2020-05-25

Welcome to Week 10!!!

Back in the day, The Righteous Brothers were chart toppers. One of the major hits was Unchained Melody which was also used in the movie Ghost with Demi Moore and Patrick Swayze (who can ever forget that movie?). Here is a video clip of Bobby Hatfield from 1965: https://www.youtube.com/watch?v=IYj2hex99gY The song has an interesting origin and now it is time for another **CONTEST**. **A nice prize will go to the first person to correctly identify the first person to sing the song and what that person was really famous for**!!! This was one of my best bar bets of all time and I never found anyone who could provide the correct answer. I will give you a couple of hints. It was not Bobby Hatfield nor was it Elvis (who did a decent job with it). Put your thinking caps on!!!

Here is a super special musical treat for you all: https://youtu.be/_Y3iT__o67M The pop star JoJo makes a surprise visit to a Zoom group of Healthcare Heroes led by one of the music therapists at UCSF Benioff Children's Hospital, none other than the great **Jenny Goldhammer**!!!

Good article in The New York Times on how people are monetizing their skills during the lockdown. There is even a platform for people writing newsletters! How did I miss this boat? I'm not sure how many loyal readers I would have if I began to charge.

Interesting STAT column on some similarities with the 1720 Bubonic Plague outbreak in France.

Sophie Zhang on the emerging COVID-19 vaccine conspiracy.

The Oxford researchers are now less certain that they can prove efficacy of the vaccine in UK field trials. The virus is on the wane in the UK as with other areas where vaccines are in trials. A couple of my loyal readers asked whether challenge trials might be a solution to this. At the end of April I did write about this issue:

> Yesterday, some readers and I had a discussion of vaccine trial policy and whether active challenge studies are useful. Here is the thorny ethical issue. This group is proposing to do challenge studies using live SARS-CoV-2 to help speed vaccine research (with a placebo arm!!!). At least one newspaper interviewed a couple of people who signed up and there have been some prominent scientists who have written on this and also here.. What I find baffling is that most often the rate limiting steps in vaccine development are the safety assessments. The 1 in 10,000 rare AE requires a trial of 30,000 to statistically show whether there is a concern. Are we going to reach the point where a vaccine is not fully characterized, and a consent form will need to bd signed off on? I know these are times to think outside the box, but this particular idea does not strike me as wise. Ask yourself if you are sitting on an Institutional Review Board, would you approve a challenge trial such as this? A French group did an interesting survey of intent to participate in a vaccine clinical trial during the pandemic. Nearly 75 % and 48 % of the survey responders were likely to accept vaccination or participation in a clinical trial against COVID-19. Vaccine hesitancy will be the major barrier to COVID-19 vaccine uptake.

It may be that we need to do human challenge trials to answer this question. However, if the virus infection rate drops down because of quasi-herd immunity, how will we ever be sure a vaccine is useful. There is still a lot we just don't understand.

Some very interesting abstracts today!

MODELING

- So far, 170,000 Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) infections have been confirmed in Germany, of which more than 5,000 have been detected in the Frankfurt am Main metropolitan region. When examining 1,000 nasopharyngeal swabs and serum samples from healthy volunteers from this region, one RT-PCR-positive and five antibody-positive persons were identified. The five positive serum samples were confirmed to be specific. Four of the five positive sera cross-neutralized SARS-CoV. [**note: even the authors of the paper are surprised by the low number of positive persons. They do note the sampling problem (these were all volunteers) which may not be representative of the greater population. As the virus appears to be waning in some areas, greater serology testing is warranted to see why this may be happening; perhaps herd immunity is much lower than with other infectious diseases.**] https://www.medrxiv.org/content/10.1101/2020.05.20.20107730v1
- Objective: To determine the prevalence of SARS-CoV-2 infection among asymptomatic COVID-19 facing and non-COVID-19 facing Healthcare Workers (HCWs), with varying job categories across different hospitals. Design: Cross-sectional analysis of a healthcare system surveillance program that included asymptomatic clinical (COVID-19 facing and non-COVID-19 facing), and non-clinical HCWs. A convenience sample of asymptomatic community residents (CR) was also tested. Proportions and 95% confidence intervals (CI) of SARS-CoV-2 positive HCWs are reported. Proportional trend across HCW categories was tested using Chi Square trend test. Logistic regression model-based likelihood estimates of SARS-CoV-2 prevalence among HCWs with varying job functions and across different hospitals are reported as adjusted odds ratios (aOR) and CI. Setting: Healthcare system comprising one tertiary care academic medical center and six large community hospitals across Greater Houston and a community sample. Participants: 2,872 self-reported asymptomatic adult (> 18 years) HCWs and CRs. Exposure: Clinical HCWs in COVID-19 and non-COVID-19 units, non-Clinical HCWs, and CRs. Job categories of Nursing, Providers, Allied Health, Support, and Administration / Research. Seven hospitals in the healthcare system. Main Outcomes: Positive reverse transcriptase polymerized chain reaction (RT-PCR) test for SARS-CoV-2 Results: Among 2,872 asymptomatic HCWs and CRs, 3.9% (CI: 3.2 - 4.7) tested positive for SARS-CoV-2. Mean (SD) age was 40.9 (11.7) years and 73% were females. Among COVID-19 facing HCWs 5.4% (CI: 4.5 - 6.5) were positive, whereas 0.6% (CI: 0.2 - 1.7%) of non COVID-19 facing HCWs and none of the non-clinical HCWs or CRs were positive (Ptrend < 0.001). Among COVID-19 facing HCWs, SARS-CoV-2 positivity was similar for all job categories (p = 0.74). However, significant differences in positivity were observed across hospitals. Conclusions and Relevance: Asymptomatic HCWs with COVID-19 patient exposure had a higher rate of SARS-CoV-2 positive testing than those not routinely exposed to COVID-19 patients and those not engaged in patient care. Among HCWs with routine COVID-19 exposure, all job types had relatively similar infection rates. These data can inform hospital surveillance and infection control

practices for patient-facing job classifications and suggest that general environmental exposure within hospitals is not a significant source of asymptomatic SARS-CoV-2 infection. [**note: infection rates among healthcare workers in Houston. Those involved in direct patient care had higher rates of infection.**]
https://www.medrxiv.org/content/10.1101/2020.05.21.20107581v1

- Importance Recent reports have shown that hypertension is the most common comorbidity associated with mortality in the current coronavirus disease 2019 (COVID-19). This has been related to the use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) as animal studies indicate that these medications increase levels of ACE2, the cellular entry point for the coronavirus SARS-CoV-2. This has prompted clinicians to recommend discontinuing ACEIs and ARBs. Objective To examine the effect of ACEIs or ARBs treatment on serum levels of ACE2 and other key enzymes in the renin-angiotensin system (RAS). Design, Setting, and Participants A single center population-based study of 5457 Icelanders from the Age, Gene/Environment Susceptibility Reykjavik Study (AGES-RS) of the elderly (mean age 75+/-6 years) stratified by ACEIs (N = 699) or ARBs (N = 753) treatment. Main Outcomes and Measures The AGES-RS study population was stratified by ACEIs and ARBs medication use and compared for age, body mass index (BMI) (kg/m2), hypertension and type 2 diabetes (T2D) as well as serum levels of renin, ACE and ACE2. Results While renin and ACE levels were significantly raised in serum of individuals on ACEIs or ARBs treatments, the ACE2 levels remained unaffected. Conclusions and Relevance Treatment with ACEIs or ARBs does not raise ACE2 levels in serum. Therefore, the present study does not support the proposed discontinuation of these medications among patients affected with COVID-19. [**note: data from Iceland showing that ACE and ARB drugs do not raise ACE2 levels which is the point of entry for SARS-CoV-2. More evidence that patients on these drugs should not discontinue use. We are still waiting to see if they might be protective in some manner.**]
https://www.medrxiv.org/content/10.1101/2020.05.21.20108738v1
- ABSTRACT. BACKGROUND. When the lockdowns are relaxed, the responsibility of mitigating the COVID-19 spread shifts from the governments to the individuals. To know how to conduct one-self, it is important for everyone to know the risks of transmission during the quotidian activities - meetings, meals, etc, from individuals who are known to them and looking healthy. METHODS. The detailed case-studies corresponding to 425 infections upon point-exposures over a specified duration are curated. The data from the case studies is summarized and reorganized to reflect different situations from the daily life. A meta-analysis of the attack rates of transmission and the number of infections per infected person are performed. RESULTS. The attack rates are very high in family dinners (66.7% (48.8-80.8%)) compared to sit-down dinners with lesser mixing among people eating at different tables (15.7% (12.1-20.1%)), both lasting a couple of hours. In an open workspace office floor organized in a two-half structure with shared elevators and restrooms and the employees speaking continuously, the average attack rate over the course of a few days was much higher in one half (78.7% (70.3-85.3%)) than the one for the entire floor (43.5% (37.0-50.1%)). Inferred data suggests that the transmission in elevators and trains may be lower under the conditions of using masks. In most of the instances we studied, the infected individuals spreading (35/44) and even super-spreading (3/6) were mostly without symptoms of coughing, sneezing or a fever. CONCLUSIONS. *Although the basic reproduction number R0 is around 3.0, the number of infections caused, including the super-spreading events, seem to be*

limited by the number of personal interactions in a group and their proximity. By acknowledging the risks in daily life, from healthy-looking persons, one may be able to organize their interactions better to reduce the chances of spreading or super-spreading infections. [**note: yes, I know I promised to stop posting modeling studies. But with a title "Eat, Pray, Work: A meta-analysis of COVID-19 Transmission Risk n Common Activities of Work and Leisure," this one was too good to pass up! I like the common sense conclusion.**]
https://www.medrxiv.org/content/10.1101/2020.05.22.20110726v1

- Influenza viruses have caused disease outbreaks in human societies for a long time. Influenza often has rapid onset and relatively short duration, both in the individual and in the population. The case fatality rate varies for different strains of the virus, as do the effects on total mortality. Outbreaks related to coronavirus infections have recently become a global concern but much less is known about the dynamics of these outbreaks and their effects on mortality. In this work, disease outbreaks in Sweden, in the time period of 1860-2020, are characterized and compared to the currently ongoing COVID-19 outbreak. The focus is on outbreaks with a sharp increase in all-cause mortality. Outbreak onset is defined as the time point when deaths counts starts to increase consistently for a period of 10 days. The duration of the outbreak is defined as the time period in which mortality rates are elevated. Excess mortality is estimated by standard methods. In total there were 15 outbreaks detected in the time period, the first 14 were likely caused by influenza virus infections, the last by SARS-CoV-2. The mortality dynamics of the SARS-CoV-2 outbreak is shown to be similar to outbreaks due to influenza virus, and in terms of the number of excess deaths, might become the worst outbreak since the 'Spanish flu' of 1918-1919. [**note: Sweden has taken a different approach and this Swedish researcher looked back at past epidemics. This one may be the worst since the 'Spanish Flu' of 1918.**]
https://www.medrxiv.org/content/10.1101/2020.05.22.20110320v1

NEWLY REGISTERED CLINICAL TRIALS

- Will check tomorrow. There are over 1800 trials registered on the National Library of Medicine database!

CLINICAL TRIAL RESULTS

- Background: There is evolving evidence of significant differences in severity and outcomes of coronavirus disease 2019 (COVID-19) in children compared to adults. Underlying medical conditions associated with increased risk of severe disease are based on adult data, but have been applied across all ages resulting in large numbers of families undertaking social shielding (vulnerable group). We conducted a retrospective analysis of children with suspected COVID-19 at a Specialist Childrens Hospital to determine outcomes based on COVID-19 testing status and underlying health vulnerabilities. Methods: Routine clinical data were extracted retrospectively from the Institutions Electronic Health Record system and Digital Research Environment for patients with suspected and confirmed COVID-19 diagnoses. Data were compared between Sars-CoV-2 positive and negative patients (CoVPos / CoVNeg respectively), and in relation to presence of underlying health vulnerabilities based on Public Health England guidance. Findings: Between 1st March and 15th May 2020, 166 children (<18 years of age) presented to a specialist childrens hospital with clinical features of possible COVID-19 infection. 65 patients (39.2%) tested positive for SARS-CoV-2 virus. CoVPos patients were older (median 9 [0.9-14] years vs

median 1 [0.1-5.7.5] years respectively, p<0.001). There was a significantly reduced proportion of vulnerable cases (47.7% vs 72.3%, p=0.002), but no difference in proportion of vulnerable patients requiring ventilation (61% vs 64.3%, p = 0.84) between CoVPos and CoVNeg groups. However, a significantly lower proportion of CoVPos patients required mechanical ventilation support compared to CoVNeg patients (27.7 vs 57.4%, p<0.001). Mortality was not significantly different between CoVPos and CoVNeg groups (1.5 vs 4% respectively, p=0.67) although there were no direct COVID-19 related deaths in this highly preselected paediatric population. Interpretation: COVID-19 infection may be associated with severe disease in childhood presenting to a specialist hospital, but does not appear significantly different in severity to other causes of similar clinical presentations. In children presenting with pre-existing COVID-19 vulnerable medical conditions at a specialist centre, there does not appear to be significantly increased risk of either contracting COVID-19 or severe complications, apart from those undergoing chemotherapy, who are over-represented. [**note: interesting UK data on children. Something is different even those with vulnerable conditions don't seem to be markedly effected.]** https://www.medrxiv.org/content/10.1101/2020.05.20.20107904v1

- Background: Hydroxychloroquine has been touted as a COVID-19 treatment. Tocilizumab, an inhibitor of IL-6, has been proposed as a treatment of critically ill patients. Objective: To describe the association between mortality and hydroxychloroquine or tocilizumab therapy among hospitalized COVID-19 patients. Design: Retrospective observational cohort study of electronic health records Setting: 13-hospital network spanning the state of New Jersey. Participants: Patients hospitalized between March 1, 2020 and April 22, 2020 with positive polymerase chain reaction results for SARS-CoV-2. Follow up was through May 5, 2020. Main Outcomes: The primary outcome was death. Results: Among 2512 hospitalized patients with COVID-19 there have been 547 deaths (22%), 1539 (61%) discharges and 426 (17%) remain hospitalized. 1914 (76%) received at least one dose of hydroxychloroquine and 1473 (59%) received hydroxychloroquine with azithromycin. After adjusting for imbalances via propensity modeling, compared to receiving neither drug, there were no significant differences in associated mortality for patients receiving any hydroxychloroquine during the hospitalization (HR, 0.99 [95% CI, 0.80-1.22]), hydroxychloroquine alone (HR, 1.02 [95% CI, 0.83-1.27]), or hydroxychloroquine with azithromycin (HR, 0.98 [95% CI, 0.75-1.28]). The 30-day unadjusted mortality for patients receiving hydroxychloroquine alone, azithromycin alone, the combination or neither drug was 25%, 20%, 18%, and 20%, respectively. Among 547 evaluable ICU patients, including 134 receiving tocilizumab in the ICU, an exploratory analysis found a trend towards an improved survival association with tocilizumab treatment (adjusted HR, 0.76 [95% CI, 0.57-1.00]), with 30 day unadjusted mortality with and without tocilizumab of 46% versus 56%. Conclusions: This observational cohort study suggests hydroxychloroquine, either alone or in combination with azithromycin, was not associated with a survival benefit among hospitalized COVID-19 patients. Tocilizumab demonstrated a trend association towards reduced mortality among ICU patients. Our findings are limited to hospitalized patients and must be interpreted with caution while awaiting results of randomized trials. [**note: observational data from hard hit New Jersey. HCQ ± azithromycin was not associated with any survival benefit. Tocilizumab use may be of use but more data is needed. TIWWDCT!**]
https://www.medrxiv.org/content/10.1101/2020.05.21.20109207v1

- Introduction: The effects of renin-angiotensin-aldosterone system (RAAS) inhibitors on the clinical outcomes of coronavirus disease-19 (COVID-19) have been conflicting in different studies. This meta-analysis was undertaken to provide more conclusive evidence. Methods: A systematic search for published articles was performed in PubMed and EMBASE from January 5 2020 till May 5 2020. Studies that reported the clinical outcomes of patients with COVID-19, stratified by the class of concomitant antihypertensive drug therapy, were included. The Mantel-Haenszel random effects model was used to estimate pooled odds ratio (OR). Results: A total of 6,997 patients with COVID-19 were included, and all of them had hypertension. The overall risk of poor patient outcomes (severe COVID-19 or death) was lower in patients taking RAAS inhibitors (OR=0.84, 95% CI: [0.73, 0.96]; P=0.017) compared with those receiving non-RAAS inhibitor antihypertensives. Patients taking angiotensin-I-converting enzyme inhibitors (ACEIs) were less likely to experience poor clinical outcomes (OR=0.73, 95% CI: [0.58-0.92]; P=0.01) compared with those receiving angiotensin-II receptor blockers (ARBs). In addition, comparison of ACEIs to the rest of non-ACEI antihypertensives gave a consistently decreased risk of poor COVID-19 outcome (OR=0.77, 95% CI: [0.63-0.93]; P=0.002). However, ARBs did not decrease the risk of poor COVID-19 outcomes compared to all other non-ARB antihypertensives (OR=1.13, 95% CI: [0.95-1.35]). Conclusion: The risk of developing severe illness or death from COVID-19 was lower in patients who received RAAS inhibitors compared with those who took non-RAAS inhibitors. ACEIs might be better in decreasing the severity and mortality of COVID-19 than ARBs. [**note: these type of meta-analyses are only useful to provide an avenue for further research. However, as noted with some other publications coming out more work needs to be done with these drugs! Look at all the wasted effort chasing HCQ, where we might have some useful protective drugs with a long history of safe use right before our eyes!**]
  https://www.medrxiv.org/content/10.1101/2020.05.21.20108993v1
- Clinical and molecular characterization by Whole Exome Sequencing (WES) is reported in 35 COVID-19 patients attending the University Hospital in Siena, Italy, from April 7 to May 7, 2020. Eighty percent of patients required respiratory assistance, half of them being on mechanical ventilation. Fiftyone percent had hepatic involvement and hyposmia was ascertained in 3 patients. Searching for common genes by collapsing methods against 150 WES of controls of the Italian population failed to give straightforward statistically significant results with the exception of two genes. This result is not unexpected since we are facing the most challenging common disorder triggered by environmental factors with a strong underlying heritability (50%). The lesson learned from Autism-Spectrum-Disorders prompted us to re-analyse the cohort treating each patient as an independent case, following a Mendelian-like model. We identified for each patient an average of 2.5 pathogenic mutations involved in virus infection susceptibility and pinpointing to one or more rare disorder(s). To our knowledge, this is the first report on WES and COVID-19. Our results suggest a combined model for COVID-19 susceptibility with a number of common susceptibility genes which represent the favorite background in which additional host private mutations may determine disease progression. [**note: from beautiful Siena interesting data about genetic susceptibility to SARS-CoV-2. Molecular epidemiologists are going to have a field day untangling this. Clearly many more patient samples will need to be analyzed but the tools to do this are available.**]
  https://www.medrxiv.org/content/10.1101/2020.05.22.20108845v1

- There is limited information describing features and outcomes of patients requiring hospitalization for COVID19 disease and still no treatments have clearly demonstrated efficacy. Demographics and clinical variables on admission, as well as laboratory markers and therapeutic interventions were extracted from electronic Clinical Records (eCR) in 4712 SARS-CoV2 infected patients attending 4 public Hospitals in Madrid. Patients were stratified according to age and stage of severity. Using multivariate logistic regression analysis, cut-off points that best discriminated mortality were obtained for each of the studied variables. Principal components analysis and a neural network (NN) algorithm were applied. A high mortality incidence associated to age >70, comorbidities (hypertension, neurological disorders and diabetes), altered vitals such as fever, heart rhythm disturbances or elevated systolic blood pressure, and alterations in several laboratory tests. Remarkably, analysis of therapeutic options either taken individually or in combination drew a universal relationship between the use of *Cyclosporine A and better outcomes as also a benefit of tocilizumab and/or corticosteroids* in critically ill patients. We present a large Spanish population-based study addressing factors influencing survival in current SARS CoV2 pandemic, with particular emphasis on the effectivity of treatments. In addition, we have generated an NN capable of identifying severity predictors of SARS CoV2. A rapid extraction and management of data protocol from eCR and artificial intelligence in-house implementations allowed us to perform almost real time monitoring of the outbreak evolution. [**note: large cohort study from Madrid. I've seen data pointing to the usefulness of steroids and tocilizumab but this is the first time cyclosporine has made an appearance (just did a search of my posts and there was a drug repurposing paper from South Korea that targeted this compound). There is a clinical trial going on in Spain: NCT04392531, perhaps based on the observational study.**]
  https://www.medrxiv.org/content/10.1101/2020.05.22.20109850v1
- Background: Some patients infected by SARS-CoV-2 in the recent pandemic have required critical care, becoming one of the main limitations of the health systems. Our objective has been to identify potential markers at admission predicting the need for critical care in patients with COVID-19 pneumonia Methods: We retrospectively collected and analyzed data from electronic medical records of patients with laboratory-confirmed SARS-CoV-19 infection by real-time RT-PCR. A comparison was made between patients staying in the hospitalization ward with those who required critical care. Univariable and multivariable logistic regression methods were used to identify risk factors predicting critical care need Findings: Between March 15 and April 15, 2020, 150 patients under the age of 75 were selected (all with laboratory confirmed SARS-CoV-19 infection), 75 patients requiring intensive care assistance and 75 remaining the regular hospitalization ward. Most patients requiring critical care were males, 76% compared with 60% in the non-critical care group (p<0,05). Multivariable regression showed increasing odds of in-hospital critical care associated with increased C-reactive protein (CRP) (odds ratio 1,052 (1,009-1,101); p=0,0043) and higher Sequential Organ Failure Assessment (SOFA) score (1,968 (1,389-2,590) p<0,0001) both at the time of hospital admission. The AUC-ROC for the combined model was 0,83 (0,76-0,90) (vs AUC-ROC SOFA p<0,05) Interpretation: Patients COVID-19 positive presenting at admission with high SOFA score ≥2 combined with CRP ≥ 9,1 mg/mL could help clinicians to identify them as a group that will more likely require critical care so further actions might be implemented to improve their prognosis [**note: more Spanish information on**

potential markers, this time C-reactive protein and SOFA score.]
https://www.medrxiv.org/content/10.1101/2020.05.22.20110429v1

- Background Infection with SARS-CoV-2 manifests itself as a mild respiratory tract infection in the majority of individuals, which progresses to a severe pneumonia and acute respiratory distress syndrome (ARDS) in 10-15% of patients. Inflammation plays a crucial role in the pathogenesis of ARDS, with immune dysregulation in severe COVID-19 leading to a hyperinflammatory response. A comprehensive understanding of the inflammatory process in COVID-19 is lacking. Methods In this prospective, multicenter observational study, patients with PCR-proven or clinically presumed COVID-19 admitted to the intensive care unit (ICU) or clinical wards were included. Demographic and clinical data were obtained and plasma was serially collected. Concentrations of IL-6, TNF-α, complement components C3a, C3c and the terminal complement complex (TCC) were determined in plasma by ELISA. Additionally, 269 circulating biomarkers were assessed using targeted proteomics. Results were compared between ICU and non ICU patients. Findings A total of 119 (38 ICU and 91 non ICU) patients were included. IL-6 plasma concentrations were elevated in COVID-19 (ICU vs. non ICU, median 174.5 pg/ml [IQR 94.5-376.3 vs. 40.0 pg/ml [16.5-81.0]), whereas TNF-α concentrations were relatively low and not different between ICU and non ICU patients (median 24.0 pg/ml [IQR 16.5-33.5] and 21.5 pg/ml [IQR 16.0-33.5], respectively). C3a and terminal complement complex (TCC) concentrations were significantly higher in ICU vs. non ICU patients (median 556.0 ng/ml [IQR 333.3-712.5]) vs. 266.5 ng/ml [IQR 191.5-384.0 for C3a and 4506 mAU/ml [IQR 3661-6595 vs. 3582 mAU/ml [IQR 2947-4300] for TCC) on the first day of blood sampling. Targeted proteomics demonstrated that IL-6 (logFC 2.2), several chemokines and hepatocyte growth factor (logFC 1.4) were significantly upregulated in ICU vs. non ICU patients. In contrast, stem cell factor was significantly downregulated (logFC -1.3) in ICU vs. non ICU patients, as were DPP4 (logFC -0.4) and protein C inhibitor (log FC -1.0), the latter two factors also being involved in the regulation of the kinin-kallikrein pathway. Unsupervised clustering pointed towards a homogeneous pathogenetic mechanism in the majority of patients infected with SARS-CoV-2, with patient clustering mainly based on disease severity. Interpretation We identified important pathways involved in dysregulation of inflammation in patients with severe COVID-19, including the IL-6, complement system and kinin-kallikrein pathways. Our findings may aid the development of new approaches to host-directed therapy. [**note: more data on markers from The Netherlands.**]
https://www.medrxiv.org/content/10.1101/2020.05.23.20110916v1
- Anti-SARS-CoV-2 antibodies have been described, but correlation with virologic outcomes is limited. Here, we find anti-SARS-CoV-2 IgG to be associated with reduced viral load. High viral loads were rare in individuals who had seroconverted. Higher viral load on admission was associated with increased 30-day mortality (OR 4.20 [95% CI: 1.62-10.86]). [**note: confirmation of the fole of IgG antibodies and viral load.**]
https://www.medrxiv.org/content/10.1101/2020.05.22.20110551v1

DRUG DEVELOPMENT

- SARS-CoV-2 infection have caused global pandemic and claimed over 5,000,000 tolls. Although the genetic sequences of their etiologic viruses are of high homology, the clinical and pathological characteristics of COVID-19 significantly differ from SARS. Especially, it seems that SARS-CoV-2 undergoes vast replication in vivo without being effectively monitored by anti-viral

immunity. Here, we show that the viral protein encoded from open reading frame 8 (ORF8) of SARS-CoV-2, which shares the least homology with SARS-CoV among all the viral proteins, can directly interact with MHC-I molecules and significantly down-regulates their surface expression on various cell types. In contrast, ORF8a and ORF8b of SARS-CoV do not exert this function. In the ORF8-expressing cells, MHC-I molecules are selectively target for lysosomal degradation by an autophagy-dependent mechanism. As a result, CTLs inefficiently eliminate the ORF8-expressing cells. Our results demonstrate that ORF8 protein disrupts antigen presentation and reduces the recognition and the elimination of virus-infected cells by CTLs. Therefore, we suggest that the inhibition of ORF8 function could be a strategy to improve the special immune surveillance and accelerate the eradication of SARS-CoV-2 in vivo. [**note: an interesting paper from China about down regulation of the immune response. Perhaps this can be another drug therapy target.**] https://www.biorxiv.org/content/10.1101/2020.05.24.111823v1

DIAGNOSTIC DEVELOPMENT

- Nothing new.

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2020-05-26

The correct answer to yesterday's contest is the great American baritone, Todd Duncan. He was famous as the first Porgy in the Gershwin opera Porgy and Bess. He was a long-time voice teacher in Washington DC. Here is a nice article on 'Unchained Melody and a clip of famous singers who covered the song (including Elvis).

I am always on the lookout for COVID-19 special music videos. Here is a fun one from opera stars Jamie Barton and Ryan McKinny, accompanied by Kathleen Kelly, entitled Coronadämmerung from Wagner's Das Rheingold: https://www.youtube.com/watch?v=n_ChqaZxLT4

Citing safety concerns the WHO has halted a trial of hydroxychloroquine.

Contact tracing in Germany. Amazing story on how Wuhan tested 6.5 million people in days.

I don't know if this is behind a paywall but Chemical and Engineering news has a good article on ACE inhibitors and ARB drugs. The magazine is free to ACS members.

I have no idea what is going to happen as states open up. There is already a report of infections from a pool in Arkansas and two hair salon workers in Missouri may have infected as many as 140 people. Lots of reports coming out of big gatherings and people not wearing masks. I have my fingers crossed and am hoping for the best.

I was surprised that there was no announcement from Merck about a COVID-19 vaccine. They are now jumping into the vaccine race according to STAT with two potential candidates. Merck developed a licensed vaccine against Ebola and has lots of experience in producing vaccines at scale (disclosure: I am

a Merck shareholder). While on Merck, they also announced a licensing deal to develop EIDD-2801, an experimental antiviral that I have discussed before.

Cautionary story about vaccine safety. While policy makers may want to get a vaccine licenses ASAP, they cannot ignore safety issues.

MODELING

- Background: Human infection challenge studies (HICS) with SARS-CoV-2 are under consideration as a way of accelerating vaccine development. We evaluate potential vaccine research strategies under a range of epidemic conditions determined, in part, by the intensity of public health interventions. Methods: We constructed a compartmental epidemiological model incorporating public health interventions, vaccine efficacy trials and a post-trial population vaccination campaign. The model was used to estimate the duration and benefits of large-scale field trials in comparison with HICS accompanied by an expanded safety trial, and to assess the marginal risk faced by HICS participants. Results: Field trials may demonstrate vaccine efficacy more rapidly than a HICS strategy under epidemic conditions consistent with moderate mitigation policies. A HICS strategy is the only feasible option for testing vaccine efficacy under epidemic suppression, and maximises the benefits of post-trial vaccination. Less successful or absent mitigation results in minimal or no benefit from post-trial vaccination, irrespective of trial design. Conclusions: SARS-CoV-2 HICS are the optimal method of vaccine testing for populations maintained under epidemic suppression, where vaccination offers the greatest benefits to the local population. [**note: included because it covers human challenge trials of vaccines.**] https://www.medrxiv.org/content/10.1101/2020.05.18.20106187v1
- Objectives: To understand SARS-Co-V-2 infection and transmission in UK nursing homes in order to develop preventive strategies for protecting the frail elderly residents. Design: An outbreak investigation. Setting: 4 nursing homes affected by COVID-19 outbreaks in central London. Participants: 394 residents and 70 staff in nursing homes. Interventions: Two point-prevalence surveys one week apart where residents underwent SARS-CoV-2 testing and had relevant symptoms documented. Asymptomatic staff from three of the four homes were also offered SARS-CoV-2 testing. Main outcome measures: All-cause mortality, and mortality attributed to COVID-19 on death certificates. Prevalence of SARS-CoV-2 infection and symptoms in residents and staff. Results: Overall, 26% (95% confidence interval 22 to 31) of residents died over the two-month period. All-cause mortality increased by 203% (95% CI 70 to 336). Systematic testing identified 40% (95% CI 35 to 46) of residents, of whom 43% (95% CI 34 to 52) were asymptomatic and 18% (95% CI 11 to 24) had atypical symptoms, as well as 4% (95% CI -1 to 9) of asymptomatic staff who tested positive for SARS-CoV-2. Conclusions: The SARS-CoV-2 outbreak was associated with a very high mortality rate in residents of nursing homes. Systematic testing of all residents and a representative sample of staff identified high rates of SARS-CoV-2 positivity across the four nursing homes, highlighting a potential for regular screening to prevent future outbreaks. [**note: nursing home data from London that is not pretty. We know that workers in such places require constant screening and disinfection**

practices need to be heightened.]
https://www.medrxiv.org/content/10.1101/2020.05.19.20105460v1

- Face masks have become an emblem of the public response to COVID-19, with many governments mandating their use in public spaces. The logic is that face masks are low cost and might help prevent some transmission. However, from the start, the assumption that face masks are "low cost" was questioned. Early on, there were warnings of the opportunity cost of public use of medical masks given shortages of personal protective equipment for healthcare providers. This led to recommendations for cloth masks and other face coverings, with little evidence of their ability to prevent transmission. However, there may also be a high cost to these recommendations if people rely on face masks in place of other more effective ways to break transmission, such as staying home. We use SafeGraph smart device location data to show that the representative American in states that have face mask mandates spent 20-30 minutes less time at home, and increase visits to a number of commercial locations, following the mandate. Since the reproductive rate of SAR-COV2, the pathogen that causes COVID-19 is hovering right around one, such substitution behavior could be the difference between controlling the epidemic and a resurgence of cases. [**note: I almost didn't post this one. I'm not sure what the aim is here. There are three things that need to be done: mask up, wash hands, and stay safe (e.g., keep a reasonable distance and avoid crowds). This is all pretty simple.**]
https://www.medrxiv.org/content/10.1101/2020.05.23.20111302v1
- Body temperatures are less likely to reach the fever range in the morning, but it is unknown how this affects practice during disease outbreaks. We retrospectively investigated fever-range temperatures (≥100.4°F, ≥38.0°C) during seasonal influenza outbreaks and the 2009 H1N1 (swine flu) pandemic, which have recently been used as preparatory models for coronavirus disease 2019 (COVID-19). Our analyses included a nationally representative sample of records from adult visits to US emergency departments (n=202,181) and data from a Boston emergency department (n=93,225). Fever-range temperatures were about half as common in the morning as in the evening, suggesting that morning temperatures can be much less diagnostic, and that revisions may be needed to the practice of once-daily temperature screens at morning arrival to workplaces and schools. Twice-daily screens could be a simple solution, but similar research is still needed on fevers in COVID-19 itself. [**note: Isn't this common knowledge? Anyone who had the flu at some point in time knows this pretty well.**]
https://www.medrxiv.org/content/10.1101/2020.05.23.20093484v1
- Objective To provide population-level knowledge on individuals at high risk of severe and fatal coronavirus disease 2019 (COVID-19) in order to inform targeted protection strategies in the general population and appropriate triage of hospital contacts. Design, Setting, and Participants Nationwide population-based cohort of all 228.677 consecutive Danish individuals tested (positive or negative) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA from the identification of the first COVID-19 case on February 27th, 2020 until April 30th, 2020. Main Outcomes and Measures We examined characteristics and predictors of inpatient hospitalization versus community-management, and death versus survival, adjusted for age-, sex- and number of comorbidities. Results We identified 9,519 SARS-CoV-2 PCR-positive cases of whom 78% were community-managed, 22% were hospitalized (3.2% at an intensive care unit) and 5.5% had died within 30 days. Median age varied from 45 years (interquartile range (IQR) 31-57) among community-managed cases to 82 years (IQR 75-89) among those who died. Age

was a strong predictor of fatal disease (odds ratio (OR) 14 for 70-79-year old, OR 26 for 80-89-year old, and OR 82 for cases older than 90 years, when compared to 50-59-year old and adjusted for sex and number of comorbidities). Similarly, the number of comorbidities was strongly associated with fatal disease (OR 5.2, for cases with ≥4 comorbidities versus no comorbidities), and 82% of fatal cases had at least 2 comorbidities. A wide range of major chronic diseases were associated with hospitalization with ORs ranging from 1.3-1.4 (e.g. stroke, ischemic heart disease) to 2.2-2.7 (e.g. heart failure, hospital-diagnosed kidney disease, chronic liver disease). Similarly, chronic diseases were associated with mortality with ORs ranging from 1.2-1.3 (e.g. ischemic heart disease, hypertension) to 2.4-2.7 (e.g. major psychiatric disorder, organ transplantation). In the absence of comorbidities, mortality was relatively low (5% or less) in persons aged up to 80 years. Conclusions and Relevance In this first nationwide population-based study, increasing age and number of comorbidities were strongly associated with hospitalization requirement and death in COVID-19. In the absence of comorbidities, the mortality was, however, lowest until the age of 80 years. These results may help in accurate identification, triage and protection of high-risk groups in general populations, i.e. when reopening societies. [**note: another demonstration of the use of national health data this time from Denmark. Comorbidities play a top role in poor outcomes. I was glad to see the age linkage really didn't kick in until age 80. I still have eight years to go!!!**]
https://www.medrxiv.org/content/10.1101/2020.05.24.20111823v1

- Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a strain of coronavirus that causes coronavirus disease 2019 (Covid-19) and has been declared a global pandemic by the World Health Organization. Total cases of SARS-CoV-2 worldwide exceed 4.8 million, with over 320,000 deaths recorded. Little is known about the body's immune response to SARS-CoV-2 infection. *In this paper, we describe SARS-CoV-2 IgG antibody responses in 11,092 patients from the New York City metropolitan area and report a SARS-CoV-2 IgG positivity rate of nearly 50%, indicating the widespread nature of the pandemic in the city and state of New York.* Additionally, we report on the correlation between SARS-CoV-2 patient symptom severity and level of SARS-CoV-2 IgG antibody found in the patient sample. [**note: I'm not sure that this is a valid extrapolation. "Assuming" it is, NYC may be approaching herd immunity.**]
https://www.medrxiv.org/content/10.1101/2020.05.23.20111427v1
- Background. During infectious disease outbreaks the weakest communities are more vulnerable to the infection and its deleterious effects. In Israel, the Arab and Ultra-Orthodox Jewish communities have unique demographic and cultural characteristics that place them at risk for infection. Objective. To examine the socioeconomic and ethnic differences in relation to COVID-19 testing, cases and deaths, and to analyze infection spread patterns in ethnically diverse communities. Methods. Consecutive data on COVID-19 diagnostic testing, confirmed cases and deaths collected from March 31st through May 1st, 2020 in 174 localities across Israel (84% of the population) were analyzed by socioeconomic ranking and ethnicity. Findings. Tests were performed on 331,594 individuals (4.29% of the total population). Of those, 14,865 individuals (4.48%) were positive and 203 died (1.37% of confirmed cases). The percentage of the population tested was 26% and the risk of testing positive was 2.16 times higher in the lowest, compared with the highest socioeconomic category. The proportion of confirmed cases was 4.96 times higher in the Jewish compared with the Arab population. The rate of confirmed cases in 2 Ultra-Orthodox localities increased relatively early and quickly. Other Jewish and Arab

localities showed consistently low rates of confirmed COVID-19 cases, regardless of socioeconomic ranking. Interpretation Culturally different communities reacted differently to the COVID-19 outbreak and to government measures, resulting in different outcomes. Therefore, socioeconomic and ethnic variables cannot fully explain communities reaction to the pandemic. Our findings stress the need for designing a culturally adapted approach for dealing with health crises. [**note: interesting finding from Israel.**] https://www.medrxiv.org/content/10.1101/2020.05.25.20111575v1

- We report very low SARS-CoV-2 seroprevalence in two San Francisco Bay Area populations. Seropositivity was 0.26% in 387 hospitalized patients admitted for non-respiratory indications and 0.1% in 1,000 blood donors. We additionally describe the longitudinal dynamics of immunoglobulin-G, immunoglobulin-M, and in vitro neutralizing antibody titers in COVID-19 patients. Neutralizing antibodies rise in tandem with immunoglobulin levels following symptom onset, exhibiting median time to seroconversion within one day of each other, and there is >93% positive percent agreement between detection of immunoglobulin-G and neutralizing titers. [**note: I had to go into the paper and find out more. The validation approach for the serology test is very good. However, they two populations they surveyed were self selecting and may not be relevant to the larger community. More work needs to be done in sampling.**] https://www.medrxiv.org/content/10.1101/2020.05.19.20107482v1

NEWLY REGISTERED CLINICAL TRIALS

- A randomised controlled trial designed to test whether an online expressive writing intervention (LIO-C) can reduce distress for English-speaking adults during the global COVID19 pandemic. Hypothesis: LIO-C will improve distress (as measured by K10) in adults at 1 week post-intervention compared to a neutral writing control during the COVID19 pandemic. The aim of this study is to test whether an online self-compassion and EW based intervention (LIO-C) can reduce the negative effects of the COVID19 pandemic on health and well-being. The intervention is based on an existing intervention, LIO, that we previously developed for use in advanced disease populations, in collaboration with clinical and health psychologists, and patient and public representatives. For this study, we have adapted the intervention for people living through the current COVID19 pandemic by altering the writing prompts, and translating the intervention to an online hub. As this is an unfacilitated intervention, the instructions involve writing from a compassionate stance to minimise any potential short term negative effects associated with writing about difficult experiences. [**note: this one is from University College in London. I wonder if COVID-19 newsletter writers can enroll.**] NCT04386668
- The purpose of this study is to determine if temporary androgen suppression improves the clinical outcomes of Veterans who are hospitalized to an acute care ward due to COVID-19. [**note: this is a VA study using the drug degarelix that is used for prostate cancer treatment. I did not see anything in the study description that discusses why this might work.** NCT04397718
- This single-center, prospective, open-label, comparator study, blind for central accessor evaluates the efficacy, safety of inhalations of low-doses of melphalan in patients with pneumonia with confirmed or suspected COVID-19. All patients will receive 0,1 mg of melphalan in 7-10 daily inhalations 1 time per day. [**note: this is a Russian trial and I'm unsure of the rationale for using it.**] NCT04380376

- This is a First In Human study designed to assess the safety, tolerability and pharmacokinetics of EIDD-2801 in healthy human volunteers. [**note: this is a Phase 1 study and I normally wouldn't post it. However, this was the topic of a couple of earlier papers in the drug development section.**] NCT04392219

CLINICAL TRIAL RESULTS

- Background: In 2020, the current outbreak of Coronavirus Disease 2019(COVID-19) has constituted a global pandemic. But the question about the immune mechanism of patients with COVID-19 is unclear and cause particular concern to the world. Here, we launched a follow-up analysis of antibodies against SARS-CoV-2 of 192 COVID-19 patients, aiming to depict a kinetics profile of antibodies against SARS-CoV-2 and explore the related factors of antibodies expression against SARS-CoV-2 in COVID-19 patient. Methods: A total of 192 COVID-19 patients enrolled in the designated hospital of Guangzhou , Guangzhou Eighth People's Hospital, from January to February 2020 were selected as the study cohort. A cohort of 130 COVID-19 suspects who had been excluded from SARS-CoV-2 infected by negative RT-PCR result and 209 healthy people were enrolled in this study. Detection of IgM and IgG against SARS-CoV-2 were performed by Chemiluminescence immunoassay in different groups . Results: It has been found that the seroconversion time of IgM against SARS-CoV-2 in most patients was 5-10 days after the symptoms onset , and then rose rapidly, reaching a peak around 2 to 3 weeks, and the median peak concentration was 2.705 AU / mL. The peak of IgM maintained within one week, and then enters the descending channel. IgG seroconverted later than or synchronously with IgM, reaching peaks around 3 to 4 weeks.The median peak concentration was 33.998AU / ml,which was higher than that of IgM . IgM titers begins to gradually decrease after reaching the peak in the 4th week, after the 8th week, a majority of IgM in patient's serum started to turn negative. On the contrary, titers of IgG began to decline slightly after the fifth week, and more than 90% of results of patients were positive after 8 weeks. Additionally, the concentration of antibodies positively correlated with the severity of the disease and the duration of virus exist in host. Conclusion: We depict a kinetics profile of antibodies against SARS-CoV-2 in COVID-19 patients and found out that the levels of antibodies were related to the disease severity,age, gender and virus clearance or continuous proliferation of COVID-19 patients. [**note: more data from China on the antibody response time and type in SARS-CoV-2 patients.**] https://www.medrxiv.org/content/10.1101/2020.05.22.20102525v1
- The epidemiological and clinical characteristics of those patients under 18 years old in the recovery stage are limited. To compare the difference of epidemiological and clinical characteristics of COVID-19 involving 25 patients under 18 years old in recovery stage between confirmed and asymptomatic infections. Methods Retrospective, single-center cohort study of COVID-19 involving 25 patients under 18 years old in the recovery stage at Guizhou Provincial Staff Hospital in Guiyang, China, from January 29, to March 31, 2020; final date of follow-up was April 22. Epidemiological, demographic, clinical, laboratory, radiological, and treatment data were collected and analyzed. Epidemiological and clinical characteristics of confirmed COVID-19 infections and asymptomatic infections were compared. Results Among the 25 COVID infections under 18 years old, 16 (64%) were mild or moderate confirmed cases, and 9 (36%) were asymptomatic. The shortest treatment period was 6 days, the longest 26 days, and the average treatment period 14 days. Four cases (44.4%) had visited Wuhan or had a living story in the city.

There were 9 (100%) asymptomatic cases were familial cluster outbreak, with an average infection number was 6 cases among all families. The number of asymptomatic COVID-19 infections with leukopenia were significantly more than confirmed cases (p=0.04). Conclusions Leukopenia mostly occurred in asymptomatic COVID-19 infections under 18 years old compared with the confirmed patients. [**note: it's a small number of young patients but again points out that we should not assume that this cohort are not affected.**]
https://www.medrxiv.org/content/10.1101/2020.05.21.20074682v1

- Objectives To describe the efficacy of convalescent plasma transfusion for COVID-19 patients. Methods Through the review of the electronic medical records of Guizhou Jiangjunshan Hospital, clinical data of 6 patients were obtained. Three of the patients used convalescent plasma therapy for the first treatment, while the other three patients were used during in the recurrence. The efficacy of convalescent plasma depends on the relief of symptoms, changes in laboratory indicators and chest imaging abnormalities. Results The PaO2 / FiO2 and lymphocyte count of patients 1, 2 and 3 treated with convalescent plasma treatment for the first treatment period were changed from abnormal to normal. The levels of inflammation markers CRP and IL-6 of the patients decreased significantly. Chest imaging examination showed that the lung lesions gradually subsided. The relapsed patients (No. 4 and No. 6), after using convalescent plasma therapy, turned negative on two consecutive throat swab tests on Day 24 and Day 3, respectively. The basic condition of patient 4 with in the recurrence was too poor, and only one round of convalescent plasma transfusion was performed, so the laryngeal swab test paper has been consistently positive so far. Conclusions Six patients with COVID-19 were treated with antivirals and systemic corticosteroids combined with appropriate rounds of convalescent plasma therapy, and their clinical conditions were effectively improved. [**note: a small number of patients and confounded in part by the use of other meds. Still we need to get mAbs developed quickly and into the clinic.**]
https://www.medrxiv.org/content/10.1101/2020.05.21.20109512v1
- Many studies suggested that genetic variants in ACE2 gene may influence the host susceptibility/resistance to SARS-CoV-2 virus according to the functional role of ACE2 in human pathophysiology. However, all these studies have been conducted in silico based on epidemiological and population data. We therefore investigated the occurrence of ACE2 variants in a cohort of 99 Italian unrelated individuals clinically diagnosed with coronavirus disease 19 (COVID-19) to experimental demonstrate allelic association with disease severity. Methods: By whole-exome sequencing we analysed 99 DNA samples of severely and extremely severely COVID-19 patients hospitalized at the University Hospital of Rome Tor Vergata and Bambino Gesù Hospital in Rome. Results: We identified three different germline variants, one intronic (c.439+4G>A) and two missense (c.2158A>G, p.Asn720Asp; c.1888G>C, p.Asp630His), in 26 patients with a similar frequency between male and female and a not statistically different frequency, except for c.1888G>C, (p.Asp630His) with the ethnically matched populations (EUR). Conclusions: Our results suggest that there is not any ACE2 exonic allelic association with disease severity. It is possible that rare susceptibility alleles are located in the non-coding region of the gene able to control ACE2 gene activity. It is therefore of interest, to explore the existence of ACE2 susceptibility alleles to SARS-Co-V2 in these regulatory regions. In addition, we found no significant evidence that ACE2 alleles is associated with disease severity/sex bias in the Italian population. [**note: I think this runs counter to some other research I've seen. Clearly more**

work needs to be done here.]
https://www.medrxiv.org/content/10.1101/2020.05.23.20111310v1

DRUG DEVELOPMENT

- Introduction. The lack of approved specific therapeutic agents to treat COVID-19 associated with SARS coronavirus 2 (SARS-CoV-2) infection has led to the rapid implementation and/or randomised controlled trials of convalescent plasma therapy (CPT) in many countries including the UK. Effective CPT is likely to require high titres of neutralising antibody levels in convalescent donations. Understanding the relationship between functional neutralising antibodies and antibody levels to specific SARS-CoV-2 proteins in scalable assays will be crucial for the success of large-scale collection and use of convalescent plasma. We assessed whether neutralising antibody titres correlated with reactivity in a range of ELISA assays targeting the spike (S) protein, the main target for human immune response. Methods. Blood samples were collected from 52 individuals with a previous laboratory confirmed SARS-CoV-2 infection at least 28 days after symptom resolution. These were assayed for SARS-CoV-2 neutralising antibodies by microneutralisation and pseudotype assays, and for antibodies by four different ELISAs. ROC analysis was used to further identify sensitivity and specificity of selected assays to identify samples containing high neutralising antibody levels suitable for clinical use of convalescent plasma. Results. All samples contained SARS-CoV-2 antibodies, whereas neutralising antibody titres of greater than 1:20 were detected in 43 samples (83% of those tested) and >1:100 in 22 samples (42%). The best correlations were observed with EUROimmun IgG ELISA S/CO reactivity (Spearman Rho correlation co-efficient 0.88; p<0.001). Based on ROC analysis, EUROimmun would detect 60% of samples with titres of >1:100 with 100% specificity using a reactivity index of 9.1 (13/22). Discussion. Robust associations between virus neutralising antibody titres and reactivity in several ELISA-based antibody tests demonstrate their possible utility for scaled-up production of convalescent plasma containing potentially therapeutic levels of anti-SARS-CoV-2 neutralising antibodies. [**note: useful information on what type of work is needed for scaling up use of convalescent plasma.**]
https://www.medrxiv.org/content/10.1101/2020.05.20.20091694v1

DIAGNOSTIC DEVELOPMENT

- The rapid onset of the global COVID-19 pandemic has led to multiple challenges for accurately diagnosing the infection. One of the main bottlenecks for COVID-19 detection is reagent and material shortages for sample collection, preservation, and purification prior to testing. Currently, most authorized diagnostic tests require RNA extraction from patient samples and detection by reverse transcription polymerase chain reaction (RT-PCR). However, RNA purification is expensive, time consuming, and requires technical expertise to perform. Additionally, there have been reported shortages of the RNA purification kits needed for most tests. With these challenges in mind, we report on extraction-free amplification of SARS-CoV-2 RNA directly from patient samples. In addition, we have developed a multiplex RT-PCR using the CDC singleplex targets. This multiplex has a limit of detection of 2 copies/µL. We have demonstrated these improvements to the current diagnostic workflow, which reduce complexity and cost, minimize reagent usage, expedite time to results, and increase testing

capacity. {**note: good work from Gates Foundation funded researchers!]**
https://www.medrxiv.org/content/10.1101/2020.05.21.20106195v1

- The recently launched high-throughput assays for the detection of antibodies against SARS-CoV-2 may change the diagnostic strategies for COVID-19. This study aimed at investigating the performance of three novel high-throughput assays on Abbott Architect, Roche Cobas, and DiaSorin Liaison platforms. In addition, we evaluated a rapid lateral flow test from Dynamiker Biotechnology. A panel consisting of 133 samples including 100 pre-pandemic samples, 20 samples from SARS-CoV-2 PCR positive individuals and 13 possible crossreactive samples were used. Sensitivity and specificity in this study were equivalent with data from Abbott and Roche but differed from those reported from DiaSorin and Dynamiker Biotechnology. The results suggest that the assays from Abbott and Roche could be considered in clinical use for individual patients. [**note: validation studies on diagnostic serology tests from Sweden.**]
https://www.medrxiv.org/content/10.1101/2020.05.22.20106294v1
- Background: Nucleic acid amplification for the detection of SARS-CoV-2 RNA in respiratory samples is the standard method for diagnosis. These tests are centralised and therefore turnaround times can be 2-5 days. Point-of-care testing with rapid turnaround times would allow more effective triage in settings where patient management and infection control decisions need to be made rapidly. Methods: Analytical and clinical sensitivity and specificity of the SAMBA II SARS-CoV-2 Test was evaluated on panels and residual clinical samples. The clinical performance was compared to the Public Health England reference tests. Results: The limit of detection of the SAMBA II SARS-CoV-2 Test is 250 cp/mL and is specific for detection of 2 regions of the SARS-CoV-2 genome. The clinical sensitivity was evaluated in 172 clinical samples provided by Public Health England, Cambridge, which showed a sensitivity of 98.9% (95% CI 94.03-99.97%), specificity of 100% (95% CI 95.55-100%), PPV of 100% and NPV of 98.78% (92.02-99.82%) compared to testing by Public Health England (PHE). SAMBA detected 3 positive samples that were initially negative by PHE. Discussion: The data shows that the SAMBA II SARS-CoV-2 Test performs equivalently to the centralised testing methods with a much quicker turnaround time. Point of care testing, such as SAMBA, should enable rapid patient management and effective implementation of infection control measures. [**note: evaluation of another point of care test kit. The SAMBA-II has already been used for HIV testing.**]
https://www.medrxiv.org/content/10.1101/2020.05.24.20100990v1
- The extent of SARS-CoV-2 infection throughout the United States population is currently unknown. High quality serology is a key tool to understanding the spread of infection, immunity against the virus, and correlates of protection. Limited validation and testing of serology assays used for serosurveys can lead to unreliable or misleading data, and clinical testing using such unvalidated assays can lead to medically costly diagnostic errors and improperly informed public health decisions. Estimating prevalence and clinical decision making is highly dependent on specificity. Here, we present an optimized ELISA-based serology protocol from antigen production to data analysis. This protocol defines thresholds for IgG and IgM for determination of seropositivity with estimated specificity well above 99%. Validation was performed using both traditionally collected serum and dried blood on mail-in blood sampling kits, using archival (pre-2019) negative controls and known PCR-diagnosed positive patient controls. Minimal cross-reactivity was observed for the spike proteins of MERS, SARS1, OC43 and HKU1 viruses and no cross reactivity was observed with anti-influenza A H1N1 HAI titer during validation. This

strategy is highly specific and is designed to provide good estimates of seroprevalence of SARS-CoV-2 seropositivity in a population, providing specific and reliable data from serosurveys and clinical testing which can be used to better evaluate and understand SARS-CoV-2 immunity and correlates of protection. [**note: good paper from the NIH researchers who are doing a large field study of serological infection data.**]
https://www.medrxiv.org/content/10.1101/2020.05.21.20109280v1

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2020-05-27

One can always listen to Bach and not be disappointed (even when Jack Benny is trying to play the double concerto with Isaac Stern. Here is a good rendition of two violin concertos in a very intimate space with Hillary Hahn: https://www.youtube.com/watch?v=nGwDSNEikFw There is a bonus piece by Piazolla for violin and accordion.

Derek Thompson writes about the need for a comprehensive strategy to reduce the kind of interactions that lead to more infections. Cannot argue against this!

Here is a fascinating story on when COVID-19 arrived in the US. The manuscript referred to in the article is here and also makes for good bedtime reading. It's likely to engender controversy and does not explain the early death in Santa Clara county following a lengthy lag in the testing of a autopsy sample. It's all quite interesting in terms of the powerful genetic analysis tools we now have.

More on the FDA decision to shut down the Seattle Coronavirus Assessment Network. Surely this could have been handled in a better manner.

Though legal, the sales of stock by these Moderna execs has horrible optics!

Derek Lowe updates the vaccine landscape in some detail.

MODELING

- Widely reported statistics on Covid-19 across the globe fail to take account of both the uncertainty of the data and possible explanations for this uncertainty. In this paper we use a Bayesian Network (BN) model to estimate the Covid-19 infection prevalence rate (IPR) and infection fatality rate (IFR) for different countries and regions, where relevant data are available. This combines multiple sources of data in a single model. The results show that Chelsea Mass. USA and Gangelt Germany have relatively higher infection prevalence rates (IPR) than Santa Clara USA, Kobe, Japan and England and Wales. In all cases the infection prevalence is significantly higher than what has been widely reported, with much higher community infection rates in all locations. For Santa Clara and Chelsea, both in the USA, the most likely IFR values are 0.3-0.4%. Kobe, Japan is very unusual in comparison with the others with values an order of magnitude less than the others at, 0.001%. The IFR for Spain is centred around 1%. England and

Wales lie between Spain and the USA/German values with an IFR around 0.8%. There remains some uncertainty around these estimates but an IFR greater than 1% looks remote for all regions/countries. We use a Bayesian technique called "virtual evidence" to test the sensitivity of the IFR to two significant sources of uncertainty: survey quality and uncertainty about Covid-19 death counts*. In response the adjusted estimates for IFR are most likely to be in the range 0.3%-0.5%*. [**note: yes, I know that this is yet another model but the reason for posting it is that it comes up with an IFR that is similar to what I have come up with in my own noodling. It's worse than seasonal flu and maybe a little worse than the 1957-58 epidemic.**]
https://www.medrxiv.org/content/10.1101/2020.05.25.20112466v1

- BACKGROUND: The coronavius disease 2019 (COVID-9) caused by the severe acute respiratory syndrome coronavirus 2 reached Spain by 31 January 2020, in April 2020, the Comunidad de Madrid suffered one of the world's highest crude mortality rate ratios. This study aimed to detect risk factors for mortality in patients with COVID-19. METHODS: Our cohort were all consecutive adult patients with laboratory-confirmed COVID-19 at a secondary hospital in Madrid, March 3-16, 2020. Clinical and laboratory data came from electronic clinical records and were compared between survivors and non-survivors, with outcomes followed up until April 4. Univariable and multivariable logistic regression methods allowed us to explore risk factors associated with in-hospital death. FINDINGS: The cohort comprised 562 patients with COVID-19. Clinical records were available for evaluation for 392 patients attended at the emergency department of our hospital, of whom 199 were discharged, 85 remained hospitalized and 108 died during hospitalization. Among 311 of the hospitalized patients, 34.7% died. Of the 392 patients with records, the median age was 71.5 years (50.6-80.7); 52.6% were men. 252 (64.3%) patients had a comorbidity, hypertension being the most common: 175 (44.6%), followed by other cardiovascular disease: 102 (26.0%) and diabetes: 97 (24.7%). Multivariable regression showed increasing odds of in-hospital death associated with age over 65 (odds ratio 8.32, 95% CI 3.01-22.96; p<0.001), coronary heart disease (2.76, 1.44-5.30; 0.002), and both lower lymphocyte count (0.34, 0.17-0.68; 0.002) and higher LDH (1.25, 1.05-1.50; 0.012) per 1-unit increase and per 100 units respectively. INTERPRETATION: COVID-19 was associated in our hospital at the peak of the pandemic with a crude mortality ratio of 19.2% and a mortality ratio of 34.7% in admitted patients, considerably above most of the ratios described in the Chinese series. These results leave open the question as to which factors, epidemiological or intrinsically viral, apart from age and comorbidities, can explain this difference in excess mortality. [**note: summary data from Madrid which shows very high mortality. I probably won't be posting these types of results going forward as we know pretty much what the impacts are on the elderly and that some communities are harder hit than others.**]
https://www.medrxiv.org/content/10.1101/2020.05.25.20112912v1
- The serologic response of individuals with mild forms of SARS-CoV-2 infection is poorly characterized. Methods: Hospital staff who had recovered from mild forms of PCR-confirmed SARS-CoV-2 infection were tested for anti-SARS-CoV-2 antibodies using two assays: a rapid immunodiagnostic test (99.4% specificity) and the S-Flow assay (~99% specificity).The neutralizing activity of the sera was tested with a pseudovirus-based assay. Results: Of 162 hospital staff who participated in the investigation, 160 reported SARS-CoV- 2 infection that had not required hospital admission and were included in these analyses. The median time from symptom onset to blood sample collection was 24 days (IQR: 21-28, range 13-39). The rapid

immunodiagnostic test detected antibodies in 153 (95.6%) of the samples and the S-Flow assay in 159 (99.4%), failing to detect antibodies in one sample collected 18 days after symptom onset (the rapid test did not detect antibodies in that patient). Neutralizing antibodies (NAbs) were detected in 79%, 92% and 98% of samples collected 13-20, 21-27 and 28-41 days after symptom onset, respectively (P=0.02). Conclusion: Antibodies against SARS-CoV-2 were detected in virtually all hospital staff sampled from 13 days after the onset of COVID-19 symptoms. This finding supports the use of serologic testing for the diagnosis of individuals who have recovered from SARS-CoV-2 infection. The neutralizing activity of the antibodies increased overtime. Future studies will help assess the persistence of the humoral response and its associated neutralization capacity in recovered patients. [**note: thanks to an astute reader who picked this one up (I do occasionally miss things). At some point, all of this data from multiple sites needs to be aggregated.**] https://www.medrxiv.org/content/10.1101/2020.05.19.20101832v2

NEWLY REGISTERED CLINICAL TRIALS

- Will check tomorrow.

CLINICAL TRIAL RESULTS

- Cell infection by the SARS-CoV-2 virus requires binding of its Spike (S) protein to the ACE2 cell surface protein and priming of the S by the serine protease TMPRSS2. One may expect that genetic variants leading to a defective TMPRSS2 protein can affect SARS-CoV-2 ability to infect cells. We used a range of bioinformatics methods to estimate the prevalence and pathogenicity of TMPRSS2 genetic variants in the human population, and assess whether TMPRSS2 and ACE2 are co-expressed in the intestine, similarly to what is observed in lungs. We generated a 3D structural model of the TMPRSS2 extracellular domain using the prediction server Phyre and studied 378 naturally-occurring TMPRSS2 variants reported in the GnomAD database. One common variant, p.V160M (rs12329760), is predicted damaging by both SIFT and PolyPhen2 and has a MAF of 0.25. Valine 160 is a highly conserved residue within the SRCS domain. The SRCS is found in proteins involved in host defence, such as CD5 and CD6, but its role in TMPRSS2 remains unknown. 84 rare variants (53 missense and 31 leading to a prematurely truncated protein, cumulative minor allele frequency (MAF) 7.34x10-4) cause structural destabilization and possibly protein misfolding, and are also predicted damaging by SIFT and PolyPhen2 prediction tools. Moreover, we extracted gene expression data from the human protein atlas and showed that both ACE2 and TMPRSS2 are expressed in the small intestine, duodenum and colon, as well as the kidneys and gallbladder. The implications of our study are that: i. TMPRSS2 variants, in particular p.V160M with a MAF of 0.25, should be investigated as a possible marker of disease severity and prognosis in COVID-19 and ii. in vitro validation of the co-expression of TMPRSS2 and ACE2 in gastro-intestinal is warranted. [**note: someone is going to figure the genetics of this out. We have a cousin at Dana Farber whose research looks at TMPRSS2 in prostate cancer and he is intrigued by the linkage here.**[https://www.biorxiv.org/content/10.1101/2020.05.26.116608v1
- Objective: We aim to determine the impact of steroid use in COVID-19 pneumonia in-hospital mortality. Design: We performed a single-centre retrospective cohort study. Setting: A University hospital in Madrid, Spain, during March 2020. Participants: Patients admitted with SARS-CoV-2 pneumonia. Exposures: Patients treated with steroids were compared to patients

not treated with steroids. A propensity-score for steroid treatment was developed. Different steroid regimens were also compared, and adjusted with a second propensity score. Main Outcomes and Measures: To determine the role of steroids in in-hospital mortality, univariable and multivariable analyses were performed, and adjusted including the propensity score as a covariate. Survival times were compared using a log-rank test. Results: During the study period, 463 out of 848 hospitalized patients with COVID19 pneumonia fulfilled inclusion criteria. Among them, 396 (46.7%) consecutive patients were treated with steroids and 67 patients were assigned to the control cohort. Global mortality was 15.1%. Median time to steroid treatment from symptom onset was 10 days (IQR 8 to13). In-hospital mortality was lower in patients treated with steroids than in controls (13.9% [55/396] versus 23.9% [16/67], OR 0.51 [0.27 to 0.96], p= 0.044). Steroid treatment reduced mortality by 41.8% relative to no steroid treatment (RRR 0,42 [0.048 to 0.65). Initial treatment with 1 mg/kg/day of methylprednisolone (or equivalent) versus steroid pulses was not associated with in-hospital mortality (13.5% [42/310] versus 15.1% [13/86], OR 0.880 [0.449-1.726], p=0.710). Conclusions: Our results show that survival of patients with SARS-CoV2 pneumonia is higher in patients treated with glucocorticoids than in those not treated. In-hospital mortality was not different between initial regimens of 1 mg/kg/day of methylprednisolone or equivalent and glucocorticoid pulses. These results support the use of glucocorticoids in SARS-CoV2 infection. [**note: from hard hit Spain, some encouraging news about glucocorticoid treatment. We need to focus on what works!**]
https://www.medrxiv.org/content/10.1101/2020.05.22.20110544v1

- Aim of this study was to analyse the impact of COVID-19 on clinical and laboratory findings and outcome of neurological patients consecutively admitted to the emergency department (ED) of a tertiary hub center. Methods: All adult patients consecutively admitted to the ED for neurological manifestations from February 20 th through April 30 th 2020 at Spedali Civili of Brescia entered the study. Demographic, clinical, and laboratory data were extracted from medical records and compared between patients with and without COVID-19. Results: Out of 505 consecutively patients evaluated at ED with neurological symptoms, 147 (29.1%) tested positive for SARS-CoV-2. These patients displayed at triage higher values of CRP, AST, ALT, and fibrinogen but not lymphopenia ($p<0.05$). They were older (73.1 + 12.4 vs 65.1 + 18.9 years, $p=0.001$) had higher frequency of stroke (34.7% vs 29.3%), encephalitis/meningitis (9.5% vs 1.9%) and delirium (16.3% vs 5.0%). Compared to patients without COVID, they were more frequently hospitalized (91.2% vs 69.3%, $p<0.0001$) and showed higher mortality rates (29.7% vs 1.8%, $p<0.0.001$) and discharge disability, independently from age. Conclusions: COVID-19 impacts on clinical presentation of neurological disorders, with higher frequency of stroke, encephalitis and delirium, and was strongly associated with increased hospitalisation, mortality and disability. [**note: from Italy, neurological linkage.**]
https://www.medrxiv.org/content/10.1101/2020.05.23.20110650v1
- Objective: The association between renin-angiotensin-aldosterone (RAAS) inhibitors and Coronavirus diseases 2019 (COVID-19) mortality is unclear. We aimed to explore the association of RAAS inhibitors, including angiotensin-converting inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) with COVID-19 mortality in patients with hypertension. Methods: MEDLINE, SCOPUS, OVID, and Cochrane Library were searched for the period of January 1, 2020 to May 20, 2020. Studies reporting the association of RAAS inhibitors (ACEi and ARBs) and mortality in patients with hypertension, hospitalized for COVID-19 were extracted. Two reviewers

independently extracted appropriate data of interest and assessed the risk of bias. All analyses were performed using random-effects models on log-transformed risk ratio estimates, and heterogeneity was quantified. Results: Data were collected on 2,065,805 individuals (mean age, 58.73 years; 53.4% male). Patients with hypertension taking RAAS inhibitors were 35% less likely to die from COVID-19 compared to patients with hypertension not taking RAAS inhibitors (pooled RR= 0.65, 95% Confidence Intervals (CI): 0.45-0.94). To explore the association of COVID-19 and specific classes of RAAS inhibitors, we conducted a subgroup analysis of ARBs and ACEi separately from studies that provided them. Pooled risk ratio estimates from ARBs and ACEi showed a lower but not significant risk of death from COVID-19 (RR=0.93, 95% CI: 0.70-1.22) and ACEi (RR=0.65, 95% CI: 0.32-1.30). Conclusions: In this meta-analysis, it was discovered that taking RAAS inhibitors, significantly decreased the risk of COVID-19 mortality in patients with hypertension. This indicates a potential protective role that RAAS-inhibitors may have in COVID-19 patients with hypertension. [**note: more observational data on the utility of RAAS inhibitors for protection. Throw out the HCQ and get everyone ACE inhibitors and ARBs. Of course TIWWDCT (you just knew I had to put this in here) and there are clinical trials going on. It would be useful to do some very large scale observational datamining and OHDSI plans to do this with the SCYLLA project.**]
https://www.medrxiv.org/content/10.1101/2020.05.21.20107003v1

DRUG DEVELOPMENT

- The recent outbreak of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, is a global threat to human health. By in vitro screening and biochemical characterization, we identified the hepatitis C virus (HCV) protease inhibitor simeprevir as an especially promising repurposable drug for treating COVID-19. We also revealed that simeprevir synergizes with the RNA-dependent RNA polymerase (RdRP) inhibitor remdesivir to suppress the replication of SARS-CoV-2 in vitro. Our results provide preclinical rationale for the combination treatment of simeprevir and remdesivir for the pharmacological management of COVID-19 patients. [**note: interesting finding and points to the need for looking at combination therapies. Where have we heard that before?]**
https://www.biorxiv.org/content/10.1101/2020.05.26.116020v1
- The outbreak of COVID-19 has so far inflicted millions of people all around the world and will have a long lasting effect on every aspect of everyone's life. Yet there is no effective approved treatment for the disease. In an effort of utilizing human ferritin as nanoplatform for drug delivery, we engineered a fusion protein by presenting receptor-binding motif (RBM) of SARS-CoV-2 virus spike glycoprotein on the N-terminus of ferritin subunits. The designed fusion protein with a cage-like structure, similar to that of corona virus, is a potential anti-SARS-CoV-2 vaccine. We hereby show the construction, preparation, and characterization of the fusion protein RBM-HFtn. Our initial affinity study confirmed its biological activity towards ACE2 receptor which suggests its mode of action against SARS-CoV-2 could be either through vaccine therapy or blocking the cellular entry of virus as antagonist of ACE2 receptor. [**note: I linked to a story several weeks ago about a Walter Reed vaccine candidate that is using the same approach.**] https://www.biorxiv.org/content/10.1101/2020.05.25.115618v1
- Introduction:Improved antisepsis of human and non-human surfaces has been identified as a key feature of transmission reduction. There are no previous studies of povidone-iodine (PVP-I)

against SARS-CoV-2. This study evaluated nasal and oral antiseptic formulations of povidone-iodine (PVP-I) for virucidal activity against SARS-CoV-2. This is the first report on the efficacy of PVP-I against the virus that causes COVID-19. Methods: PVP-I nasal antiseptic formulations and PVP-I oral rinse antiseptic formulations from 1-5% concentrations as well as controls were studied for virucidal efficacy against the SARS-CoV-2 virus. Test compounds were evaluated for ability to inactivate SARS-CoV-2 as measured in a virucidal assay. SARS-CoV-2 was exposed directly to the test compound for 60 seconds, compounds were then neutralized and surviving virus was quantified. Results: All concentrations of nasal antiseptics and oral rinse antiseptics evaluated completely inactivated the SARS-CoV-2 virus. Conclusions: Nasal and oral PVP-I antiseptic solutions are effective at inactivating the SARS-CoV-2 virus at a variety of concentrations after 60s exposure times. The formulations tested may help to reduce the transmission of SARS-CoV-2 if used for nasal decontamination, oral decontamination or surface decontamination in known or suspected cases of COVID-19. [**note: there are several clinical trials of povidone/iodine going on.**]
https://www.medrxiv.org/content/10.1101/2020.05.25.20110239v1

- The study reviews the evidence presented in a recent study linking vitamin D levels and Covid-19 infection and mortality. It was argued that correlation alone may not be useful in establishing a relationship between vitamin D levels and Covid-19 infections and mortality. Appropriate controls need to be included for improved understanding of the relationship. We proposed life expectancy as a potential control. Including this control in a regression model, we find that vitamin D levels are not a statistically significant predictor of Covid-19 infections or mortality. Life expectancy, on the other hand, was found to be statistically significant predictor of infections and mortality at country level. [**note: I guess I better throw out my Vitamin D capsules as they may not be helping.**]
https://www.medrxiv.org/content/10.1101/2020.05.25.20110338v1

DIAGNOSTIC DEVELOPMENT

- Here, we developed and evaluated a novel microsphere-based antibody assay (MBA) for the detection of immunoglobulin G (IgG) against SARS-CoV-2 nucleoprotein (NP) and spike protein receptor binding domain (RBD). Method: We developed a microsphere-based assay (MBA) to determine the levels of IgG against SARS-CoV-2 NP and spike RBD. The seropositive cut-off mean fluorescent intensity (MFI) was set using a cohort of 294 anonymous serum specimens collected in 2018. The specificity was assessed using serum specimens collected from organ donors or influenza patients before 2020. Seropositive rate was determined among patients with COVID-19. Time-to-seropositivity and signal-to-cutoff (S/CO) ratio were compared between MBA and EIA. Results: MBA had a specificity of 100% (93/93; 95% confidence interval [CI], 96-100%) for anti-NP IgG and 98.9% (92/93; 95% CI 94.2-100%) for anti-RBD IgG. The MBA seropositive rate for convalescent serum specimens of COVID-19 patients were 89.8% (35/39) for anti-NP IgG and 79.5% (31/39) for anti-RBD IgG. The time-to-seropositivity was shorter with MBA than that of EIA. When compared with EIA, MBA could better differentiate between COVID-19 patients and negative controls with significantly higher S/CO ratio for COVID-19 patients and lower S/CO ratio with negative controls. MBA also had fewer specimens in the equivocal range (S/CO 0.9-1.1) than EIA. Conclusion: MBA is robust and simple, and is suitable for clinical microbiology laboratory for the accurate determination of anti-SARS-CoV-2 antibody for retrospective

diagnosis, serosurveillance, and vaccine trials. [**note: another new approach to serology testing.**] https://www.medrxiv.org/content/10.1101/2020.05.26.20113191v1

- Data provided in this study supports the utility of a newly-designed lateral flow immunoassay (LFA) for detecting SARS-CoV-2 IgM and IgG antibodies. We employed a clinical cohort of 1,892 SARS-CoV-2 patients and controls, including individuals diagnosed by RT-qPCR at Yale New Haven Hospital, The First Affiliated Hospital of Anhui Medical University, the Chinese Center for Disease Control and Prevention of Hefei City (Hefei CDC), Anhui Province (Anhui Province CDC), and Fuyang City (Fuyang CDC). The LFA studied here detects SARS-CoV-2 IgM and IgG antibodies with a specificity of 97.9-100% for IgM, 99.7-100% for IgG, and sensitivities ranging from 94.1-100% for patients >14-days post symptom onset. Sensitivity decreases in patients <14-days post symptom onset, which is likely due to lower IgG/IgM antibody levels in this population. Finally, we developed a visual intensity reporting system that we believe will be suitable for laboratory and point-of-care settings, and will provide granular information about antibody levels. Overall our results support the widespread utility of this and other LFAs in assessing population-level epidemiological statistics. [**note: these Yale researchers carefully validate a lateral flow antibody test and find it works very well. This is the kind of stuff that needs to be done so we can do more field work!! This test comes from a Finnish company, BIOHIT HealthCare.**] https://www.medrxiv.org/content/10.1101/2020.05.25.20112227v1
- Metagenomics could detect SARS-CoV-2 in all eight nasopharyngeal/throat swabs with high/low viral loads, and rhinovirus in a co-infected patient. The sequenced viruses belonged to lineage B1. Because metagenomics could detect novel pathogen and co-infection, and generate sequence data for epidemiological investigation, it is an attractive approach for infectious-disease diagnosis. [**note: I'm not sure what metagenomics is but this is a Vietnamese group and we need to acknowledge the work of all researchers who are trying to make a difference.**] https://www.medrxiv.org/content/10.1101/2020.05.24.20110205v1
- Non-invasive SARS-CoV-2 antibody testing is urgently needed to estimate the incidence and prevalence of SARS-CoV-2 infection at the general population level. Precise knowledge of population immunity could allow government bodies to make informed decisions about how and when to relax stay-at-home directives and to reopen the economy. We hypothesized that salivary antibodies to SARS-CoV-2 could serve as a non-invasive alternative to serological testing for widespread monitoring of SARS-CoV-2 infection throughout the population. We developed a multiplex SARS-CoV-2 antibody immunoassay based on Luminex technology and tested 167 saliva and 324 serum samples, including 134 and 118 negative saliva and serum samples, respectively, collected before the COVID-19 pandemic, and 33 saliva and 206 serum samples from participants with RT-PCR-confirmed SARS-CoV-2 infection. We evaluated the correlation of results obtained in saliva vs. serum and determined the sensitivity and specificity for each diagnostic media, stratified by antibody isotype, for detection of SARS-CoV-2 infection based on COVID-19 case designation for all specimens. Matched serum and saliva SARS-CoV-2 antigen-specific IgG responses were significantly correlated. Within the 10-plex SARS-CoV-2 panel, the salivary anti-nucleocapsid (N) protein IgG response resulted in the highest sensitivity for detecting prior SARS-CoV-2 infection (100% sensitivity at ≥10 days post-SARS-CoV-2 symptom onset). The salivary anti-receptor binding domain (RBD) IgG response resulted in 100% specificity. Among individuals with SARS-CoV-2 infection confirmed with RT-PCR, the temporal kinetics of IgG, IgA, and IgM in saliva were consistent with those observed in serum. SARS-CoV-2

appears to trigger a humoral immune response resulting in the almost simultaneous rise of IgG, IgM and IgA levels both in serum and in saliva, mirroring responses consistent with the stimulation of existing, cross-reactive B cells. SARS-CoV-2 antibody testing in saliva can play a critically important role in large-scale 'sero'-surveillance to address key public health priorities and guide policy and decision-making for COVID-19. [**note: this is way cool!!! Who knew that saliva could be used for serology testing!!! Apparently Salimetrics, LLC does!**]
https://www.medrxiv.org/content/10.1101/2020.05.24.20112300v1

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2020-05-28

OK opera fans, we have had some arias, piano transcriptions, duets, but why not a full opera you might ask. Asked and answered is my reply. The Rome Opera is putting some very nice productions on line to view for FREE (just like this newsletter!!). Here is video recorded back in 2015. Some fine singing and great scenery: https://www.youtube.com/watch?v=h746rBi1Hdw Remember to read your newsletter before settling in to watch Floria Tosca do her thing.

Will the pandemic turn into an endemic? That's the question this Washington Post article raises.

NEJM remdesivir preliminary trial results and an editorial. I wish I could share their optimism.

Everyone should reconsider high doses of Vitamin D. Regarding high doses of anything, here is an amusing anecdote. A lot of years ago, I was invited to Upjohn (remember them?) to speak at a conference on pre-clinical safety testing of biological products. The meeting was held at their conference center located on the old Upjohn family estate. There was a fishing pond and if you caught anything the cook would prepare it for your dinner that evening. At lunch I was sitting next to Jay Goodman from Michigan State (and a winner of the PhRMA award for Foundation Award in Excellence in Pharmacology/Toxicology). He was eating chocolate cake, drinking coffee and it prompted my question, 'as a toxicologist, aren't you worried about foods that are potential carcinogens?' He laughed and said he always goes by his grandmother's rule, '…eat lots of different foods in moderation.' I've tried to adhere to that maxim as well.

Here is a nice piece in Science on reducing the transmission of SARS-CoV-2. Masking up is of course one of the suggestions! However, I'm still not convinced of the micro-droplet route of exposure. Part of the issue for me is the number of infectious particles per droplet. There is also a big difference between outdoor and indoor exposure, and we still have conflicting data on the effect of heat, sunlight and humidity. I do mask up when going to the store but when I'm walking outside, I do not wear a mask, just stay 20+ feet away from others.

Scott Gottlieb weighs in on the vaccination rate. This means we don't need 300 million doses. However, which vaccine should be chosen?

I have posted several abstracts on wastewater testing. Here is a nice column on the topic.

Blitz virus testing in one census district in San Francisco has real implications for pandemic control.

Some very interesting new clinical trials have been registered.

MODELING

- Children are strikingly underrepresented in COVID-19 case counts. In the United States, children represent 22% of the population but only 1.7% of confirmed SARS-CoV-2 cases. One possibility is that symptom-based viral testing is less likely to identify infected children, since they often experience milder disease than adults. To better assess the frequency of pediatric SARS-CoV-2 infection, we serologically screened 1,775 residual samples from Seattle Children's Hospital collected from 1,076 children seeking medical care during March and April of 2020. Only one child was seropositive in March, but nine were seropositive in April for a period seroprevalence of >1%. Most seropositive children (8/10) were not suspected of having had COVID-19. The sera of most seropositive children had neutralizing activity, including one that neutralized at a dilution >1:18,000. Therefore, among children seeking medical care, the frequency of SARS-CoV-2 infection increased markedly during the early Seattle outbreak despite few positive viral tests. [**note: this is limited data and more needs to be gathered to understand the impact on young people.**] https://www.medrxiv.org/content/10.1101/2020.05.26.20114124v1
- Developing models to quantify the risk of poor outcomes in infected patients could help develop strategies to shield the most vulnerable during de-confinement. Objective To develop and externally validate COVID-19 Estimated Risk (COVER) scores that quantify a patient's risk of hospital admission (COVER-H), requiring intensive services (COVER-I), or fatality (COVER-F) in the 30-days following COVID-19 diagnosis. Design Multinational, distributed network cohorts. Setting We analyzed a federated network of electronic medical records and administrative claims data from 13 data sources and 6 countries, mapped to a common data model. Participants Model development used a patient population consisting of >2 million patients with a general practice (GP), emergency room (ER), or outpatient (OP) visit with diagnosed influenza or flu-like symptoms any time prior to 2020. The model was validated on patients with a GP, ER, or OP visit in 2020 with a confirmed or suspected COVID-19 diagnosis across four databases from South Korea, Spain and the United States. Outcomes Age, sex, historical conditions, and drug use prior to index date were considered as candidate predictors. Outcomes included i) hospitalization with pneumonia, ii) hospitalization with pneumonia requiring intensive services or death, and iii) death in the 30 days after index date. Results Overall, 43,061 COVID-19 patients were included for model validation, after initial model development and validation using 6,869,127 patients with influenza or flu-like symptoms. We identified 7 predictors (history of cancer, chronic obstructive pulmonary disease, diabetes, heart disease, hypertension, hyperlipidemia, and kidney disease) which combined with age and sex could discriminate which patients would experience any of our three outcomes. The models achieved high performance in influenza. When transported to COVID-19 cohorts, the AUC ranges were, COVER-H: 0.73-0.81, COVER-I: 0.73-0.91, and COVER-F: 0.82-0.90. Calibration was overall acceptable, with overestimated risk in the most elderly and highest risk strata. Conclusions and relevance A 9-predictor model performs well for COVID-19 patients for predicting hospitalization, intensive services and death. The models could aid in providing reassurance for low risk patients and shield high risk patients from COVID-19 during de-confinement to reduce the virus' impact on morbidity and mortality. [**note: this paper is from the OHDSI group.**] https://www.medrxiv.org/content/10.1101/2020.05.26.20112649v1

- During the COVID-19 pandemic, there is no agreement, until the current date, about the recommendations of homemade face mask use for the general population, and one of the reasons is a lack of information about their real protective rule on spreading aerosols and viruses. This is a comparative study regarding the relative efficiencies of commercial respiratory masks (medical masks) and homemade fabric masks, which may guide authorities across the globe, following the 'Advice on the use of masks in the context of COVID-19', by the World Health Organization. We described two optical methodologies for charactering respiratory masks. It happens that the aerosol scattering coefficient is linear as a function of its concentration inside the mask chamber. Quantitative optical properties of scattering for a large batch fabrication of masks were demonstrated, making the mask N95 suitable for use as a reference standard. [**note: this Brazilian paper is a very interesting read. They come up with an innovative way to test various materials for masks. Paper towels work incredibly well for a while until they accumulate moisture and then disintegrate.**] https://www.medrxiv.org/content/10.1101/2020.05.26.20100529v1

NEWLY REGISTERED CLINICAL TRIALS

- There is evidence that resveratrol might help fight coronavirus as well as help protect the body from the effects of disease (COVID-19) caused by the infection. In this proof-of-concept pilot study we will compare the effects of resveratrol to placebo to assess the safety of resveratrol and explore effectiveness. [**note; I would be very interested in what kind of evidence this investigator has. It's not clear that it does much of anything. HOWEVER, it is present in blueberries and I have a heaping amount on my cereal every morning. It's also in peanuts so I need up my intake of peanut butter sandwiches. Too bad the Girl Scout Do-Si-Do cookies are not available right now as those would be a great source of reservatrol. I'll add this one to my daily fexofenadine, and AREDs-2 vitamin supplement. I'm protected (cough, cough, hey…I cannot smell anything….0**] NCT04400890
- The overall objective is to evaluate the efficacy, tolerability, and safety of a single dose of RBT-9 versus placebo in coronavirus disease 2019 (COVID-19) infection in non-critically ill adults who are at high risk of progression. [**note: I don't know anything more than this company, Renibus Therapeutics is working on drugs for kidney disease.**] NCT04364763
- There is an urgent need to evaluate interventions that could be effective against the infection with SARS-CoV 2. Tannins based wood extracts are an inexpensive and safe product with protective effect in both bacterial and viral infections likely due to its anti- inflammatory, anti-oxidative effects and their modulation of the intestinal microbiota. This randomized controlled trial seeks to evaluate the efficacy of the tannins based dietary supplement ARBOX in positive COVID-19 patients. [**note: it must be natural products day. The investigators will realize a prospective, double-blind, randomized trial to assess the effect of treatment with a dietary supplement (ARBOX), a molecular complex of quebracho and chestnut tannins extract and Vit B12, compared with placebo. 140 COVID-19 patients will be recruited in a single center in Buenos Aires Argentina. 70 patients will receive conventional treatment plus ARBOX (treated group) and 70 patients will receive conventional treatment plus placebo (control group). The effects will be evaluated during the 28 days follow up. The primary end point will be the time of discharge from the hospital. A panel of 27 cytokines level, intestinal microbiota**

composition and its metabolites will be assessed at day 1 and 14. Throw things at the wall long enough and something will stick.] NCT04403646

- The Açaí trial will be testing if the açaí berry extract, a safe natural product with anti-inflammatory properties, can be used as a treatment option in adult patients with COVID-19 in the community. The virus origins have been studied and evidence so far suggests it originates in bats, with spread to humans likely mediated by an intermediate mammalian. Bats have a dampened Nod-like receptor family, pyrin-containing 3 (NLRP3)-mediated inflammation. Dampening NLRP3-mediated inflammation has been associated with the asymptotic viral status, therefore it is plausible that the pathogenic inflammatory response of SARS-CoV-2 might be associated with activation of NLRP3 inflammasome. Data show that the natural extract of Açaí Palm Berry (Euterpe oleracea Mart.) is a potent inhibitor of NLRP3. This is a safe, inexpensive, and readily available natural health supplement which could be a rapid response treatment intervention for patients with COVID-19. [**note: and on we go with natural products, this time with one of my fave crossword puzzle answers! The rationale for this study is actually better than some I have read for HCQ. Let's hope this one sticks to the wall!!**] NCT04404218
- The COPE Trial is a randomized controlled trial that will provide currently isolated yet generally physically healthy 18-64 year old adults who are pre-retirement with the opportunity to receive a free 3-month subscription to either a yoga or moderate-to-high intensity aerobic exercise app or be randomized to a waitlist control group. Study outcomes include measures of psychological wellbeing and physical health. [**note: darn, I'm outside the age group for this trial. I'm still paying $82/month to the YMCA right up the street and it's been closed for the past two months!! They did call to check in on me as they did all their senior citizen members.**] NCT04400279

CLINICAL TRIAL RESULTS

- Surprisingly, no news today. The published remdesivir study was already cited above. We still await some of the big trial data.

DRUG DEVELOPMENT

- In all of the clinical trials for COVID-19 conducted thus far and among those ongoing involving chloroquine or hydroxychloroquine, the drug substance used has invariably been chloroquine (CQ) diphosphate or hydroxychloroquine (HCQ) sulfate, i.e., the phosphoric or sulfuric acid salt of a racemic mixture of R- and S-enantiomer (50/50), respectively. As a result, the clinical outcome from previous CQ or HCQ trials were, in fact, the collective manifestation of both R and S enantiomers with inherent different pharmacodynamic, pharmacokinetic properties, and toxicity liabilities. Our data for the first time demonstrated the stereoselective difference of CQ and HCQ against SARS-CoV-2 in a Biosafety Level 3 laboratory. S-chloroquine (S-CQ) and S-hydroxychloroquine (S-HCQ) were found to be 27% and 60% more active against SARS-CoV-2, as compared to R-CQ and R-HCQ, respectively. With these data and previous work on stereoselective metabolism of CQ and HCQ, we recommend that clinical studies using S-HCQ as a potentially superior drug substance be conducted for the treatment of COVID-19 for improved therapeutic index. [**note: while I don't wish to resurrect HCQ, there is something to this research as we know from several examples of pharma enantiomeric compounds.**] https://www.biorxiv.org/content/10.1101/2020.05.26.114033v1

- COVID-19, caused by SARS-CoV-2, lacks effective therapeutics. Additionally, no antiviral drugs or vaccines were developed against the closely related coronavirus, SARS-CoV-1 or MERS-CoV, despite previous zoonotic outbreaks. To identify starting points for such therapeutics, we performed a large-scale screen of electrophile and non-covalent fragments through a combined mass spectrometry and X-ray approach against the SARS-CoV-2 main protease, one of two cysteine viral proteases essential for viral replication. Our crystallographic screen identified 71 hits that span the entire active site, as well as 3 hits at the dimer interface. These structures reveal routes to rapidly develop more potent inhibitors through merging of covalent and non-covalent fragment hits; one series of low-reactivity, tractable covalent fragments was progressed to discover improved binders. These combined hits offer unprecedented structural and reactivity information for on-going structure-based drug design against SARS-CoV-2 main protease. [**note: pretty cool research showing how various sites on the protease can be looked at for drug design.**] https://www.biorxiv.org/content/10.1101/2020.05.27.118117v1

DIAGNOSTIC DEVELOPMENT

- We here describe the development and validation of IMMUNO-COV, a high-throughput clinical test to quantitatively measure SARS-CoV-2-neutralizing antibodies, the specific subset of anti-SARS-CoV-2 antibodies that block viral infection. The test measures the capacity of serum or purified antibodies to neutralize a recombinant Vesicular Stomatitis Virus (VSV) encoding the SARS-CoV-2 spike glycoprotein. This recombinant virus (VSV-SARS-CoV-2-S-Δ19CT) induces fusion in Vero cell monolayers, which is detected as luciferase signal using a dual split protein (DSP) reporter system. VSV-SARS-CoV-2-S-Δ19CT infection was blocked by monoclonal anti-SARS-CoV-2-spike antibodies and by plasma or serum from SARS-CoV-2 convalescing individuals. The assay exhibited 100% specificity in validation tests, and across all tests zero false positives were detected. In blinded analyses of 230 serum samples, only two unexpected results were observed based on available clinical data. We observed a perfect correlation between results from our assay and 80 samples that were also assayed using a commercially available ELISA. To quantify the magnitude of the anti-viral response, we generated a calibration curve by adding stepped concentrations of anti-SARS-CoV-2-spike monoclonal antibody to pooled SARS-CoV-2 seronegative serum. Using the calibration curve and a single optimal 1:100 serum test dilution, we reliably measured neutralizing antibody levels in each test sample. Virus neutralization units (VNUs) calculated from the assay correlated closely ($p < 0.0001$) with PRNT(EC50) values determined by plaque reduction neutralization test against a clinical isolate of SARS-CoV-2. Taken together, these results demonstrate that the IMMUNO-COV assay accurately quantitates SARS-CoV-2 neutralizing antibodies in human sera and therefore is a potentially valuable addition to the currently available serological tests. The assay can provide vital information for comparing immune responses to the various SARS-CoV-2 vaccines that are currently in development, or for evaluating donor eligibility in convalescent plasma therapy studies. [**note: a new approach to identifying and quantifying neutralizing antibodies. Vyriad, Imanis Life Sciences, Regeneron, and Mayo Clinic are collaborating in the commercial development of this assay.**] https://www.biorxiv.org/content/10.1101/2020.05.26.117549v1
- Digital manufacturing, especially 3D printing, has been promulgated as an important approach for the rapid development of new products as well as a replacement manufacturing technique for many traditional manufacturing methods, including injection molding, when supply chains

are disrupted. Herein we report the use of Digital Light Synthesis (DLS) for the design and large-scale deployment of nasopharyngeal (NP) swabs for testing of coronavirus SARS-CoV-2 infections in humans. NP swabs have been one of society's essential products hardest hit by the supply chain disruptions caused by COVID-19. A latticed tip NP swab was designed and fabricated by DLS from a liquid resin previously developed and approved for use to make dental night guard devices. These latticed NP swabs demonstrated non-inferiority in a human clinical study of patients suspected of being infected with SARS-CoV-2. [**note: cool 3-D printing technology to make nasal swabs. Good thinking.**]
https://www.medrxiv.org/content/10.1101/2020.05.25.20112201v1

- In response to the growing COVID-19 pandemic, Rapid Diagnostic Tests (RDTs) have been developed to detect specific antibodies, IgG and IgM, to SARS-CoV-2 virus in human whole blood. We conducted a real-life study to evaluate the performance of two RDTs, COVID-PRESTO and COVID-DUO, compared to the gold standard, RT-PCR. Methods RT-PCR testing of SARS-Cov-2 was performed from nasopharyngeal swab specimens collected in adult patients visiting the infectious disease department at the hospital (Orleans, France). Fingertip whole blood samples taken at different time points after onset of the disease were tested with RDTs. The specificity and sensitivity of the rapid test kits compared to test of reference (RT-PCR) were calculated. Results Among 381 patients with symptoms of COVID-19 who went to the hospital for a diagnostic, 143 patients were RT-PCR negative. Results of test with RDTs were all negative for these patients, indicating a specificity of 100% for both RDTs. In the RT-PCR positive subgroup (n=238), 133 patients were tested with COVID-PRESTO and 129 patients were tested with COVID-DUO (24 patients tested with both). The further the onset of symptoms was from the date of collection, the greater the sensitivity. The sensitivity of COVID-PRESTO test ranged from 10.00% for patients having experienced their 1st symptoms from 0 to 5 days ago to 100% in patients where symptoms had occurred more than 15 days before the date of tests. For COVID-DUO test, the sensitivity ranged from 35.71% [0-5 days] to 100% (> 15 days). Conclusion COVID-PRESTO and DUO RDTs turned out to be very specific (none false positive) and to be sensitive enough after 15 days from onset of symptom. These easy to use IgG/IgM combined test kits are the first ones allowing a screening with capillary blood sample, by typing from a finger prick. These rapid tests are particularly interesting for screening in low resource settings. [**note: French study on two rapid serology tests shows they can be effective in screening situations.**]
https://www.medrxiv.org/content/10.1101/2020.05.27.20112888v1

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2020-05-29

Stan Getz and Chet Baker were true icons in the jazz world. Both were intensely melodic musicians and both were seduced into heroin use and addiction. Getz successfully kicked the habit, Baker did not. Here is a fine performance of the two from a 1983 Stockholm performance:
https://www.youtube.com/watch?v=0p72L4bMdPA

Larry Kramer passed away Wednesday morning at age 84. He is best remembered as one of the earliest AIDS activists and he didn't tolerate any fools or those who were not champions for faster approval of

HIV drugs. I was one of the industry representatives to the Public Health Service Parallel Track Working Group back in mid-1980. Larry was on the group along with a number of other activists, Tony Fauci, and several FDA representatives. There were some fractious discussions but in the end we came up with a sound approach to expanded access of experimental drugs without compromising clinical trials. Here is the New York Times obituary and here are some remembrances courtesy of STAT. I cannot say that I knew him well, there were others on the work group who were knowledgeable about the nuts and bolts of clinical trials with whom I had frequent discussions but his singular drive was important and needed at that time.

This falls into the bizarre what are these people thinking category. "The Trump administration with no advance notice removed warning contained in guidance for the reopening of houses of worship that singing in choirs can spread the coronavirus." I guess they are reinventing the truth about the superspread of SARS-CoV-2 that took place within the Washington state choir practice. I am certainly not going back to choir rehearsals until all of this is sorted out; it falls into the category of risky behavior.

Lots of stuff to untangle as researchers look at why there are differential mortality effects between Asian and Euro/US countries.

There was some discussion yesterday among readers about herd immunity and the level of recovered people in New York City. The New York Times has a good article on this with a nice graphic that shows the percent infected relative to what is needed assuming 60% for herd immunity. I was surprised at how low Stockholm is given Sweden's approach.

More on how wearable tech can help detect SARS-CoV-2. We need to get all this stuff!!

I honestly don't know what to make of some of these pre-prints. Here is one from Germany urging a relaxation of censorship on Twitter as it is a useful platform to for rapid research response. I guess someone had to do this research but as a non-Twitter user the validity of the conclusion is unclear.

Good overview on contact tracing. Some states get this!

MODELING

- Importance: New York State (NYS) is an epicenter of the United States' COVID-19 epidemic. Reliable estimates of cumulative incidence of SARS-CoV-2 infection in the population are critical to tracking the extent of transmission and informing policies, but US data are lacking, in part because societal closure complicates study conduct. Objective: To estimate the cumulative incidence of SARS-CoV-2 infection and percent of infections diagnosed in New York State, overall and by region, age, sex, and race and ethnicity. Design: Statewide cross-sectional seroprevalence study, conducted April 19-28, 2020. Setting: Grocery stores (n=99) located in 26 counties throughout NYS, which were essential businesses that remained open during a period of societal closure and attract a heterogenous clientele. Participants: Convenience sample of patrons >=18 years and residing in New York State, recruited consecutively upon entering stores and via an in-store flyer. Exposures: Region (New York City, Westchester/Rockland, Long Island, Rest of New York State), age, sex, race and ethnicity. Main Outcomes: Primary outcome: cumulative incidence of SARS-CoV-2 infection, based on dry-blood spot (DBS) SARS-CoV-2

antibody reactivity; secondary outcome: percent of infections diagnosed. Results: Among 15,101 adults with suitable DBS specimens, 1,887 (12.5%) were reactive using a validated SARS-CoV-2 IgG microsphere immunoassay (sensitivity 87.9%, specificity 99.75%). Following post-stratification weighting on region, sex, age, and race and ethnicity and adjustment for assay characteristics, estimated cumulative incidence through March 29 was 14.0% (95% CI: 13.3-14.7%), corresponding to 2,139,300 (95% CI: 2,035,800-2,242,800) infection-experienced adults. Cumulative incidence was higher among Hispanic/Latino (29.2%, 95% CI: 27.2-31.2%), non-Hispanic black/African American (20.2% 95% CI, 18.1-22.3%), and non-Hispanic Asian (12.4%, 95% CI: 9.4-15.4%) adults than non-Hispanic white adults (8.1%, 95% CI: 7.4-8.7%, p<.0001). Cumulative incidence was highest in New York City (NYC) 22.7% (95% CI: 21.5%-24.0). Dividing diagnoses reported to NYS by estimated infection-experienced adults, an estimated 8.9% (95% CI: 8.4-9.3%) of infections were diagnosed, with those ≥55 years most likely to be diagnosed (11.3%, 95% CI: 10.4-12.2%). Conclusions and Relevance: Over 2 million adults were infected through late March 2020, with substantial variations by subpopulations. As this remains below herd immunity thresholds, monitoring, testing, and contact tracing remain essential public health strategies. [**note: serology data from New York State. The sample size is pretty large and they tried to do random testing. It still remains below herd immunity threshold. More testing and contact tracing continue to be the cornerstone of getting out of this.**] https://www.medrxiv.org/content/10.1101/2020.05.25.20113050v1

- This paper evaluates the dynamic impact of various policies, such as school, business, and restaurant closures, adopted by the US states on the growth rates of confirmed Covid-19 cases and social distancing behavior measured by Google Mobility Reports, where we take into consideration of people's voluntarily behavioral response to new information of transmission risks. Using the US state-level data, our analysis finds that both policies and information on transmission risks are important determinants of people's social distancing behavior, and shows that a change in policies explains a large fraction of observed changes in social distancing behavior. Our counterfactual experiments indicate that removing all policies on April 1st of 2020 would have lead to 30 to 200 times more additional cases by late May. Removing only the non-essential businesses closures (while maintaining restrictions on movie theaters and restaurants) would have increased the weekly growth rate of cases between -0.02 and 0.06 and would have lead to -10% to 40% more cases by late May. Finally, nationally mandating face masks for employees on April 1st would have reduced the case growth rate by 0.1-0.25. This leads to 30% to 57% fewer reported cases by late May, which translates into, roughly, 30-57 thousand saved lives. [**note: such a simple solution!!!! Of course all of us who are interested in public health wear masks when out in public places. It's the right thing to do, yet we see so many pictures of people not doing the simple thing. This remains a great mystery to me.**] https://www.medrxiv.org/content/10.1101/2020.05.27.20115139v1

NEWLY REGISTERED CLINICAL TRIALS

- The rapid increase in trial activity has raised questions about efficiency and lack of coordination. Our objective was to develop a user-friendly, open access, online database of interventional trials of medicinal products to monitor and rapidly identify trials of medicinal products. Methods and Findings: Using the US clinicaltrials.gov (NCT) registry, the EU Clinical Trials Register (EUCTR) and the WHO International Clinical Trials Registry Platform (WHO ICTRP), we identified all

COVID-19 trials of medicinal products and combined data from the 3 sources into a single data table. Trials that were out of scope and duplicates were excluded. A manual encoding was performed to ascertain key information (e.g. trial aim, type of intervention etc). The database, Covid19db, was published online at: http://www.redo-project.org/covid19db/ . Descriptive statistics of the database from April 4th 2020 through to May 19th show an increase from 186 to 955 trials, or an average of 17 new trials registered per day. Over this period, the proportion of trials including a repurposing arm decreased slightly over time (from a maximum of 75% to 68% at the end of the covered period) as did the proportion of trials aiming to prevent infection (from a maximum of 16% to 12% at the end of the covered period). The most popular intervention is hydroxychloroquine (180 trials), followed by azithromycin (57 trials), chloroquine, tocilizumab and lopinavir/ritonavir (36 trials). Total planned enrolment is 468,559 participants as of 19th May 2020. Conclusions: we have developed an open access, online and regularly updated tool to monitor clinical trials of medicinal products to prevent or treat infection by SARS-CoV-2 globally. *Our analysis shows a high number of 'me-too' trials, in particular for some repurposed drugs, such as hydroxychloroquine, azithromycin and tocilizumab, substantiating calls for better coordination and better use of trial resources*. [**note: I'm glad someone did this work, but I pretty much came to the same conclusion over a month ago without having to spend this kind of effort. Loyal readers already know of my on-line paper on Clinical Trials during a Pandemic. Still it's good to have this type of database!!**]
https://www.medrxiv.org/content/10.1101/2020.05.27.20114371v1

- Will check for new trials tomorrow.

CLINICAL TRIAL RESULTS

- To describe the association between D-dimer, CRP, IL-6, ferritin, LDH, and clinical outcomes in a cohort of COVID-19 patients treated on the inpatient medical service at a university hospital in Washington, DC. Design: In this retrospective study, we included all adults admitted to the inpatient medicine service at George Washington University Hospital between March 12, 2020 and May 9, 2020 with laboratory confirmed COVID-19. Clinical and laboratory data were extracted from electronic medical records and compared between survivors not requiring ICU transfer, survivors requiring ICU transfer, survivors requiring intubation, and non-survivors. Key Results: 299 patients were included in our study, of whom 69 required transfer to the ICU, 39 required intubation, and 71 died. Threshold values for IL-6 (>50 pg/mL), D-dimer (>3 mcg/mL), ferritin (>450 ng/mL), CRP (>100 mg/L), and LDH (1,200 u/L) were found to be statistically significant and independently associated with higher odd of clinical deterioration and death. Hypertension, CVA and heart disease independently had an increased risk of all three outcomes, while CKD had only an increased risk of death. Patient co-morbidities had no effect on the different biomarkers' significant association with poor patient clinical outcomes, except cancer. Conclusion: Laboratory markers of inflammation and coagulopathy can help clinicians identify patients who are at high risk for clinical deterioration, independent of clinically significant medical comorbidities [**note: more on biomarkers for disease progression.**]
https://www.medrxiv.org/content/10.1101/2020.05.27.20115105v1
- This study investigates the association between the treatment with heparin and mortality in patients admitted with Covid-19. Methods: Routinely recorded, clinical data, up to the 24th of April 2020, from the 2075 patients with Covid-19, admitted in 17 hospitals in Spain between the

1st of March and the 20th of April 2020 were used. The following variables were extracted for this study: age, gender, temperature, and saturation of oxygen on admission, treatment with heparin, hydroxychloroquine, azithromycin, steroids, tocilizumab, a combination of lopinavir with ritonavir, and oseltamivir, together with data on mortality. Multivariable logistic regression models were used to investigate the associations. Results: At the time of collecting the data, 301 patients had died, 1447 had been discharged home from the hospitals, 201 were still admitted, and 126 had been transferred to hospitals not included in the study. Median follow up time was 8 (IQR:5-12) days. Heparin had been used in 1734 patients. Heparin was associated with lower mortality when the model was adjusted for age and gender, with OR (95%CI): 0.55 (0.37-0.82) p=0.003. This association remained significant when saturation of oxygen <90%, and temperature >37C were added to de model with OR: 0.54(0.36-0.82) p=0.003, and also when all the other drugs were included as covariates OR: 0.42 (0.26-0.66) p<0.001. Conclusions: The association between heparin and lower mortality observed in this study can be acknowledged by clinicians in hospitals and in the community. Randomized controlled trials to assess the causal effects of heparin in different therapeutic regimes are required. [**note: this is not getting as much attention as remdesivir but may be more important in terms of treating very sick patients.**] https://www.medrxiv.org/content/10.1101/2020.05.27.20114694v1

- We included all patients with COVID-19 pneumonia admitted to the intensive care unit (ICU) at the safety net hospital for San Francisco through April 8, 2020. Each patient had ≥15 days of follow-up. Among 26 patients, the median age was 54 years (interquartile range, 43 to 62), 65% were men, and 77% were Latinx. Mechanical ventilation was initiated for 11 (42%) patients within 24 hours of ICU admission and 20 patients (77%) overall. The median duration of mechanical ventilation was 13.5 days (interquartile range, 5 to 20). Patients were managed with lung protective ventilation (tidal volume <8 ml/kg of ideal body weight and plateau pressure ≤30 cmH2O on 98% and 78% of ventilator days, respectively). Prone positioning was used for 13 of 20 (65%) ventilated patients for a median of 5 days (interquartile range, 2 to 10). Seventeen (65%) patients were discharged home, 1 (4%) was discharged to nursing home, 3 (12%) were discharged from the ICU, and 2 (8%) remain intubated in the ICU at the time of this report. Three (12%) patients have died. Conclusions: Good outcomes were achieved in critically ill patients with COVID-19 by using standard therapies for acute respiratory distress syndrome (ARDS) such as lung protective ventilation and prone positioning. Ensuring hospitals can deliver sustained high-quality and evidence-based critical care to patients with ARDS should remain a priority. [**note: experience in a front line San Francisco hospital.**] https://www.medrxiv.org/content/10.1101/2020.05.27.20114090v1
- The genetic variation of ACE2 function and expression across populations is still poorly understood. This study aims at better understanding the genetic basis of COVID-19 outcomes by studying association between genetic variation in ACE2 and disease severity in the Iranian population. Methods: We analyzed two large Iranian cohorts and several publicly available human population variant databases to identify novel and previously known ACE2 exonic variants present in the Iranian population and considered those as candidate variants for association between genetic variation and disease severity. We genotyped these variants across three groups of COVID-19 patients with different clinical outcomes (mild disease, severe disease, and death) and evaluated this genetic variation with regard to clinical outcomes. Results: We identified 32 exonic variants present in Iranian cohorts or other public variant databases. Among

those, 11 variants are novel and have thus not been described in other populations previously. Following genotyping of these 32 candidate variants, only the synonymous polymorphism (c.2247G>A) was detected across the three groups of COVID-19 patients. Conclusion: Genetic variability of known and novel exonic variants was low among our COVID-19 patients. *Our results do not provide support for the hypothesis that exonic variation in ACE2 has a sizeable impact on COVID-19 severity across the Iranian population.* [**note: genetic date on ACE2 receptor from Iran points to no genetic impact in the variants they studied with respect to infection.**] https://www.medrxiv.org/content/10.1101/2020.05.27.20115071v1

- In addition to the many factors that can influence these discrepancies, we suggest a biological aspect, the genetic variation at the viral S protein receptor in human cells, ACE2 (angiotensin I-converting enzyme 2), which may contribute to the worse clinical outcome in males and in some regions worldwide. We performed exomics analysis in native and admixed South American populations, and we also conducted in silico genomics databank investigations in populations from other continents. Interestingly, at least ten polymorphisms in coding, noncoding and regulatory sites were found that can shed light on this issue and offer a plausible biological explanation for these epidemiological differences. In conclusion, ACE2 polymorphisms should influence epidemiological discrepancies observed among ancestry and, moreover, between sexes. [**note: this Brazilian study looks at some polymorphisms that may impact infectivity. Clearly more work needs to be done (and is being done) on this matter.**] https://www.medrxiv.org/content/10.1101/2020.05.27.20114843v1

DRUG DEVELOPMENT

- Since the outbreak of the COVID-19 pandemic in December 2019 and its rapid spread worldwide, the scientific community has been under pressure to react and make progress in the development of an effective treatment against the virus responsible for the disease. Here, we implement an original virtual screening (VS) protocol for repositioning approved drugs in order to predict which of them could inhibit the main protease of the virus (M-pro), a key target for antiviral drugs given its essential role in the virus' replication. Two different libraries of approved drugs were docked against the structure of M-pro using Glide, FRED and AutoDock Vina, and only the equivalent high affinity binding modes predicted simultaneously by the three docking programs were considered to correspond to bioactive poses. In this way, we took advantage of the three sampling algorithms to generate hypothetic binding modes without relying on a single scoring function to rank the results. Seven possible SARS-CoV-2 M-pro inhibitors were predicted using this approach: Perampanel, Carprofen, Celecoxib, Alprazolam, Trovafloxacin, Sarafloxacin and ethyl biscoumacetate. Carprofen and Celecoxib have been selected by the COVID Moonshot initiative for in vitro testing; they show 3.97 and 11.90% M-pro inhibition at 50 µM, respectively. [**note: This came across my newsfeed yesterday and is the second paper that has identified celecoxib as a possible treatment. Weird seeing trovafloxacin on this list; I don't think that one will be given a try in the clinic. Caprofen is a veterinary NSAID. Pfizer marketed it for human use at one time but pulled it off the market as there were other, better drugs.**] https://www.mdpi.com/1422-0067/21/11/3793
- Group B Coxsackieviruses belonging to the genus, Enterovirus, contain six serotypes that induce various diseases, whose occurrence may involve the mediation of more than one serotype. We recently identified immunogenic epitopes within CVB3 viral protein 1 that induce antiviral T cell

responses in mouse models of CVB infections. In our investigations to determine the protective responses of the viral epitopes, we unexpectedly noted that animals immunized with complete Freunds adjuvant (CFA) alone and later challenged with CVB3 were completely protected against myocarditis. Similarly, the pancreatitis inducing ability of CVB3 was remarkably reduced to only 10% in the CFA group as opposed to 73.3% in the control group that received no CFA. Additionally, no mortalities were noted in the CFA group, whereas 40% of control animals died during the course of 21 days post-infection with CVB3. Taken together, our data suggest that the adjuvant effects of CFA may be sufficient for protection against CVB infections. These observations may provide new insights into our understanding of the occurrence of viral infections. One example is Coronavirus disease 19 (COVID 19) as individuals suffering from COVID-19 who have been vaccinated with Bacillus Calmette Guerin appear to have fewer morbidities and mortalities than unvaccinated individuals. [**note: Freunds adjuvant for all!! What a cheap solution and we don't need to spend any more time on vaccine research. All joking aside, this is pretty interesting.**]
https://www.biorxiv.org/content/10.1101/2020.05.27.120121v1

- Our idea is focused on the *development of "monoclonal-type" plastic antibodies* based on Molecularly Imprinted Polymers (MIPs) able to selectively bind a portion of the novel coronavirus SARS-CoV-2 spike protein to block its function and, thus, the infection process. Molecular Imprinting, indeed, represents a very promising and attractive technology for the synthesis of MIPs characterized by specific recognition abilities for a target molecule. Given these characteristics, MIPs can be considered tailor-made synthetic antibodies obtained by a templating process. In the present study, the developed imprinted polymeric nanoparticles were characterized in terms of particles size and distribution by Dynamic Light Scattering (DLS) and the imprinting effect and selectivity were investigated by performing binding experiments using the receptor-binding domain (RBD) of the novel coronavirus and the RBD of SARS-CoV spike protein, respectively. Finally, the hemocompatibility of the prepared MIP-based plastic antibodies was also evaluated. [**note: I confess to not fully understanding this technology but with "monoclonal-type plastic antibodies for SARS-CoV-2" in the title really grabs me!**]
https://www.biorxiv.org/content/10.1101/2020.05.28.120709v1
- The ongoing COVID-19 pandemic, caused by infection with SARS-CoV-2, is having a dramatic and deleterious impact on health services and the global economy. Grim public health statistics highlight the need for vaccines that can rapidly confer protection after a single dose and be manufactured using components suitable for scale-up and efficient distribution. In response, we have rapidly developed repRNA-CoV2S, a stable and highly immunogenic vaccine candidate comprised of an RNA replicon formulated with a novel Lipid InOrganic Nanoparticle (LION) designed to enhance vaccine stability, delivery and immunogenicity. We show that intramuscular injection of LION/repRNA-CoV2S elicits robust anti-SARS-CoV-2 spike protein IgG antibody isotypes indicative of a Type 1 T helper response as well as potent T cell responses in mice. Importantly, a single-dose administration in nonhuman primates elicited antibody responses that potently neutralized SARS-CoV-2. These data support further development of LION/repRNA-CoV2S as a vaccine candidate for prophylactic protection from SARS-CoV-2 infection. [**note: did not see this one coming. Another novel vaccine approach with some good animal data. I wonder how soon they can get this into human testing.**]
https://www.biorxiv.org/content/10.1101/2020.05.28.121640v1

DIAGNOSTIC DEVELOPMENT

- A novel '2019 Novel Coronavirus Detection Kit (nCoV-DK)' halves detection time by eliminating the steps of RNA extraction and purification. We evaluated concordance between the nCoV-DK and direct PCR. The virus was detected in 53/71 fresh samples by the direct method and 55/71 corresponding frozen samples by the nCoV-DK. The overall concordance rate of the virus detection between the two methods was 94.4% (95% CI, 86.2-98.4). Concordance rates were 95.2% (95% CI, 83.8-99.4), 95.5% (95% CI, 77.2-99.9), 85.7% (95% CI, 42.1-99.6) in nasopharyngeal swab, saliva, and sputum samples, respectively. These results indicate that the nCoV-DK effectively detects SARS-CoV-2 in all types of the samples including saliva, while reducing time required for detection, labor, and risk of human error. [**note: good work from Japan on a new approach to PCR testing.**]
  https://www.biorxiv.org/content/10.1101/2020.05.27.120410v1

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2020-05-30

Here is another COVID-19 performance from a group that is new to me. The quartet NOVA is minimalist with a guitarist, bass player, drummer and vocalist. Here is a nice split screen performance of one of my faves, Corcovado: https://www.youtube.com/watch?v=wl6NVR88kgQ I want to hear more from this group!

This one goes above the fold. Here are four case studies of cytokine storm in children who presented at Mt. Sinai in New York. We know from published reports that the young are often asymptomatic or have very mild cases. This should remind us all that this is not always the case.

Derek Lowe has been very busy with a column on using AI to discover antivirals and on famotidine as a drug candidate.

A group of scientists have questioned The Lancet article on the large observational HCQ study that was published last week. The Lancet has referred questions to the authors and I'm sure we will see a response.

Did you know that *dataveillance* is a word? I get the Oxford English Dictionary word of the day in my inbox and this is the word of the day!!

I'm not weighing in on some of the decisions going on about the WHO and CDC mishaps. I assume all my readers are knowledgeable about the current events. Otherwise, it is a slow day for preprints.

MODELING

- New York City (NYC) has emerged as one of the epicenters of the current SARS-CoV-2 pandemic. To identify the early transmission events underlying the rapid spread of the virus in the NYC metropolitan area, we sequenced the virus causing COVID-19 in patients seeking care at the Mount Sinai Health System. Phylogenetic analysis of 84 distinct SARS-CoV2 genomes indicates multiple, independent but isolated introductions mainly from Europe and other parts of the United States. Moreover, we find evidence for community transmission of SARS-CoV-2 as suggested by clusters of related viruses found in patients living in different neighborhoods of the city. [**note: a very thorough analysis from the Mt. Sinai research group.**] https://science.sciencemag.org/content/early/2020/05/28/science.abc1917
- We aim to provide the first evidence of belief in conspiracy theory regarding the COVID-19 virus as a predictor of the mental health and well-being of healthcare workers. Methods: We conducted a survey of 252 healthcare workers in Ecuador from April 10 to May 2, 2020. Results: In Ecuador, 32.54% of the sampled healthcare workers experienced distress disorder, and 28.17% had anxiety disorder. Compared to healthcare workers who were not sure where the virus originated, those who believed the virus was developed intentionally in a lab reported higher levels of distress and anxiety, and lower levels of job satisfaction and life satisfaction. Older healthcare workers and those who exercise more reported higher job satisfaction. Married healthcare workers, those who exercise more, and those not infected reported higher life satisfaction. Conclusion: This paper identifies belief in a COVID-19 conspiracy theory as an important predictor of distress, anxiety, and job and life satisfaction of healthcare workers. It enables mental health services to better target and help mentally vulnerable healthcare workers during the ongoing COVID-19 pandemic. [**note: it is with great trepidation that I post this one. I am NOT a believer in conspiracy theories (I do love to read about them and refer my readers to one of the seminal works on this, Richard Hofstadter's "The Paranoid Style of American Politics"), but some are. These Ecuadoran researchers try to get at the root cause of mental health issues among healthcare workers. I am sure this approach can be extrapolated to other populations and geographical areas.]** https://www.medrxiv.org/content/10.1101/2020.05.26.20113258v1

NEWLY REGISTERED CLINICAL TRIALS

- This is a randomized, double blind, placebo controlled, first-in-human (FIH) study to assess safety, reactogenicity, and immunogenicity of SCB-2019 at multiple dose levels, administered as 2 injections IM in healthy subjects. Each study vaccine dose level will be evaluated with and without adjuvant. [**note: this is a new entrant into the vaccine arena. More information on the company and vaccine is here.**] NCT04405908
- This randomized clinical on-line study examines whether whether a daily practice of meditation or Kundalini Yoga with anxiety reduction training leads to a greater reduction in anxiety than anxiety reduction training alone. [**note: maybe this is the one for me! I need to get my Yoga book out and get started.**] NCT04386291
- A major event in aging is the loss of the central metabolite nicotinamide adenine dinucleotide (NAD+) that appear to be important in the proinflammatory environment that occur during aging. Notably, recent work from our and other groups suggest that aging can be ameliorated by even a short-term treatment of the NAD+ precursor nicotinamide riboside. Nicotinamide riboside has recently been shown to be able to return aging tissues to a younger state even after

short term treatment. This vitamin B3- analog is naturally occurring, is readily taken up through oral administration and has been tested in human trials with few side effects. In this randomized double blinded case-control trial, the investigators will treat elderly (>70 year old) COVID19 patients with 1 g of nicotinamide riboside (NR-E) or placebo for 2 weeks and investigate if this affects the clinical course of the disease. [**note: I had no idea that this might be an anti-aging compound.**] NCT04407390

CLINICAL TRIAL RESULTS

- We conducted a multicenter one arm proof of concept interventional study. Patients with Covid-19 disease with moderate-to-severe Acute Respiratory Distress Syndrome, elevated C-reactive Protein and need for mechanical ventilation and/or CPAP were enrolled. One to three 250-300 ml unit of hyperimmune plasma (neutralizing antibodies titer ≥1:160) were administered. Primary outcome was 7-days hospital mortality. Secondary outcomes were PaO2/FiO2, laboratory and radiologic changes, as well as weaning from mechanical ventilation and safety. RESULTS The study observed 46 patients from March, 25 to April, 21 2020. Patients were aged 63, 61% male, 30 on CPAP and 7 intubated. PaO2/FiO2 was 128 (SD 47). Symptoms and ARDS duration were 14 (SD 7) and 6 days (SD 3). Three patients (6.5%) died within 7 days. The upper one-sided 90%CI was 13.9%, allowing to reject the null hypothesis of a 15% mortality. PaO2/FiO2 increased by 112 units (95%CI 82 to142) in survivors, the chest radiogram severity decreased in 23% (95%CI 5% to 42%); CRP, Ferritin and LDH decreased by 60, 36 and 20% respectively. Weaning from CPAP was obtained in 26/30 patients and 3/7 were extubated. Five serious adverse events occurred in 4 patients (2 likely, 2 possible treatment related). CONCLUSIONS Hyperimmune plasma in Covid-19 shows promising benefits, to be confirmed in a randomized controlled trial. This proof of concept study could open to future developments including hyperimmune plasma banking, development of standardized pharmaceutical products and monoclonal antibodies. [**note: from Italy, a one arm study of hyperimmune plasma shows benefit. We need to get mAbs deployed ASAP.**]
https://www.medrxiv.org/content/10.1101/2020.05.26.20113373v1

DRUG DEVELOPMENT

- Recently emerged beta-coronavirus, SARS-CoV-2 has resulted in the current pandemic designated COVID-19. COVID-19 manifests as severe illness exhibiting systemic inflammatory response syndrome, acute respiratory distress syndrome (ARDS), thrombotic events, and shock, exacerbated further by co-morbidities and age. Recent clinical reports suggested that the pulmonary failure seen in COVID-19 may not be solely driven by acute ARDS, but also microvascular thrombotic events, likely driven by complement activation. However, it is not fully understood how the SARS-CoV-2 infection mechanisms mediate thrombotic events, and whether such mechanisms and responses are unique to SARS-CoV-2 infection, compared to other respiratory infections. We address these questions here, in the context of normal lung epithelia, in vitro and in vivo, using publicly available data. Our results indicate that plasmin is a crucial mediator which primes interactions between complement and platelet-activating systems in lung epithelia upon SARS-CoV-2 infection, with a potential for therapeutic intervention. [**note: here is another potential point of intervention.**]
https://www.biorxiv.org/content/10.1101/2020.05.28.120162v1

DIAGNOSTIC DEVELOPMENT

- Convalescent serum is being used for treatment and for isolation of patient-derived antibodies. However, currently there is not a simple means to estimate serum bulk neutralizing capability. Here we present an efficient competitive serological assay that can simultaneously determine an individual's seropositivity against the SARS-CoV-2 Spike protein and estimate the neutralizing capacity of anti-Spike antibodies to block interaction with the human angiotensin converting enzyme 2 (ACE2) required for viral entry. In this ELISA-based assay, we present natively-folded viral Spike protein receptor binding domain (RBD)-containing antigens via avidin-biotin interactions. Sera are then supplemented with soluble ACE2-Fc to compete for RBD-binding serum antibodies, and antibody binding quantified. Comparison of signal from untreated serum and ACE2-Fc-treated serum reveals the presence of antibodies that compete with ACE2 for RBD binding, as evidenced by loss of signal with ACE2-Fc treatment. In our test cohort of nine convalescent SARS-CoV-2 patients, we found all patients had developed anti-RBD antibodies targeting the epitope responsible for ACE2 engagement. This assay provides a simple and high-throughput method to screen patient sera for potentially neutralizing anti-Spike antibodies to enable identification of candidate sera for therapeutic use. [**note: from UCSF, a nice way to screen patient plasma for neutralizing antibodies and improve selection of hyperimmune sera.**] https://www.medrxiv.org/content/10.1101/2020.05.27.20114652v1

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2020-05-31

For reflection Sunday let us turn to Beethoven for the second week in a row. This time have a listen to the delightful Symphony #6, The Pastorale. As with last week, it is the Frankfurt Radio Symphony under the direction of Andrés Orozco-Estrada: https://www.youtube.com/watch?v=Zv4PIFRpYcw&t=250s

Noah Feldman has a good podcast up on the accuracy of antibody tests. He talks with Alex Marson from UCSF and you need to select the "How Accurate Are Antibody Tests?" from the play list. Listen especially to the conversation at minute 19, Marson discusses something I noted several weeks ago, on how the adult entertainment industry developed a workable approach to testing for STDs and how elements of this are applicable to SARS-CoV-2.

After a light day of abstracts yesterday, there are a plethora of interesting findings today. Pay special attention to the second paper in the *Drug Development* section. It is from a Cal Tech and Rockefeller University group and discusses how a profile of neutralizing antibodies can be developed from sera. If they can develop a profile for neutralizing antibodies, it should be applicable to vaccine development and maybe negate the need for human challenge trials.

The Israeli army results on long duration of viral positive testing in a young population may be problematic from a public health perspective.

Enjoy your Sunday reading!

MODELING

- Background: Given the continuing coronavirus disease 2019 (COVID-19) pandemic and much of the U.S. implementing social distancing due to the lack of alternatives, there has been a push to develop a vaccine to eliminate the need for social distancing. Methods: In 2020, we developed a computational model of the U.S. simulating the spread of COVID-19 coronavirus and vaccination. Results: Simulation experiments revealed that when vaccine efficacy exceeded 70%, coverage exceeded 60%, and vaccination occurred on day 1, the attack rate dropped to 22% with daily cases not exceeding 3.2 million (reproductive rate, R0, 2.5). When R0 was 3.5, the attack rate dropped to 41% with daily cases not exceeding 14.4 million. Increasing coverage to 75% when vaccination occurred by day 90 resulted in 5% attack rate and daily cases not exceeding 258,029when R0 was 2.5 and a 26% attack rate and maximum daily cases of 22.6 million when R0 was 3.5. When vaccination did not occur until day 180, coverage (i.e., those vaccinated plus those otherwise immune) had to reach 100%. A vaccine with an efficacy between 40% and 70% could still obviate the need for other measures under certain circumstances such as much higher, and in some cases, potentially unachievable, vaccination coverages. Conclusion: Our study found that to either prevent or largely extinguish an epidemic without any other measures (e.g., social distancing), the vaccine has to have an efficacy of at least 70%. [**note: this is the first time I've seen a paper that discusses what efficacy is needed for a SARS-CoV-2 vaccine. It's an interesting read.]**
  https://www.medrxiv.org/content/10.1101/2020.05.29.20117184v1
- Introduction Determinants of hospitalization, intensive care unit (ICU) admission and death are still unclear for Covid-19 and only a few studies have adjusted for confounding for different clinical outcomes including all reported cases in a country in the analysis. We used routine surveillance data from Portugal to identify risk factors for COVID-19 outcomes, in order to support risk stratification, clinical and public health interventions, and to improve scenarios to plan health care resources. Methods We conducted a retrospective cohort study including 20,293 laboratory confirmed cases of COVID-19 in Portugal to 28 April 2020, electronically through the National Epidemic Surveillance System of the Directorate-General of Health(DGS). We calculated absolute risks, relative risks (RR) and adjusted relative risks (aRR) to identify demographic and clinical factors associated with hospitalization, admission to ICU and death using Poisson regressions. Results Increasing age after 60 years was the greatest determinant for all outcomes. Assuming 0-50 years as reference, being aged 80-89 years was the strongest determinant of hospital admission (aRR-5.7), 70-79 years for ICU(aRR-10.4) and >90 years for death(aRR-226.8) with an aRR of 112.7 in those 70-79 . Among comorbidites, Immunodeficiency, cardiac disease, kidney disease, and neurologic disease were independent risk factors for hospitalization (aRR 1.83, 1.79, 1.56, 1.82), for ICU these were cardiac, Immunodeficiency, kidney and lung disease (aRR 4.33, 2.76, 2.43, 2.04), and for death they were kidney, cardiac and chronic neurological disease (aRR: 2.9, 2.6, 2.0) Male gender was a risk factor for all outcomes. There were statistically significant differences for the 3 outcomes between regions. Discussion and Conclusions Older age stands out as the strongest risk factor for all outcomes specially for death as absolute is risk was small for those younger than 50. These findings have implications

in terms of risk stratified public health measures that should prioritize protecting older people. Epidemiologic scenarios and clinical guidelines may consider the estimated risks, even though under-ascertainment of mild and asymptomatic cases should be considered in different age groups. [**note: large data study from Portugal on hospitalization outcomes. More confirmation of at risk groups.**]
https://www.medrxiv.org/content/10.1101/2020.05.29.20115824v1

- Contact tracing, both manual and potentially with digital apps, is considered a key ingredient in the control of infectious disease outbreaks, and in the strategies making it possible to alleviate the lock-down and to return to a quasi-normal functioning of society in the COVID-19 crisis. However, the current leading modeling framework for evaluating contact tracing is highly stylized, lacking important features and heterogeneities present in real-world contact patterns that are relevant for epidemic dynamics. Here, we fill this gap by considering a modeling framework extensively informed by real-world, high-resolution contact data to analyze the impact of digital (app-based) containment strategies for the COVID-19 pandemic. More specifically, we investigate how well contact tracing apps, coupled with the quarantine of identified contacts, can mitigate a spread in realistic scenarios such as a university campus, a workplace, or a high school. We find that restrictive policies are more effective in confining the epidemics but come at the cost of quarantining a large part of the population with a consequent social cost. It is possible to design less limiting policies, considering at risk only contacts with longer exposure and at shorter distance, in order to avoid this effect. Our results also show that isolation and tracing alone are unlikely to be sufficient to keep an outbreak under control, and additional measures need to be implemented simultaneously. Moreover, we confirm that a high level of app adoption is crucial to make digital contact tracing an effective measure. Finally, given the currently implemented infectiousness, we find that strategies focusing on long exposure times, even for weak links, perform better than approaches that emphasize close-range contacts for shorter time-periods. Our results have implications for the app-based contact tracing efforts currently being implemented across several countries worldwide. [**note: this one is useful to read about how digital contact tracing can be implemented. Of course, the public has to buy into the technology which is easier said than done.**]
https://www.medrxiv.org/content/10.1101/2020.05.29.20115915v1
- Policies determining the duration of quarantine and return to work for confirmed COVID-19 patients still lack evidence. We report our findings regarding viral RNA positivity duration among a cohort of young patients with mild disease. Between March 20th, 2020, and May 10th, 2020, 219 soldiers were admitted to the Israel Defense Forces Medical Corps (IDF-MC) COVID-19 rehabilitation center following a positive RT-PCR test for SARS-CoV-2. 119 of these patients, 84 (70.6%) males, 35 (29.4%) females with a median age of 21 (IQR 19-25) were classified as having mild disease and had two consecutive negative RT-PCR tests by May 10th, 2020. The median time for SARS-CoV-2 positivity in nasopharyngeal or oropharyngeal swabs in the study population was 21 days (IQR 15-27) from symptom onset, with a range of 4 to 45 days. The results of this study suggest that in young and healthy adult patients with COVID-19, the median duration of viral positivity is around three weeks. This duration is higher than previously reported in other populations. Young and healthy adults comprise much of the population workforce, and the results of this study may assist in determining the isolation period for symptomatic adults and confirmed COVID-19 patients with mild symptoms. Further studies on

this topic should look to expand and determine the intervals of serial testing for confirmed patients and determine the duration of SARS-CoV-2 positivity in other populations. [**note: this Israeli study looks at viral clearance in soldiers with positive PCR tests. This is a young population. The duration of viral positive tests is about three weeks which is disturbing from a public health perspective. The question is what the possibility of disease transmission is. If it is throughout this whole period, it makes masking up even more imperative as a control measure. I wonder if the Navy has done similar testing on the seamen from the TR Roosevelt.**] https://www.medrxiv.org/content/10.1101/2020.05.28.20116145v1

NEWLY REGISTERED CLINICAL TRIALS

- Will post tomorrow.

CLINICAL TRIAL RESULTS

- Coronavirus disease 2019 (COVID-19) is characterized by a high incidence of acute respiratory failure. The underlying immunopathology of that failure and how it compares to other causes of severe respiratory distress, such as influenza virus infection, are not fully understood. Here we addressed this by developing a prospective observational cohort of COVID-19 and influenza subjects with varying degrees of disease severity and assessing the quality and magnitude of their immune responses at the cellular and protein level. Additionally, we performed single-cell RNA transcriptional profiling of peripheral blood mononuclear cells from select subjects. The cohort consists of 79 COVID-19 subjects, 26 influenza subjects, and 15 control subjects, including 35 COVID-19 and 7 influenza subjects with acute respiratory failure. While COVID-19 subjects exhibited largely equivalent or greater activated lymphocyte counts compared to influenza subjects, they had fewer monocytes and lower surface HLA-class II expression on monocytes compared to influenza subjects and controls. At least two distinct immune profiles were observed by cytokine levels in severe COVID-19 patients: 3 of 71 patients were characterized by extreme inflammation, with greater than or equal to ~50% of the 35 cytokines measured greater than 2 standard deviations from the mean level of other severe patients (both influenza and COVID-19); the other immune profile, which characterized 68 of 71 subjects, had a mixed inflammatory signature, where 28 of 35 cytokines in COVID-19 patients had lower mean cytokine levels, though not all were statistically significant. Only 2 cytokines were higher in COVID-19 subjects compared to influenza subjects (IL-6 and IL-8). Influenza and COVID-19 patients could be distinguished statistically based on cytokine module expression, particularly after controlling for the significant effects of age on cytokine expression, but again with lower levels of most cytokines in COVID-19 subjects. Further, high circulating levels of IL-1RA and IL-6 were associated with increased odds of intubation in the combined influenza and COVID-19 cohort [OR = 3.93 and 4.30, respectively] as well as among only COVID-19 patients. Single cell transcriptional profiling of COVID-19 and influenza subjects with respiratory failure identified profound suppression in type I and type II interferon signaling in COVID-19 patients across multiple clusters. In contrast, COVID-19 cell clusters were enriched for alterations in metabolic, stress, and apoptotic pathways. These alterations were consistent with an increased glucocorticoid response in COVID-19 patients compared to influenza. *When considered across the spectrum of innate and adaptive immune profiles, the immune pathologies underlying severe influenza and COVID-19 are substantially distinct. The majority of COVID-19 patients with acute*

respiratory failure do not have a cytokine storm phenotype but instead exhibit profound type I and type II IFN immunosuppression when compared to patients with acute influenza. Upregulation of a small number of inflammatory mediators, including IL-6, predicts acute respiratory failure in both COVID-19 and influenza patients. [**note: this is an interesting study that looks at the difference in immune system profiles between COVID-19 and influenza patients.]** https://www.medrxiv.org/content/10.1101/2020.05.28.20115667v1

- Several studies have revealed that the hyper-inflammatory response induced by SARS-CoV-2 is a major cause of disease severity and death in infected patients. However, predictive biomarkers of pathogenic inflammation to help guide targetable immune pathways are critically lacking. We implemented a rapid multiplex cytokine assay to measure serum IL-6, IL-8, TNF-α, and IL-1β in hospitalized COVID-19 patients upon admission to the Mount Sinai Health System in New York. Patients (n=1484) were followed up to 41 days (median 8 days) and clinical information, laboratory test results and patient outcomes were collected. In 244 patients, cytokine measurements were repeated over time, and effect of drugs could be assessed. Kaplan-Meier methods were used to compare survival by cytokine strata, followed by Cox regression models to evaluate the independent predictive value of baseline cytokines. We found that high serum IL-6, IL-8, and TNF-α levels at the time of hospitalization were strong and independent predictors of patient survival. Importantly, when adjusting for disease severity score, common laboratory inflammation markers, hypoxia and other vitals, demographics, and a range of comorbidities, IL-6 and TNF-α serum levels remained independent and significant predictors of disease severity and death. *We propose that serum IL-6 and TNF-α levels should be considered in the management and treatment of COVID-19 patients to stratify prospective clinical trials, guide resource allocation and inform therapeutic options. We also propose that patients with high IL-6 and TNF-α levels should be assessed for combinatorial blockade of pathogenic inflammation in this disease*. [**note: another report similar to the one above on cytokine profiles. We are getting close to a fundamental understanding of what is going on with the immune system dysfunction in severe disease**.]
  https://www.medrxiv.org/content/10.1101/2020.05.28.20115758v1
- Objectives: To the best of our knowledge, there is no published study regarding use of IFN beta-1a in the treatment of severe COVID-19. In this randomized clinical trial efficacy and safety of IFN β-1a has been evaluated in patients with severe COVID-19. Methods: Forty-two patients in the interferon group received IFN beta-1a in addition to the standard of care. Each 44 micrograms/ml (12 million IU/ml) of interferon beta-1a was subcutaneously injected three times weekly for two consecutive weeks. The control group received only the standard of care. Primary outcome of study was time to reach clinical response. Secondary outcomes duration of hospital stay, length of ICU stay, 28-day mortality, effect of early or late administration of IFN on mortality, adverse effects and complications during the hospitalization. Results: As primary outcome, time to the clinical response was not significantly different between the IFN and the control groups (9.7 +/- 5.8 vs. 8.3 +/- 4.9 days respectively, P=0.95). On day 14, 66.7% vs. 43.6% of patients in the IFN group and the control group were discharged, respectively (OR= 2.5; 95% CI: 1.05- 6.37). The 28-day overall mortality was significantly lower in the IFN then the control group (19% vs. 43.6% respectively, p= 0.015). Early administration significantly reduced mortality (OR=13.5; 95% CI: 1.5-118). Conclusion: Although did not change time to reach the clinical response, adding to the standard of care significantly increased discharge rate on day 14

and decreased 28-day mortality. [**note: finally, a result from a randomized trial. From an Iranian group, the use of Interferon beta-1a seems to be useful in reducing mortality. However, it is a small patient study.**]
https://www.medrxiv.org/content/10.1101/2020.05.28.20116467v1

DRUG DEVELOPMENT

- The COVID-19 pandemic caused by the novel coronavirus SARS-CoV-2 has led to accelerated efforts to develop therapeutics, diagnostics, and vaccines to mitigate this public health emergency. A key target of these efforts is the spike (S) protein, a large trimeric class I fusion protein that is metastable and difficult to produce recombinantly in large quantities. Here, we designed and expressed over 100 structure-guided spike variants based upon a previously determined cryo-EM structure of the prefusion SARS-CoV-2 spike. Biochemical, biophysical and structural characterization of these variants identified numerous individual substitutions that increased protein yields and stability. The best variant, HexaPro, has six beneficial proline substitutions leading to ~10-fold higher expression than its parental construct and is able to withstand heat stress, storage at room temperature, and multiple freeze-thaws. A 3.2 Å-resolution cryo-EM structure of HexaPro confirmed that it retains the prefusion spike conformation. High-yield production of a stabilized prefusion spike protein will accelerate the development of vaccines and serological diagnostics for SARS-CoV-2. [**note: most interesting thing about this paper is that it might be another vaccine approach. The authors report a filing for a SARS-CoV-2 vaccine. I've not seen this reported anywhere else.**]
https://www.biorxiv.org/content/10.1101/2020.05.30.125484v1
- Neutralizing antibody responses to coronaviruses focus on the trimeric spike, with most against the receptor-binding domain (RBD). Here we characterized polyclonal IgGs and Fabs from COVID-19 convalescent individuals for recognition of coronavirus spikes. Plasma IgGs differed in their degree of focus on RBD epitopes, recognition of SARS-CoV, MERS-CoV, and mild coronaviruses, and how avidity effects contributed to increased binding/neutralization of IgGs over Fabs. Electron microscopy reconstructions of polyclonal plasma Fab-spike complexes showed recognition of both $S1^A$ and RBD epitopes. In addition, a 3.4 Å cryo-EM structure of a neutralizing monoclonal Fab-S complex revealed an epitope that blocks ACE2 receptor-binding on up RBDs. Modeling suggested that IgGs targeting these sites have different potentials for inter-spike crosslinking on viruses and would not be greatly affected by identified SARS-CoV-2 spike mutations. These studies structurally define a recurrent anti-SARS-CoV-2 antibody class derived from VH3-53/VH3-66 and similarity to a SARS-CoV VH3-30 antibody, providing criteria for evaluating vaccine-elicited antibodies. [**note: I think this is a profound paper and perhaps an approach to vaccine efficacy evaluation. If we can pinpoint the locus of antibody binding that is required for neutralization, then profiling of vaccinated individuals might be the right way to make a regulatory decision without doing human challenge trials.**]
https://www.biorxiv.org/content/10.1101/2020.05.28.121533v1
- SARS-CoV-2 has emerged as a world public health threat. Herein, we report that the clinical approved auranofin could significantly inhibit the activity of 3-chymotrypsin-like cysteine protease (Mpro or 3CLpro) of SARS-CoV-2. Phenyl isothiocyanate and gold cluster could perfectly inhibit 3CLpro of SARS-COV-2. Vitamin K3 could well suppress the activity of 3CLpro. For Mpro inhibition, IC50 of auranofin, Vitamin K3, phenyl isothiocyanate, gold cluster are about

0.51 micromolar/L, 7.96 micromolar/L, 3.68 micromolar/L, 1.61 micromolar/L, respectively. These compounds may be with potentials for treatment SARS-CoV-2 virus replication. Especially for FDA approved auranofin, it is an anti-inflammation drug in clinic, thus it may with strong potential to inhibit virus replication and suppress the inflammation damage in COVID-19 patients. Gold cluster is with better safety index and well anti-inflammation in vitro/vivo, therefore it is with potential to inhibit virus replication and suppress the inflammation damage caused by COVID-19 virus. [**note: this is an old drug and who knows, maybe it is useful against SARS-CoV-2**] https://www.biorxiv.org/content/10.1101/2020.05.28.120642v1

DIAGNOSTIC DEVELOPMENT

- The classical RT-PCR laboratory platforms must be complemented with rapid and simplified technologies to enhance efficiency of large testing strategies. To this aim, we developed EasyCoV, a direct saliva RT-LAMP based SARS-CoV-2 virus detection assay that do not requires any RNA extraction step. It allows robust and rapid response under safe and easy conditions for healthcare workers and patients. EasyCov test was assessed under double blind clinical conditions (93 asymptomatic healthcare worker volonteers, 10 actively infected patients, 20 former infected patients tested during late control visit). EasyCov results were compared with classical laboratory RT-PCR performed on nasopharyngeal samples. Our results show that compared with nasopharyngeal laboratory RT-PCR, EasyCov SARS-CoV-2 detection test has a sensitivity of 72.7%. Measured on healthcare worker population the specificity was 95.7%. LAMP technology on saliva is clearly able to identify subjects with infectivity profile. Among healthcare worker population Easycov test detected one presymptomatic subject. Because it is simple, rapid and painless for patients, EasyCov saliva SARS-Cov-2 detection test may be useful for large screening of general population. [**note: French group refines saliva PCR testing. I'm troubled by the low sensitivity relative to the nasal swab technique.]** https://www.medrxiv.org/content/10.1101/2020.05.30.20117291v1
- Serology testing of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is increasingly being used during the current pandemic of Coronavirus Disease 2019 (COVID-19). The clinical and epidemiologic utilities of antibody-based SARS-CoV-2 testing are under debate. Characterizing these assays helps to understand the disease and provide scientific basis to decide how to best use these assays. The study assessed one chemiluminescent assay (Abbott COVID-2 IgG) and two lateral flow assays (STANDARD Q [SQ] IgM/IgG Duo and Wondfo Total Antibody Test). Validation included 113 blood samples from 71 PCR-confirmed COVID-19 patients and 1182 samples from negative controls and interferences/cross-reactions, including 1063 pre-pandemic samples. IgM antibodies against SARS-CoV-2 were detected as early as post-symptom onset days 3-4. IgG antibodies were first detected post-onset days 5-6 by SQ assays. The detection rates increased gradually, and SQ IgG, Abbott IgG and Wondfo Total detected antibodies from all the PCR-confirmed patients 14 days after symptom onset. Overall agreements between SQ IgM/IgG and Wondfo Total reached 88.5% and 94.6% between SQ IgG and Abbott IgG (Kappa = 0.75, 0.89). No cross-reaction with other endemic coronavirus infections were identified. Viral hepatitis and autoimmune samples were the main cross-reactions observed. However, the interferences/cross-reactions were low. The specificities were 100% for SQ IgG and Wondfo Total and 99.62% for Abbott IgG and 98.87% for SQ IgM. These findings demonstrate high sensitivity and specificity of appropriately validated antibody-based

SARS-CoV-2 assays with implications for clinical use and epidemiological seroprevalence studies. [**note: another university lab validation of serology tests. What I still don't understand is why good Lateral Flow tests are not being more widely deployed in field studies.**] https://www.biorxiv.org/content/10.1101/2020.05.29.124776v1

- We report the development and validation of a at-home finger-prick dried blood spot collection kit and an analysis method. We demonstrated 100% sensitivity and specificity using at-home collected specimens across the US. Such methods may facilitate the conduct of unbiased serosurveys within hard to reach populations and help reduce the sample collection burden of serological testing on both health care systems and individuals alike. [**note: this is from a company Enable Biosciences and focuses on a finger prick collection method.**] https://www.medrxiv.org/content/10.1101/2020.05.29.20116004v1
- High-volume, community-wide ascertainment of SARS-CoV-2 prevalence by PCR and antibody testing was successfully performed using a community-led, drive-through model with strong operational support, well-trained testing units, and an effective technical platform. [**note: this shows that testing can be done on a community level even in rural areas such as Bolinas, CA. Good work by the UCSF team.**] https://www.medrxiv.org/content/10.1101/2020.05.29.20116426v1
- In the context of the Covid-19 pandemic, the development and validation of rapid and easy-to-perform diagnostic methods are of high priority. We compared the performance of four rapid antigen detection tests for SARS-CoV-2 in respiratory samples. Immunochromatographic SARS-CoV-2 assays from RapiGEN, Liming bio, Savant, and Bioeasy were evaluated using universal transport medium containing naso-oropharyngeal swabs from suspected Covid-19 cases. The diagnostic accuracy was determined in comparison to SARS-CoV-2 RT-PCR. A total of 111 samples were included; 80 were RT-PCR positive. Median patients' age was 40 years, 55% were female, and 88% presented within the first week after symptom onset. The evaluation of the Liming bio assay was discontinued due to insufficient performance. The overall sensitivity values of RapiGEN, Liming bio, and Bioeasy tests were 62.0% (CI95% 51.0–71.9), 16.7% (CI95% 10.0–26.5), and 85.0% (CI95% 75.6–91.2), respectively, with specificities of 100%. Sensitivity was significantly higher in samples with high viral loads (RapiGEN, 84.9%; Bioeasy, 100%). The study highlighted the significant heterogeneity of test performance among evaluated assays, which might have been influenced by the use of a non-validated sample material. The high sensitivity of some tests demonstrated that rapid antigen detection has the potential to serve as an alternative diagnostic method, especially in patients presenting with high viral loads in early phases of infection. This is particularly important in situations with limited access to RT-PCR or prolonged turnaround time. Further comparative evaluations are necessary to select products with high performance among the growing market of diagnostic tests for SARS-CoV-2.[**note: good work from Chile on comparing four new rapid antigen tests with PCR. This type of validation research has to be done by labs to make a selection decision on what test to use.**] https://www.biorxiv.org/content/10.1101/2020.05.27.119255v1
- The rapid spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has prompted a global emergency. In order to facilitate mass community testing for tracing SARS CoV-2 transmission, we propose the use of a SYBR green-based one-step semi-quantitative reverse-transcription (qRT)-PCR reaction. We demonstrate that this could be used directly on saliva to detect SARS-CoV-2 RNA. We suggest this as a complementary method to commercial

hydrolysis probe-based kits, which have systemic issues including non-specific amplification and poor probe design. [**note: another approach to simplifying PCR testing from Australia. Their approach works on saliva.**] https://www.biorxiv.org/content/10.1101/2020.05.29.109702v1

- Rapid, inexpensive, robust diagnostics are essential to control the spread of infectious diseases. Current state of the art diagnostics are highly sensitive and specific, but slow, and require expensive equipment. We developed a molecular diagnostic test for SARS-CoV-2, FIND (Fast Isothermal Nucleic acid Detection), based on an enhanced isothermal recombinase polymerase amplification reaction. FIND has a detection limit on patient samples close to that of RT-qPCR, requires minimal instrumentation, and is highly scalable and cheap. It can be performed in high throughput, does not cross-react with other common coronaviruses, avoids bottlenecks caused by the current worldwide shortage of RNA isolation kits, and takes ~45 minutes from sample collection to results. FIND can be adapted to future novel viruses in days once sequence is available. [**note: and yet another quick, scalable, and inexpensive diagnostic approach.**] https://www.biorxiv.org/content/10.1101/2020.05.28.118059v1