughput surveillance could greatly ameliorate comprehensive community prevalence assessments by providing robust, rapid*

estimates. [**note: here is a nice wastewater study from my home town of San Diego. The UCSD researchers develop a high-throughput system to measure for SARS-CoV-2.**] https://www.medrxiv.org/content/10.1101/2020.11.16.20232900v1

- Background Coronavirus disease 19 (COVID-19) has frequently been colloquially compared to the seasonal influenza, but comparisons based on empirical data are scarce. Aims To compare in-hospital outcomes for patients admitted with community-acquired COVID-19 to patients with community-acquired influenza in Switzerland. Methods Patients >18 years, who were admitted with PCR proven COVID-19 or influenza A/B infection to 14 participating Swiss hospitals were included in a prospective surveillance. Primary and secondary outcomes were the in-hospital mortality and intensive care unit (ICU) admission between influenza and COVID-19 patients. We used Cox regression (cause-specific models, and Fine & Gray subdistribution) to account for time-dependency and competing events with inverse probability weighting to account for confounders. Results In 2020, 2843 patients with COVID-19 were included from 14 centers and in years 2018 to 2020, 1361 patients with influenza were recruited in 7 centers. Patients with COVID-19 were predominantly male (n=1722, 61% vs. 666 influenza patients, 48%, p<0.001) and were younger than influenza patients (median 67 years IQR 54-78 vs. median 74 years IQR 61-84, p<0.001). 363 patients (12.8%) died in-hospital with COVID-19 versus 61 (4.4%) patients with influenza (p<0.001). *The final, adjusted subdistribution Hazard Ratio for mortality was 3.01 (95% CI 2.22-4.09, p<0.001) for COVID-19 compared to influenza, and 2.44 (95% CI, 2.00-3.00, p<0.001) for ICU admission. Conclusion Even in a national healthcare system with sufficient human and financial resources, community-acquired COVID-19 was associated with worse outcomes compared to community-acquired influenza, as the hazards of in-hospital death and ICU admission were ~3-fold higher*. [**note: this Swiss paper should drive a stake through the heart of those who maintain that COVID-19 is like a 'little bit of flu.'**] https://www.medrxiv.org/content/10.1101/2020.11.17.20233080v1

NEWLY REGISTERED CLINICAL TRIALS

- I don't report on Thursdays.

CLINICAL TRIAL RESULTS

- SARS-CoV-2 entry into type II pneumocytes is depended on the TMPRSS2 proteolytic enzyme. The only known promoter of TMPRSS2 in humans is an androgen response element. As such, androgen sensitivity may be a risk factor for COVID-19. Previously, we have reported a retrospective cohort analysis demonstrating the protective effect of 5-alpha-reductase inhibitors (5ARis) in COVID-19. Men using 5ARis were less likely to be admitted to the ICU than men not taking 5ARis. Additionally, men using 5ARis had drastically reduced frequency of symptoms compared to men not using 5ARis in an outpatient setting. Here we aim to determine if 5ARis will be a beneficial treatment if given after SARS-CoV-2 infection. Methods: A double-blinded, randomized, prospective, investigational study of dutasteride for the treatment of COVID-19 (NCT04446429). Subjects confirmed positive for SARS-CoV-2 were treated in an outpatient setting. Endpoints for the study were remission times for a predetermined set of symptoms: fever or feeling feverish, cough, shortness of breath, sore throat, body pain or muscle pain/ache, fatigue, headache, nasal congestion, nasal discharge (runny nose), nausea or vomiting, diarrhea, loss of appetite, and loss of taste or smell (Ageusia or Anosmia). Results: *A total of 130 SARS-*

CoV-2 positive men were included in the study, 64 subjects in the dutasteride arm and 66 subjects in the placebo-controlled group. The differences in the average remission times for fatigue and anosmia or ageusia was statistically different between the groups (5.8 versus 10.1 days for fatigue and 7.3 versus 13.4 days for anosmia or ageusia, in dutasteride and placebo groups, respectively), however, the total remission time was significantly reduced for the men given dutasteride; 9.0 days versus 15.6 days in the placebo group ($p < 0.001$). Excluding loss of taste and smell the average total remission time was 7.3 days in the dutasteride group versus 11.7 in the placebo arm ($p < 0.001$). Conclusion: The total remission time for men using 5ARis was significantly reduced compared to men not taking 5ARis. [**note: here is the first report on a clinical trial of dutasteride. It appears that this drug is useful in reducing remission times in an outpatient setting.]** https://www.medrxiv.org/content/10.1101/2020.11.16.20232512v1

- The rapid rise of coronavirus disease 2019 patients who suffer from vascular events after their initial recovery is expected to lead to a worldwide shift in disease burden. We aim to investigate the impact of COVID-19 on the pathophysiological state of blood vessels in convalescent patients. Here, convalescent COVID-19 patients with or without preexisting conditions (i.e. hypertension, diabetes, hyperlipidemia) were compared to non-COVID-19 patients with matched cardiovascular risk factors or healthy participants. *Convalescent patients had elevated circulating endothelial cells (CECs), and those with underlying cardiovascular risk had more pronounced endothelial activation hallmarks (ICAM1, P-selectin or CX3CL1) expressed by CECs. Multiplex microbead-based immunoassays revealed some levels of cytokine production sustained from acute infection to recovery phase. Several proinflammatory and activated T lymphocyte-associated cytokines correlated positively with CEC measures, implicating cytokine-driven endothelial dysfunction. Finally, the activation markers detected on CECs mapped to the counter receptors (i.e. ITGAL, SELPLG, and CX3CR1) found primarily on CD8+ T cells and natural killer cells, suggesting that activated endothelial cells could be targeted by cytotoxic effector cells. Clinical trials in preventive therapy for post-COVID-19 vascular complications may be needed*. [**note: this is from Singapore and shows another health issue in convalescing patients.**] https://www.medrxiv.org/content/10.1101/2020.11.16.20232835v1
- Massive research efforts have been made in response to the COVID-19 (coronavirus disease-2019) pandemic. Utilization of clinical data can accelerate these research efforts to fight against the pandemic since important characteristics of the patients are often found by examining the clinical data. To provide shareable clinical data to catalyze COVID-19 research, we present Columbia Open Health Data for COVID-19 Research (COHD-COVID), a publicly accessible database providing clinical concept prevalence, clinical concept co-occurrence, and clinical symptom prevalence for hospitalized COVID-19 patients. COHD-COVID also provides data on hospitalized influenza patients and general hospitalized patients as comparator cohorts. The data used in COHD-COVID were obtained from Columbia University Irving Medical Center's electronic health records. *We expect COHD-COVID will provide researchers and clinicians quantitative measures of COVID-19 related clinical features to better understand and fight against the pandemic*. [**note: I salute these Columbia Univ researchers. We need more of these types of efforts!**] https://www.medrxiv.org/content/10.1101/2020.11.17.20232983v1
- While recent investigations have revealed viral, inflammatory and vascular factors involved in SARS-CoV-2 lung pathogenesis, the pathophysiology of neurological disorders in COVID-19 remains poorly understood. Yet, olfactory and taste dysfunction are rather common in COVID-

19, especially in pauci-symptomatic patients which constitutes the most frequent clinical manifestation of the infection. We conducted a virologic, molecular, and cellular study of the olfactory system from COVID-19 patients presenting acute loss of smell, and report evidence that the olfactory epithelium represents a highly significant infection site where multiple cell types, including olfactory sensory neurons, support cells and immune cells, are infected. Viral replication in the olfactory epithelium is associated with local inflammation. *Furthermore, we show that SARS-CoV-2 induces acute anosmia and ageusia in golden Syrian hamsters, both lasting as long as the virus remains in the olfactory epithelium and the olfactory bulb. Finally, olfactory mucosa sampling in COVID-19 patients presenting with persistent loss of smell reveals the presence of virus transcripts and of SARS-CoV-2-infected cells, together with protracted inflammation. Viral persistence in the olfactory epithelium therefore provides a potential mechanism for prolonged or relapsing symptoms of COVID-19, such as loss of smell, which should be considered for optimal medical management and future therapeutic strategies*. [**note: more on the loss of smell in COVID-19 patients.**]
https://www.biorxiv.org/content/10.1101/2020.11.18.388819v1

DRUG DEVELOPMENT

- Although knowledge of airborne transmission has long been known, there is little in the way of adequate intervention that can protect the individual, or even prevent further spread. This study focuses on a nasal applicant with the capacity to combat such issues, by focussing on the SARS-CoV-2 virus. Formulation of a spray containing polysaccharides known for their mucoadhesive properties was undertaken and characterised for their mechanical, spray patterns and antiviral properties. *The ability to engineer key behaviours such as yielding have been shown, through systematic understanding of a composite mixture containing two polymers: gellan and Lambda-carrageenan. Furthermore, spray systems demonstrated highly potent antiviral capacities, resulting in complete inhibition of the virus when studied for both prophylaxis and prevention of spread. Finally, a mechanism has been proposed to explain such findings. Therefore, demonstrating the first fully preventative device, targeted to protect the lining of the upper respiratory pathways*. [**note: this is an interesting approach to a nasal spray that might block SARS-CoV-2 attachment.**]
https://www.biorxiv.org/content/10.1101/2020.11.18.388645v1
- SARS-CoV-2 replicates efficiently in the upper airway during prodromal stage with resulting viral shedding into the environment from patients with active disease as well as from asymptomatic individuals. So far, virus spread has been exclusively contained by non-pharmacological interventions (social distancing, face masks, hand washing and several measures limiting business activities or movement of individuals). There is a need to find pharmacological interventions to mitigate the viral spread, supporting yet limiting the existing health protection measures while an effective and safe vaccine will hopefully become available. Hypothiocyanite and lactoferrin as part of the innate human immune system were shown to have a large spectrum of cidal activity against bacteria, fungi and viruses. To test their virucidal activity against SARS-CoV-2 we conducted an in-vitro study. Here we show a dose-dependent virucidal activity of hypothiocyanite at micromolar concentrations, slightly improved by the presence of lactoferrin. *The two substances are devoid of any cytotoxicity and may be administered combined by aerosol to exploit their antiviral activity at the port of entry (mouth, nasal cavity,*

conjunctiva) or exit (mouth, through emission of respiratory droplets) of SARS-CoV-2 in the human body. Furthermore, aerosol with hypothiocyanite and lactoferrin combined could also have a therapeutic effect in the lower respiratory tract, at the level of gas exchange units of the lung, preventing the devastating infection of alveolar type II cells where ACE2 is highly expressed. An in-vivo validation of in-vitro results is urgently required. [**note: here is another aerosol formulation approach.}** https://www.biorxiv.org/content/10.1101/2020.11.17.387571v1

- Renessans is an iodine complex which has proven in vitro antiviral activity including Anti-SARS-CoV-2 activity. The present study was designed to determine its efficacy against SARS-CoV-2 in monkeys (Rhesus macaque). A total of 14 monkeys were divided into four groups: A) Prophylactic group (n=03), (B) Treatment group (n=03), (C) infection control group (n=04) and (D) negative control group (n=04) and were housed in BSL-3 Animal facility while group D was housed at another animal house. Group A was administered with Renessans @ 2.85 mg/7 kg from 5 days prior to the infection to 08 days post infections (DPI). Group B was administered with Renessans from 03-08 DPI @ 2.85 mg/7 kg. Group C was administered with WIF only. The infection @ 2 x 106 TCID of SARS-CoV-2 was given to all group monkeys through intranasal and oral route under anesthesia. Nasal swab samples (at different times) and fecal matter on daily basis were collected for the detection of SARS-CoV-2 through real-time quantitative PCR. Three monkeys (one from each of group A, B and C) were euthanized at 07 DPI to determine the gross pathological lesions and SARS-CoV-2 detection from internal tissues. *Nasal swabs from all the monkeys from group A, B and C were positive for SARS-CoV-2 at 02 and 07 DPI (Day 05 of treatment). At 14 DPI, all (100%) nasal swabs from group A were negative for SARS-CoV-2 while 50% and 100% were positive from group B and C, respectively. At 21 DPI, monkeys from group B were negative and all in group C were still positive for SARS-CoV-2. Similarly, fecal matter of monkeys in group A and B was returned negative in significantly lesser time as compared to monkeys from infection control group. Based on these research findings it is concluded that the Renessans has in-vivo SARS-CoV-2 activity and may result in early clearance of SARS-CoV-2. Therefore, a clinical trial of the drug in COVID-19 patients may reveal its anti-COVID-19 potential.* **[note: this is from Pakistan and looks at an iodine complex as a potential anti-viral. They see *in vivo* activity in monkeys.**] https://www.biorxiv.org/content/10.1101/2020.11.17.377432v1
- An inexpensive readily manufactured COVID-19 vaccine that protects against severe disease is needed to combat the pandemic. We have employed the LVS ΔcapB vector platform, previously used successfully to generate potent vaccines against the Select Agents of tularemia, anthrax, plague, and melioidosis, to generate a COVID-19 vaccine. The LVS ΔcapB vector, a replicating intracellular bacterium, is a highly attenuated derivative of a tularemia vaccine (LVS) previously administered to millions of people. We generated vaccines expressing SARS-CoV-2 structural proteins and evaluated them for efficacy in the golden Syrian hamster, which develops severe COVID-19 disease. *Hamsters immunized intradermally or intranasally with a vaccine co-expressing the Membrane (M) and Nucleocapsid (N) proteins, then challenged 5-weeks later with a high dose of SARS-CoV-2, were protected against severe weight loss and lung pathology and had reduced viral loads in the oropharynx and lungs. Protection by the vaccine, which induces murine N-specific interferon-gamma secreting T cells, was highly correlated with pre-challenge serum anti-N TH1-biased IgG. This potent vaccine against severe COVID-19 should be safe and easily manufactured, stored, and distributed, and given the high homology between MN proteins of SARS-CoV and SARS-CoV-2, has potential as a universal vaccine against the SARS subset of*

pandemic causing β-coronaviruses. [**note: here's another vaccine that looks good in animals. This uses a much different vector system than all the previous vaccine approaches that I've seen but one that has been used in the past. I like that they include the N protein as well.**] https://www.biorxiv.org/content/10.1101/2020.11.17.387555v1

- The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen responsible of coronavirus disease 2019 (COVID-19), has devastated public health services and economies worldwide. Despite global efforts to contain the COVID-19 pandemic, SARS-CoV-2 is now found in over 200 countries and has caused an upward death toll of over 1 million human lives as of November 2020. To date, only one FDA-approved therapeutic drug (Remdesivir) and a monoclonal antibody, MAb (Bamlanivimab), but no vaccines, are available for the treatment of SARS-CoV-2. As with other viruses, studying SARS-CoV-2 requires the use of secondary approaches to detect the presence of the virus in infected cells. To overcome this limitation, we have generated replication-competent recombinant (r)SARS-CoV-2 expressing fluorescent (Venus or mCherry) or bioluminescent (Nluc) reporter genes. Vero E6 cells infected with reporter-expressing rSARS-CoV-2 can be easily detected via fluorescence or luciferase expression and display a good correlation between reporter gene expression and viral replication. Moreover, rSARS-CoV-2 expressing reporter genes have comparable plaque sizes and growth kinetics to those of wild-type virus, rSARS-CoV-2/WT. We used these reporter-expressing rSARS-CoV-2 to demonstrate their feasibility to identify neutralizing antibodies (NAbs) or antiviral drugs. *Our results demonstrate that reporter-expressing rSARS-CoV-2 represent an excellent option to identify therapeutics for the treatment of SARS-CoV-2, where reporter gene expression can be used as valid surrogates to track viral infection. Moreover, the ability to manipulate the viral genome opens the feasibility of generating viruses expressing foreign genes for their use as vaccines for the treatment of SARS-CoV-2 infection*. [**note: here is a new method that can be a surrogate for viral infection and might be used for drug development.**] https://www.biorxiv.org/content/10.1101/2020.11.16.386003v1
- The current SARS-CoV-2/COVID-19 pandemic represents an unprecedented medical and socioeconomic crisis. Highly efficient treatment options preventing morbidity and mortality are not broadly available and approved drugs are hardly affordable in developing countries. Even after vaccine approvals, it will take several months until the vaccinated and convalescent individuals establish herd immunity. Meanwhile, non-pharmaceutical interventions and antiviral treatments are indispensable to curb the death toll of the pandemic. To identify cost-effective and ubiquitously available options, we tested common herbs consumed worldwide as herbal teas. *We found that aqueous infusions prepared by boiling leaves of the Lamiaceae plants perilla and sage elicit potent antiviral activity against SARS-CoV-2 in human cells. Sustained antiviral activity was evident even when cells were treated for only half an hour, and in therapeutic as well as prophylactic regimens. Given the urgency, such inexpensive and broadly available substances might provide help during the pandemic - especially in low-income regions*. [**note: this for you herbal tea drinkers. Stock up and stay safe from COVID-19!!**] https://www.biorxiv.org/content/10.1101/2020.11.18.388710v1
- The SARS-coronavirus 2 (SARS-CoV-2) spike (S) protein mediates viral entry into cells expressing the angiotensin-converting enzyme 2 (ACE2). The S protein engages ACE2 through its receptor-binding domain (RBD), an independently folded 197-amino acid fragment of the 1273-amino acid S-protein protomer. The RBD is the primary SARS-CoV-2 neutralizing epitope and a critical

target of any SARS-CoV-2 vaccine. Here we show that this RBD conjugated to each of two carrier proteins elicited more potent neutralizing responses in immunized rodents than did a similarly conjugated proline-stabilized S-protein ectodomain. Nonetheless, the native RBD expresses inefficiently, limiting its usefulness as a vaccine antigen. *However, we show that an RBD engineered with four novel glycosylation sites (gRBD) expresses markedly more efficiently, and generates a more potent neutralizing responses as a DNA vaccine antigen, than the wild-type RBD or the full-length S protein, especially when fused to multivalent carriers such as an H. pylori ferritin 24-mer. Further, gRBD is more immunogenic than the wild-type RBD when administered as a subunit protein vaccine. Our data suggest that multivalent gRBD antigens can reduce costs and doses, and improve the immunogenicity, of all major classes of SARS-CoV-2 vaccines*. [**note: the vaccine approaches continue to increase! This is from the Scripps Institutes and shows how to improve the potency and perhaps lessen the cost and number of doses.**]
https://www.biorxiv.org/content/10.1101/2020.11.18.388934v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Understanding the causes of the diverse outcome of COVID-19 pandemic in different geographical locations is important for the vaccine implementation and pandemic control responses. Here, we examined the SARS-CoV-2-specific CD4+ T-cell responses in unexposed individuals and patients recovered from mild COVID-19. Using HLA class II predicted peptide megapools, we identified SARS-CoV-2 cross-reactive CD4+ T cells in around 70% of the unexposed individuals. Moreover, we found detectable immune reactivity up to 5 months in mild COVID-19 recovered patients in the two major arms of protective adaptive immunity; CD4+ T cells and B cells. Interestingly, the persistent immune reactivity in COVID-19 patients is predominantly targeted towards the Spike glycoprotein of the SARS-CoV-2. *This study provides the evidence of both high magnitude pre-existing and persistent immune memory in Indian population. By providing the knowledge on cellular immune responses to SARS-CoV-2, our work has implication for the evaluation and implementation of vaccines against COVID-19*. [**note: here is a paper from India on persistent T cell response after infection. It also shows some cross reactivity in unexposed patients but I don't know what to make of that.**]
https://www.medrxiv.org/content/10.1101/2020.11.16.20232967v1

DIAGNOSTIC DEVELOPMENT

- Nothing today, *but I will note we need lots of tests to get through the next couple of months. The more home testing that can be utilized the better!!!!!*

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2020-11-20

More madness for today, this time from Bellini. Here is the mad scene from Il Pirata. From Madrid, here is Sonya Yoncheva singing the role of Imogene in 2019:
https://www.youtube.com/watch?v=Ehj0Jvr-yNs

Vaccine Update: Pfizer/BioNTech will file for an EUA from FDA today.

The Washington Post has the sad story of a contact tracer in North Dakota who laments she cannot do her job because the virus is so rampant. The CDC recommends not traveling for Thanksgiving. Make sure your residence has adequate humidity this winter. We just started ours. The talk about a lockdown is a distraction. Here is an op-ed on keeping schools open. In a show of solidarity, some NY City healthcare workers are going to Utah to help out with the crowded hospitals.

In The New York Times, Dr. Rosenthal talks with Dr. Fauci. The WHO has rejected remdesivir as a treatment for COVID-19. Univ of Michigan is still battling COVID-19 outbreaks. [**note:** as my readers know I follow Mitch Daniels' Purdue University. In a partially good sign, testing for COVID-19 shows a small drop this week from 7% to just above 6%. Ideally, it needs to get below 3%.] The White House corona virus task force had a public meeting for the first time in several months.

The Atlantic has sobering news about the current COVID-19 outbreak.

STAT also covers the WHO remdesivir decision. Hospitals are trying to solve logistical and ethical challenges surrounding the Lilly mAb treatment. Here is an opinion on the shortage of hospital physicians and the implications for treatment.

The Lancet has an article on viral load dynamics and duration of shedding. *Although SARS-CoV-2 RNA shedding in respiratory and stool samples can be prolonged, duration of viable virus is relatively short-lived. SARS-CoV-2 titres in the upper respiratory tract peak in the first week of illness. Early case finding and isolation, and public education on the spectrum of illness and period of infectiousness are key to the effective containment of SARS-CoV-2.* Here is an editorial on COVID-19 vaccines, noting that this is no time for complacency.

Science has an article on ensuring vaccine safety. Taking a cue from the Rumsfeld Paradigm, here is an article on the known unknowns of T-cell immunity to COVID-19.

Medscape report that FDA has issued an EUA for the combination treatment of baricitnib and remdesivir for hospitalized COVID-19.

Derek Lowe on vaccine possibilities and new vaccine data.

MODELING

- Introduction: SARS-CoV-2, which causes COVID-19, has spread rapidly across the world. A dedicated surveillance system was implemented in France in January 2020 to improve early detection of cases and their contacts and limit secondary transmission. Our objective was to use contact-tracing data collected during this initial phase of the epidemic to better characterize SARS-CoV-2 transmission. Methods: We analyzed data collected during contact tracing and retrospective epidemiological investigations in France from 24 January to 30 March 2020. We assessed the secondary clinical attack rate and characterized the risk of a contact becoming a case. We described chains of transmission and estimated key parameters of spread. Results: Over the study period, 6,082 contacts of 735 confirmed cases were traced. The overall secondary clinical attack rate was 4.1% (95%CI 3.6-4.6) and increased with age of the index case and of the contact. Family contacts were at higher risk of becoming cases (adjusted odds ratio 2.1 (95%CI 1.4-3.0)) while nosocomial contacts were at lower risk (adjusted odds ratio 0.3 (95%CI 0.1-0.7)), compared to coworkers/friends. *We identified 328 infector/infectee pairs, 49%*

of which were family members. The distribution of secondary cases was highly over-dispersed with 80% of secondary cases being caused by 10% of cases. The mean serial interval was 5.1 days (interquartile range 2-8 days) in contact-tracing pairs where late transmission events may be censored, and 6.8 (3-8) days in pairs investigated retrospectively. Conclusion: This study contributes to improving our knowledge of SARS-CoV-2 transmission, such as the importance of superspreading events. Contact-tracing data are challenging to collect but are key to better understand emerging pathogens. [**note: here is a contact tracing effort in France during the early days of the pandemic. There is some useful data in this paper.**]
https://www.medrxiv.org/content/10.1101/2020.11.17.20232264v1

NEWLY REGISTERED CLINICAL TRIALS

- Why are you looking at this section? It is Friday.

CLINICAL TRIAL RESULTS

- There is an urgent need to elucidate the molecular mechanisms underlying the transmissibility and pathogenesis of SARS-CoV-2. ACE2 is a host ectopeptidase with well-described anti-inflammatory and tissue protective functions and the receptor for the virus. Understanding SARS-CoV-2-ACE2 interaction and the expression of antiviral host genes in early infection phase is crucial for fighting the pandemic. We tested the significance of soluble ACE2 enzymatic activity longitudinally in positive nasopharyngeal swabs at two time points after symptom consultation, along with gene expression profiles of ACE2, its proteases, ADAM17 and TMPRRS2, and interferon-stimulated genes (ISGs), DDX58, CXCL10 and IL-6. Soluble ACE2 activity decreased during infection course, in parallel to ACE2 gene expression. On the contrary, SARS-CoV-2 infection induced expression of the ISG genes in positive SARS-CoV-2 samples at baseline compared to negative control subjects, although this increase wanes with time. These changes positively correlated with viral load. *Our results demonstrate the existence of mechanisms by which SARS-CoV-2 suppress ACE2 expression and function casting doubt on the IFN-induced upregulation of the receptor. Moreover, we show that initial intracellular viral sensing and subsequent ISG induction is also rapidly downregulated. Overall, our results offer new insights into ACE2 dynamics and inflammatory response in the human upper respiratory tract that may contribute to understand the early antiviral host response to SARS-CoV-2 infection*. [**note: this paper from Barcelona shows another possible mechanism for the virus's mode of action.**]
https://www.biorxiv.org/content/10.1101/2020.11.18.388850v1
- One of the entry routes of SARS-CoV-2 is the nasal epithelium. Although mounting evidence suggests the presence of olfactory dysfunction, and even anosmia, in patients with COVID-19, it is not clear whether these patients also suffer from other 'nasal' symptoms that may influence their olfaction. A group of 35 patients with COVID-19 (and a control group matched in gender and age) were surveyed about the presence of a variety of nasal symptoms that may be associated to drastic perturbations experienced in the nasal cavity (e.g., 'excessive dryness' and/or a continual sensation of having had a 'nasal douche'). We used a cross-sectional, retrospective survey, targeted at the general population by means of non-quoted, non-random, snowball sampling. Symptoms were assessed with absence/presence responses. The possible association between two continuously distributed latent variables from categorical variables was estimated by means of polychoric correlations. More than 68% of the patients reported at

least one 'nasal' symptom. *The clinical group also experienced 'a strange sensation in the nose' and having excessive nasal dryness significantly more often than the control group. Fifty-two percent of the patients (but only 3% of the control group) reported a constant sensation of having had a strong nasal douche. Nasal symptoms predominantly co-occurred with anosmia/hyposmia, and ageusia/hypogeusia, appeared principally before or during the other symptoms of COVID-19, and lasted for twelve days, in average. The presence of these nasal symptoms, and their early occurrence, could potentially facilitate early diagnosis of COVID-19 and initial social distancing efforts*. [**note: from Barcelona, nasal dryness may be another symptom of COVID-19**] https://www.medrxiv.org/content/10.1101/2020.11.18.20233874v1

DRUG DEVELOPMENT

- Mutation-driven evolution of SARS coronavirus-2 (SARS-CoV-2) highlights the need for innovative approaches that simultaneously suppress viral replication and circumvent viral escape routes from host immunity and antiviral therapeutics. Here, we employed genome-wide computational prediction and single-nucleotide resolution screening to reprogram CRISPR-Cas13b against SARS-CoV-2 genomic and subgenomic RNAs. Reprogrammed Cas13b effectors targeting accessible regions of Spike and Nucleocapsid transcripts achieved >98% silencing efficiency in virus free-models. Further, optimized and multiplexed gRNAs suppressed viral replication by up to 90% in mammalian cells infected with replication-competent SARS-CoV-2. *Unexpectedly, the comprehensive mutagenesis of guide-target interaction demonstrated that single-nucleotide mismatches do not impair the capacity of a potent single gRNA to simultaneously suppress ancestral and mutated SARS-CoV-2 in infected mammalian cells, including the highly infectious and globally disseminated Spike D614G mutant. The specificity, efficiency and rapid deployment properties of reprogrammed Cas13b described here provide a molecular blueprint of antiviral therapeutics to simultaneously suppress a wide range of SARS-CoV-2 mutants, and is readily adaptable to other emerging pathogenic viruses*. [**note: this is from Australia and uses reprogrammed CRISPR-CAS13B to suppress SARS-CoV-2 replication. I confess to not fully understanding this.**]
https://www.biorxiv.org/content/10.1101/2020.11.18.389312v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Background It is critical to understand whether infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) protects from subsequent reinfection. Methods We investigated the incidence of SARS-CoV-2 PCR-positive results in seropositive and seronegative healthcare workers (HCWs) attending asymptomatic and symptomatic staff testing at Oxford University Hospitals, UK. Baseline antibody status was determined using anti-spike and/or anti-nucleocapsid IgG assays and staff followed for up to 30 weeks. We used Poisson regression to estimate the relative incidence of PCR-positive results and new symptomatic infection by antibody status, accounting for age, gender and changes in incidence over time. Results A total of 12219 HCWs participated and had anti-spike IgG measured, 11052 were followed up after negative and 1246 after positive antibody results including 79 who seroconverted during follow up. 89 PCR-confirmed symptomatic infections occurred in seronegative individuals (0.46 cases per 10,000 days at risk) and no symptomatic infections in those with anti-spike antibodies. Additionally, 76 (0.40/10,000 days at risk) anti-spike IgG seronegative individuals had PCR-

positive tests in asymptomatic screening, compared to 3 (0.21/10,000 days at risk) seropositive individuals. *Overall, positive baseline anti-spike antibodies were associated with lower rates of PCR-positivity (with or without symptoms) (adjusted rate ratio 0.24 [95%CI 0.08-0.76, p=0.015]). Rate ratios were similar using anti-nucleocapsid IgG alone or combined with anti-spike IgG to determine baseline status. Conclusions Prior SARS-CoV-2 infection that generated antibody responses offered protection from reinfection for most people in the six months following infection. Further work is required to determine the long-term duration and correlates of post-infection immunity*. [**note: here is a large UK study showing antibodies against the virus can prevent reinfection. The big question is still how long immune memory can last.**] https://www.medrxiv.org/content/10.1101/2020.11.18.20234369v1

DIAGNOSTIC DEVELOPMENT

- Nothing new today.

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2020-11-21

Will there be no end to this madness? Not yet! Here is the 'mad scene' from I Puritani where poor Elvira has been stood up by Arturo. Jessica Pratt sings "Ah! Vieni al tempio" from Vincenzo Bellini's I Puritani. Performance of the 19th of April 2018. Courtesy of Teatro Massimo di Palermo: https://www.youtube.com/watch?v=nmSfAJygfc8

On the vaccine front, Noah Feldman has a very good interview with Paul Offitt from UPenn that covers the current vaccine landscape. Dr. Offitt is on the FDA Vaccines Advisory Committee and an inventor of a rotavirus vaccine. There is an excellent explanation of how the new vaccines are constructed and work; a good listen for my non-scientific readers!!!

The Washington Post reports on the recent Danish publication that masks may not provide protection. I noted that this ran counter to other studies. Sure enough the anti-mask groups are now running with this as proof that they don't need to wear masks and should not be forced to. This was entirely predictable. Counties in Kansas that adopted mask mandates during the summer saw COVID-19 cases drop compared to counties that did not. Alert reader will know of the Jena Germany study that was published a couple of months ago that showed the same thing. A comparably sized city did not impose their mandate for several weeks and continued to see cases of COVID-19 while Jena's dropped to close to zero. Obviously, it is not ethical to do an experimental trial on infectious agents with and without masks so we have to rely on these 'natural' experiments. For me it is CLEAR: MASK UP when you go out and may encounter others. Here is a very sad commentary of taxpayers money at work. Senator Johnson should subscribe to my free newsletter!!! Here is an op-ed on why we could have done better.

The New York Times reports on what some epidemiologists are doing for Thanksgiving. Here is a first person account from a Wisconsin medical examiner. This action by the Univ of California football program is just WRONG! Times reporter Carl Zimmer tells you what 95% effective means; it is not what you think.

The Atlantic's Ed Yong profiles a Nebraska hospital that is "America's best-prepared."

MODELING

- Importance: Resurgent COVID-19 cases have resulted in the re-institution non-pharmaceutical interventions, including school closure, which can have adverse effects on families. Understanding the impact of schools on the number of incident and cumulative COVID-19 cases is critical for decision-making. Objective: To determine the quantitative effect of schools being open relative to community-based non-pharmaceutical interventions on the number of COVID-19 cases. Design: An agent-based transmission model. Setting: A synthetic population of one million individuals based on the characteristics of the population of Ontario, Canada. Participants: Members of the synthetic population clustered into households, neighborhoods or rural districts, cities or a rural region, day care facilities, classrooms (primary, elementary or high school), colleges or universities and workplaces. Exposure: School reopening on September 15, 2020, versus schools remaining closed under different scenarios for non-pharmaceutical interventions. Main Outcome and Measures: Incident and cumulative COVID-19 cases between September 1, 2020 and October 31, 2020. Results: The percentage of infections among students and teachers acquired within schools was less than 5% across modelled scenarios. Incident case numbers on October 31, 2020, were 4,414 (95% credible interval, CrI: 3,491, 5,382) and 4,740 (95% CrI 3,863, 5,691), for schools remaining closed versus reopening, respectively, with no other community-based non-pharmaceutical intervention; 714 (95%, CrI: 568, 908) and 780 (95% CrI 580, 993) for schools remaining closed versus reopening, respectively, with community-based non-pharmaceutical interventions implemented; 777 (95% credible CrI: 621, 993) and 803 (95% CrI 617, 990) for schools remaining closed versus reopening, respectively, applied to the observed case numbers in Ontario in early October 2020. *Contrasting the scenarios with implementation of community-based interventions versus not doing so yielded a mean difference of 39,355 cumulative COVID-19 cases by October 31, 2020, while keeping schools closed versus reopening them yielded a mean difference of 2,040 cases. Conclusions and relevance: Our simulations suggest that the majority of COVID-19 infections in schools were due to acquisition in the community rather than transmission within schools and that the effect of school reopening on COVID-19 case numbers is relatively small compared to the effects of community-based non-pharmaceutical interventions.* [**note: this study comes from Ontario and looks at the impact of school closure relative to other interventions. Yes, keeping schools, particularly primary schools open does not markedly increase the disease burden.**]
  https://www.medrxiv.org/content/10.1101/2020.11.18.20234351v1
- The SARS-CoV-2 virus has been rapidly spreading globally since December 2019, triggering a pandemic, soon after its emergence, with now more than one million deaths around the world. While Iran was among the first countries confronted with rapid spread of virus in February, no real-time SARS-CoV-2 whole-genome tracking is performed in the country. To address this issue, we provided 50 whole-genome sequences of viral isolates ascertained from different geographical locations in Iran during March-July 2020. The corresponding analysis on origins, transmission dynamics and genetic diversity, represented at least two introductions of the virus into the country, constructing two major clusters defined as B.4 and B.1*. *The first entry of the virus occurred around 26 December 2019, as suggested by the time to the most recent common ancestor, followed by a rapid community transmission, led to dominancy of B.4 lineage in early epidemic till the end of June. Gradually, reduction in dominancy of B.4 occurred possibly as a result of other entries of the virus, followed by surge of B.1.* lineages, as of mid-May. Remarkably, variation tracking of the virus indicated the increase in frequency of D614G*

mutation, along with B.1 lineages, which showed continuity till October 2020. According to possible role of D614G in increased infectivity and transmission of the virus, and considering the current high prevalence of the disease, dominancy of this lineage may push the country into a critical health situation. Therefore, current data warns for considering stronger prohibition strategies preventing the incidence of larger crisis in future.* [**note: this is a survey of the outbreak in Iran that shows two distinct events. Interesting that they time the first event in late December of 2019.**] https://www.medrxiv.org/content/10.1101/2020.11.16.20229047v1

NEWLY REGISTERED CLINICAL TRIALS

- Take a deep breath and think, Tomorrow.

CLINICAL TRIAL RESULTS

- Abstract It has been estimated that individuals with COVID-19 can shed replication-competent virus up to a maximum of twenty days after initiation of symptoms. This report describes two patients with mild forms of the disease who shed replication-competent virus for 24 and 37 days, respectively, after symptom onset [**note this comes from Brazil and only covers two cases. It's not known what the total number of cases might be so this might be an extremely rare event. There is also no serology or other clinical lab data that might explain why the two women are shedding virus for so long.**]
https://www.medrxiv.org/content/10.1101/2020.11.18.20232546v1
- Rationale: Remdesivir and dexamethasone reduced the severity of COVID-19 in clinical trials. However, their individual or combined effectiveness in clinical practice remains unknown. Objectives: To examine the effectiveness of remdesivir with or without dexamethasone. Methods: We conducted a multicenter, retrospective cohort study between March 4 and August 29, 2020. Eligible COVID cases were hospitalized patients treated with remdesivir with or without dexamethasone. We applied a Cox proportional hazards model with propensity score matching to estimate the effect of these treatments on clinical improvement by 28 days (discharge or a 2-point decrease in WHO severity score) and 28-day mortality. Measurements and Main Results: Of 2485 COVID-19 patients admitted between March 4 and August 29, 2020, 342 received remdesivir and 157 received remdesivir plus dexamethasone. Median age was 60 years; 45% were female; 81% were non-white. Remdesivir recipients on room air or nasal cannula oxygen had a faster time to clinical improvement (median 5.0 days [IQR 4.0, 8.0], remdesivir vs. 7.0 days [IQR 5.0, 12.0], control; adjusted hazard ratio (aHR) 1.55 [1.28; 1.87]), yet those requiring higher levels of respiratory support did not benefit. Remdesivir recipients had lower, but statistically insignificant, 28-day mortality (7.6% [23 deaths], remdesivir vs. 14.9% [45 deaths], control). Adding dexamethasone trended toward lower 28-day mortality compared to remdesivir alone (5.1% [8 deaths] vs. 9.2% [17 deaths]; aHR 0.14 [0.02; 1.03]). Conclusions: *Remdesivir offered a significantly faster time to clinical improvement among a cohort of predominantly non-white patients hospitalized with COVID-19, particularly with mild-moderate disease. Remdesivir plus dexamethasone may reduce mortality*. [**note: here is a study of remdesivir + dexamethasone from Johns Hopkins.**]
https://www.medrxiv.org/content/10.1101/2020.11.19.20234153v1
- While changes in SARS-CoV-2 viral load over time have been documented, detailed information on the impact of remdesivir and how it might alter intra-host viral evolution is limited.

Sequential viral loads and deep sequencing of SARS-CoV-2 recovered from the upper respiratory tract of hospitalised children revealed that remdesivir treatment suppressed viral RNA levels in one patient but not in a second infected with an identical strain. Evidence of drug resistance to explain this difference was not found. Reduced levels of subgenomic (sg) RNA during treatment of the second patient, suggest an additional effect of remdesivir on viral replication that is independent of viral RNA levels. Haplotype reconstruction uncovered persistent SARS-CoV-2 variant genotypes in four patients. We conclude that these are likely to have arisen from within-host evolution, and not co-transmission, although superinfection cannot be excluded in one case. *Sample-to-sample heterogeneity in the abundances of variant genotypes is best explained by the presence of discrete viral populations in the lung with incomplete population sampling in diagnostic swabs. Such compartmentalisation is well described in serious lung infections caused by influenza and Mycobacterium tuberculosis and has been associated with poor drug penetration, suboptimal treatment and drug resistance. Our data provide evidence that remdesivir is able to suppress SARS-CoV-2 replication in vivo but that its efficacy may be compromised by factors reducing penetration into the lung. Based on data from influenza and Mycobacterium tuberculosis lung infections we conclude that early use of remdesivir combined with other agents should now be evaluated*. [**note: this is from the UK and shows that remdesivir action can be compromised if it cannot get to where the virus is.**]
https://www.medrxiv.org/content/10.1101/2020.11.18.20230599v1

DRUG DEVELOPMENT

- Coronavirus disease 2019 (COVID-19) has caused serious public health, social, and economic damage worldwide and effective drugs that prevent or cure COVID-19 are urgently needed. Approved drugs including Hydroxychloroquine, Remdesivir or Interferon were reported to inhibit the infection or propagation of severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2), however, their clinical efficacies have not yet been well demonstrated. To identify drugs with higher antiviral potency, we screened approved anti-parasitic/anti-protozoal drugs and identified an anti-malarial drug, Mefloquine, which showed the highest anti-SARS-CoV-2 activity among the tested compounds. Mefloquine showed higher anti-SARS-CoV-2 activity than Hydroxychloroquine in VeroE6/TMPRSS2 and Calu-3 cells, with IC50=1.28 µM, IC90=2.31 µM, and IC99=4.39 µM in VeroE6/TMPRSS2 cells. Mefloquine inhibited viral entry after viral attachment to the target cell. Combined treatment with Mefloquine and Nelfinavir, a replication inhibitor, showed synergistic antiviral activity. Our mathematical modeling based on the drug concentration in the lung predicted that Mefloquine administration at a standard treatment dosage could decline viral dynamics in patients, reduce cumulative viral load to 7% and shorten the time until virus elimination by 6.1 days. These data cumulatively underscore Mefloquine as an anti-SARS-CoV-2 entry inhibitor. [**note: from Japan, *in vitro* data for the anti-malarial mefloquine as a viral entry inhibitor. Maybe it works better than HCQ and maybe it doesn't. At least this group has a plausible mechanism.**]
https://www.biorxiv.org/content/10.1101/2020.11.19.389726v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- Objective: To determine the longevity and immunophenotype of SARS-CoV-2-specific Bmem cells in COVID-19 patients. Methods: Recombinant spike receptor binding domain (RBD) and

nucleocapsid protein (NCP) were produced for ELISA-based serology, and biotinylated for fluorescent tetramer generation to identify SARS-CoV-2-specific Bmem cells by flow cytometry with a panel of 13 mAbs. 36 blood samples were obtained from 25 COVID-19 patients (11 paired) between 4-242 days post-symptom onset for detection of neutralizing antibodies, IgG serology and flow cytometry. Results: The recombinant RBD and NCP were specifically recognized by serum IgG in all patients and reactivity declined >20 days post-symptom onset. All patients had detectable RBD- and NCP-specific Bmem cells at 8.23-267.6 cells/ml of blood (0.004-0.13% of B cells) regardless of sampling time. RBD- and NCP-specific Bmem cells predominantly expressed IgM or IgG1, with the latter formed slightly later than the former. RBD-specific IgG+ Bmem were predominantly CD27+, and numbers significantly correlated with circulating follicular helper T cell numbers. Conclusion: *RBD- and NCP-specific Bmem cells persisted for 8 months, indicating that the decline in serum antibodies after 1 month does not indicate waning of immunity but a contraction of the immune response. Flowcytometric detection of SARS-CoV-2-specific Bmem cells enables detection of long-term functional immunity following infection or vaccination for COVID-19*. [**note: this is from Australia and looks at B cell memory in convalescent patients.**]
https://www.medrxiv.org/content/10.1101/2020.11.17.20233544v1

DIAGNOSTIC DEVELOPMENT

- Nothing exciting today. We still need home tests that are easy to use!!!!!

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2020-11-22

For reflection Sunday, how about a full-length opera? What better choice for the pandemic than Verdi's La Traviata (La Boheme might also be appropriate)? Here is a just-opened production from Madrid with Marina Rebeka as Violetta and one of my favorite tenors, Michael Fabiano as Alfredo. It's interesting that the chorus come out wearing masks and there are lines on the stage that keep them socially distanced. Once they start singing the masks come off and I hope they all had COVID-19 tests. The string players in the pit are all wearing masks. This is a very nice production courtesy of the OperaVision YouTube channel: https://www.youtube.com/watch?v=0SqpcFOchjA It is good to see that live performances are still taking place in parts of our world.

I'll give a quick shout out to our local recital series, Vocal Arts DC, that is doing all virtual recitals this season as the Kennedy Center is closed because of COVID-19. For those interested in classical song recitals, this is a good chance to see some wonderful singers. First up is tenor Matthew Polenzani accompanied by Natalia Katyukova. Streaming information on this and other upcoming recitals is at: https://vocalartsdc.org/ Tickets for the stream are reasonable at $20. I would urge all of my readers to support the arts in some fashion during this period.

The Washington Post has an article about healthcare professionals wanting more data before championing vaccines to end the pandemic. Personally, I trust the FDA and the Vaccines Advisory Committee to make the right decision. This whole thing is a bit like the Heisenberg Uncertainty Principle, you can either know where something is or how fast it is traveling, but not both. Who should get vaccinated first? I say healthcare workers, first responders and schoolteachers! The vaccine rollout

will take some time and we cannot afford to stop being vigilant. The Regeneron monoclonal antibody cocktail received FDA approval.

The New York Times has a nice article on the development of both the Pfizer/BioNTech and Moderna mRNA vaccines.

MODELING

- Nothing today.

NEWLY REGISTERED CLINICAL TRIALS (Yes today is the day you can read this section)

- This is the first study of COVI-VAC in humans. The purpose of the study is to evaluate the safety and immune response of COVI-VAC (a live attenuated vaccine to prevent COVID-19) in healthy adults aged 18 to 30 years. Approximately 48 participants will be enrolled into 1 of 3 dose groups (low, medium, high). Within each of these dose groups, participants will be assigned randomly to receive either 2 doses of COVI-VAC 28 days apart, 2 doses of placebo (saline), or 1 dose of COVI-VAC and 1 dose of placebo. COVI-VAC or placebo is administered by drops into each nostril. Neither the participants nor the researchers will know whether COVI-VAC or placebo has been received. [**note: this is a new vaccine trial of an attenuated virus from Codagenix.**] NCT04619628
- SARS-CoV-2 is the agent responsible for a new infectious respiratory disease called Covid-19 (for CoronaVirus Disease 2019) which is mainly characterized by potentially severe and fatal lung damage. The severity of the clinical signs associated with this pathology requires the admission to hospital of approximately 20% of patients, 5%-10% of whom will be admitted to intensive care. The most severe cases of this pathology begin with dyspnea which worsens rapidly around the 7th-10th day of the disease into an acute respiratory distress syndrome (ARDS) which requires the patient to be put under mechanical ventilation in the intensive care unit and is responsible for the majority of deaths. Certain biological parameters suggest a massive and brutal release of cytokines (interleukins IL-6, IL-8 and IL-10 mainly) secondary to a syndrome of macrophagic activation mainly in the pulmonary level. Several therapeutic trials aimed at reducing or controlling this immune storm are in progress (anti IL-6 antibodies, anti r IL6 Ab, corticosteroids). Molecular hydrogen acts on the final path of this complex inflammatory cascade by inhibiting the cellular action of reactive oxygen species. Its early use combined with nasal oxygen therapy could prevent this worsening of the respiratory system, so could be likely to limit the risk of overflow of intensive care services during the pandemic and save lives. The aim of this study is to evaluate the safety and the Dose Limiting Toxicity (DLT) of hydrogen therapy delivered by a nasal cannula in addition to conventional oxygen therapy in patients with moderate Covid-19 [**note: I'm not sure about the rationale of using hydrogen. They better make sure the patients are tethered so they don't float away.**] NCT04633980
- Single-center study with a parallel group scheme, double-blind, randomized, placebo-controlled, to evaluate whether the addition to the investigator's hospital standard therapy of two vials of Bioarginina® per day in subjects with SARS-CoV-2 is useful for treatment of this pathology. Preliminary experiences conducted in patients affected by SARS-CoV-2 infection by adding the daily oral administration of two vials of Bioarginina® to the standard therapy have shown

favorable effects on discharge times, on the recovery of the number of lymphocytes and on the P \ F ratio between arterial pO2 and FiO2 breathed. In particular, for the latter parameter there is almost a doubling of the recovery speed. [**note: this is a dietary supplement of L-arginine. Not sure this will work but any port in a storm.**] NCT04637906

- To evaluate the safety and tolerability, the antiviral activity, and plasma pharmacokinetics (PK) of zotatifin administered intravenously (IV) to adults with mild or moderate COVID-19 [**note: this study is sponsored by Effector Therapeutics.**] NCT04632381

CLINICAL TRIAL RESULTS

- Therapies to interrupt progression of early COVID-19 remain elusive. Among them, convalescent plasma in hospitalized patients was unsuccessful, perhaps because antibody should be administered earlier. We advanced plasma infusions to the first 72 hours of symptoms to arrest COVID-19 progression. Methods. A randomized, double-blind, placebo-controlled trial of convalescent plasma with high IgG titers against SARS-CoV2 in elderly subjects within 72 hours of mild COVID-19 symptoms. The primary endpoint was severe respiratory disease defined as a respiratory rate ≥30 and/or an O2 sat<93% in room air. The study was interrupted at 76% of its projected sample size, because cases in the region decreased considerably and steady enrollment of study subjects became virtually impossible. Results. 160 patients underwent randomization. In the intention-to-treat analysis (ITT), 13/80(16.2%) patients receiving plasma vs. 25/80(31.2%) receiving placebo experienced severe respiratory disease [RR(95%CI)= 0.52(0.29,0.94); p=0.026)] with an RRR=48%. A modified ITT analysis, excluding six subjects who experienced the primary endpoint before infusion, showed a larger effect size [RR(95%CI) = 0.40(0.20, 0.81), p=0.007]. High- and low-titer donor analyses, based on a median IgG titer=1:3,200, evidenced a dose-dependent response with an RRR=73.3% for recipients of high-titer plasma (p=0.016) and a number needed to treat (NNT)=4.4. *All secondary endpoints exhibited trends towards protection. No solicited adverse events were observed. Conclusions. Early administration of high-titer convalescent plasma against SARS-CoV2 to mildly ill infected seniors reduced COVID-19 progression. This safe, inexpensive, outpatient intervention facilitates access to treatment from industrialized to LMIC, can decompress demands on hospitals, and may contribute to save lives*. [**note: here is a trial of high titer convalescent plasma in elderly patients. Plasma is given very early on.**
https://www.medrxiv.org/content/10.1101/2020.11.20.20234013v1
- Background: It has been reported that a few recovered COVID-19 patients could suffer repeat positive, testing positive for the SARS-CoV-2 virus again after they were discharged from hospital. Understanding the epidemiological characteristics of patients with repeat positive is vital in preventing a second wave of COVID-19. Methods: In this study, the epidemiological and clinical features for 20,280 COVID-19 patients from multiple centers between 31 December 2019 and 4 August 2020 in Wuhan were collected and followed. *In addition, the RT-qPCR testing results for 4,079 individuals who had close contact with the patients suffering repeat positive were also obtained. Results: 2,466 (12.16%) of 20,280 patients presented with a repeat positive of SARS-CoV-2 after they were discharged from hospital. 4,079 individuals had close contact with them. The PCR result were negative for the 4,079 individuals. Conclusions: By a follow-up study in Wuhan, we show the basic characteristics of patients with repeat positive and no new infections caused by patients with repeat positive of COVID-19*. [**note: here is data from Wuhan on**

patients who suffered from repeat positive tests for SARS-CoV-2 following discharge from the hospital. This has always been confounding in that patients may be totally asymptomatic and not capable of transmitting virus.]
https://www.medrxiv.org/content/10.1101/2020.11.18.20232892v1

DRUG DEVELOPMENT

- Among therapeutic options, the use of the anti-parasitic drug ivermectin (IVM), has been proposed, given its possible anti-SARS-CoV-2 activity. Ivermectin is a positive allosteric modulator of the alpha-7 nicotinic acetylcholine receptor, which has been suggested to represent a target for the control of Covid-19 infection, with a potential immunomodulatory activity. We assessed the effects of IVM in SARS-CoV-2-intranasally-inoculated golden Syrian hamsters. *Even though ivermectin had no effect on viral load, SARS-Cov-2-associated pathology was greatly attenuated. IVM had a sex-dependent and compartmentalized immunomodulatory effect, preventing clinical deterioration and reducing olfactory deficit in infected animals. Importantly, ivermectin dramatically reduced the Il-6/Il-10 ratio in lung tissue, which likely accounts for the more favorable clinical presentation in treated animals. Our data support IVM as a promising anti-COVID-19 drug candidate*. [**note: here is some animal data on ivermectin. I've seen other papers on this as well. However, there are a number of registered controlled trials for the drug and no results have come out yet. I put more faith in the human trials than animal or *in vitro* data.**] https://www.biorxiv.org/content/10.1101/2020.11.21.392639v1

VIRUS BIOCHEMISTRY & IMMUNOLOGY

- SARS-CoV-2 has initiated a global pandemic and vaccines are being rapidly developed. Using the reference strain SARS-CoV-2 USA-WA1/2020, we evaluated modes of transmission and the ability of prior infection or vaccine-induced immunity to protect against infection in ferrets. Ferrets were semi-permissive to infection with the USA-WA1/2020 isolate. When transmission was assessed via the detection of vRNA at multiple timepoints, direct contact transmission was efficient to 3/3 and 3/4 contact animals in two respective studies, while respiratory transmission was poor to only 1/4 contact animals. To assess the durability of immunity, ferrets were re-challenged 28 or 56 days post-primary infection. Following viral challenge, no infectious virus was recovered in nasal wash samples. In addition, levels of vRNA in the nasal wash were several orders of magnitude lower than during primary infection, and vRNA was rapidly cleared. To determine if intramuscular vaccination protected ferrets against infection, ferrets were vaccinated using a prime-boost strategy with the S-protein receptor-binding domain formulated with an oil-in-water adjuvant. *Upon viral challenge, none of the mock or vaccinated animals were protected against infection, and there were no significant differences in vRNA or infectious virus titers in the nasal wash. Combined these studies demonstrate that in ferrets direct contact is the predominant mode of transmission of the SARS-CoV-2 USA-WA1/2020 isolate and immunity to SARS-CoV-2 is maintained for at least 56 days. Our studies also indicate protection of the upper respiratory tract against SARS-CoV-2 will require vaccine strategies that mimic natural infection or induce site-specific immunity*. [**note: here is some data on immunity and reinfection in the ferret model. I don't know what make of the lack of protection noted for the vaccinated animals. It does appear that antibody protection in this model is lasting and prevents reinfection.**] https://www.biorxiv.org/content/10.1101/2020.11.20.392381v1

DIAGNOSTIC DEVELOPMENT

- The association of mortality with early humoral response to SARS-CoV-2 infection within the first few days after onset of symptoms (DAOS) has not been thoroughly investigated partly due to a lack of sufficiently sensitive antibody testing methods. Here we report two sensitive and automated testing-on-a-probe (TOP) biosensor assays for SARS-CoV-2 viral specific total antibodies (TAb) and surrogate neutralizing antibodies (SNAb), which are suitable for clinical use. The TOP assays employ an RBD-coated quartz probe using a Cy5-Streptavidin-polysacharide conjugate to improved sensitivity and minimize interference. Disposable cartridge containing pre-dispensed reagents requires no liquid manipulation or fluidics during testing. The TOP-TAb assay exhibited higher sensitivity in the 0-7 DAOS window than a widely used FDA-EUA assay. The rapid (18 min) and automated TOP-SNAb correlated well with two well-established SARS-CoV-2 virus neutralization tests. The clinical utility of the TOP assays was demonstrated by evaluating early antibody responses in 120 SARS-CoV-2 RT-PCR positive adult hospitalized patients. Higher baseline TAb and SNAb positivity rates and more robust antibody responses were seen in patients who survived COVID-19 than those who died in the hospital. Survival analysis *using the Cox Proportional Hazards Model showed that patients who were TAb and SNAb negative at initial hospital presentation were at a higher risk of in-hospital mortality. Furthermore, TAb and SNAb levels at presentation were inversely associated with SARS-CoV-2 viral load based on concurrent RT-PCR testing. Overall, the sensitive and automated TAb and SNAb assays allow detection of early SARS-CoV-2 antibodies which associate with mortality*. [**note: this is a nifty study from Cornell Medical School on a sensitive bioassay for antibodies.**] https://www.medrxiv.org/content/10.1101/2020.11.19.20235044v1

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