2020-03-22

NEWLY REGISTERED CLINIAL TRIALS

- Tocilizumab has been registered for a multicenter Phase trial at 24 sites in Italy. This is a Roche/Genentech MAb and has been approved for other uses: NCT04317092
- Regeneron/Sanofi have registered a Phase 2 study in New York City. The drug has been approved for other uses: NCT04315298

CLINICAL TRIAL RESULTS

- Comparative clinical trial of favipiravir and arbidol compared to conventional therapy. 120 patients in each drug arm. The primary outcome was 7 day's clinical recovery rate. Duration of fever, cough relief time and auxiliary oxygen therapy or noninvasive mechanical ventilation rate were the secondary outcomes. 7 day's clinical recovery rate was 55.86% in the arbidol group and 71.43% in the favipiravir group (P = 0.0199). These were patients with ordinary and not critical clinical symptoms: https://www.medrxiv.org/content/10.1101/2020.03.17.20037432v1.full.pdf

DRUG DEVELOPMENT

- Tri-phosphate analogs of sofosfuvir, alovudine, tenolovir alafonamide, and AZT were prepared and strongly inhibited the RNA-dependent RNA polymerase in vitro. I'm not sure about the usefulness of this as requirement for the triphosphate may not survive an in vivo use: https://www.biorxiv.org/content/10.1101/2020.03.18.997585v1
- β-D-N4-hydroxycytidine is a broad spectrum antiviral that also has a pro-drug form with improved bioavailability. It has been shown to be active in a variety of coronaviruses in addition to SARS-CoV-2 https://www.biorxiv.org/content/10.1101/2020.03.19.997890v1
- A South Korean Group identified 24 drugs that exhibited antiviral efficacy against SARS-CoV-2 These are all FDA approved and two of them stood out for further testing: nicloamide and ciclesonide. I'm not sure about ciclesonide given the current issue that steroid treatment may exacerbate things but I'm not aware of the use of inhaled products. These might be better in treating mild cases. The full list which is quite an array of interesting molecules: Tilorone, Cyclosporine, Loperamide, Mefloquine, Amodiaquine, Proscillaridin, Digitoxin, Digoxin, Hexachlorophene, Hydroxyprogesterone caproate, Salinomycin, Ouabain, Cepharanthine, Ciclesonide, Oxyclozanide, Anidulafungin, Gilteritinib, Berbamine, Tetrandrine, Abemaciclib, Ivacaftor, Bazedoxifene, Niclosamide, and Eltrombopag. https://www.biorxiv.org/content/10.1101/2020.03.20.999730v1
- Potential inhibitors of SARS-CoV-2 main protease by examination of the principal ligand binding site (all FDA approved drugs): darunavir (antiviral), mitoxatrone (anticancer), nelfinavir (antiviral), moexpril (anti-hypertensive), daunorubicin (anticancer), rosuvastatin (anti-hypercholsterolemia), saquinavir (antiviral), metamizole (anti-inflamatory), bepotastine (antihistaminic), benzonatate (anti-tussive), atovaqoue (antimalarial) https://chemrxiv.org/articles/Identification_of_FDA_Approved_Drugs_Targeting_COVID-19_Virus_by_Structure-Based_Drug_Repositioning/12003930

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2020-03-23

Gilead has put emergency access to remdesivir on hold so that there will be enough clinical trial material (this is not a surprise). Exceptions will be for pregnant women and those under 18 years of age with severe clinical symptoms

NEWLY REGISTERED CLINIAL TRIALS

- None the I could find but yesterday was Sunday.

CLINICAL TRIAL RESULTS

- I thought it would be useful to give you the link to the French hydroxy-chloroquine trial. It was a small open label non-randomized CT and some patients were also given azithromycin. The end point was presence/absence of virus at day 6 post inclusion. This was a messy trial and six to the 26 patients on drug were lost to follow up. There are larger trials going on with this drug and we need to see that data. Unfortunately, there has been an over-prescription of this class of anti-malarial drugs in the US. https://www.mediterranee-infection.com/wp-content/uploads/2020/03/Hydroxychloroquine_final_DOI_IJAA.pdf

DRUG DEVELOPMENT

- In a lengthy pre-print from a large group of researchers many protein-protein interactions between SARS-CoV-2 were identified using affinity-purification mass spectrometry. [aside: I believe this is the same group that was featured in a New York Times story early last week]. They identified 66 potential targets that could be tested with 69 existing FDA-approved drugs, drugs in clinical trials and/or pre-clinical compounds that the group is current evaluating. It's a very long paper and the table listing proposed drugs has chemical structures so it's not amenable to cutting and pasting. Here is the link that I hope works for those interested: https://doi.org/10.1101/2020.03.22.002386 It links to the abstract and the PDF can be downloaded from a button on the right.
- Not drug development: a pre-print from China hypothesizes that SARS-CoV-2 attacks the 1-β chain of hemoglobin, inhibiting heme metabolism. "chloroquine could prevent orf1ab, ORF3a, and ORF10 to attack the heme to form the porphyrin, and inhibit the binding of ORF8 and surface glycoproteins to porphyrins to a certain extent, effectively relieve the symptoms of respiratory distress. Favipiravir could inhibit the envelope protein and ORF7a protein bind to porphyrin, prevent the virus from entering host cells, and catching free porphyrins. Because the novel coronavirus is dependent on porphyrins, it may originate from an ancient virus." https://chemrxiv.org/articles/COVID-19_Disease_ORF8_and_Surface_Glycoprotein_Inhibit_Heme_Metabolism_by_Binding_to_Porphyrin/11938173 I don't know if you have to be a member of the American Chemical Society to access this.

- A Stanford group has focused on the transmembrane serine protease that appears to be one factor responsible for entry of pathogenic coronaviruses into cells. It cleaves and activates the viral Spike (S) protein. This is co-expressed in lung tissue with angiotensin converting enzyme 2 (there are currently attempts to use this latter point for drug development). Camostat, developed in Japan, works via this mechanism and is in Chinese trials. This Stanford group identifies six anti-coagulant drugs that have stronger binding affinities than Camostat but note these would likely pose clinical safety issues if used widely. https://chemrxiv.org/articles/Homology_Modeling_of_TMPRSS2_Yields_Candidate_Drugs_That_May_Inhibit_Entry_of_SARS-CoV-2_into_Human_Cells/12009582

DIAGNOSTIC DEVELOPMENT

- I'm just taking a casual glance at what is going on in this area. As we all know the lack of testing is a problem for society at large in terms of knowing R_0 and it's more imperative for healthcare workers to get quick diagnoses of patients who might have SARS-CoV-2 infections. From time to time, I'll add to this section as things come up.
- Many academic hospitals created their own lab tests following the problems with the CDC test in February. Wider help may come from the approval a point of care gene test for COVID-19. It runs on their automated machines that are easy to use and give results in 45 minutes. This will be used in healthcare settings. A cool video and other info is here: https://www.cepheid.com/coronavirus I do not know what the installed base of this machine is in the US or how fast they can ramp up manufacturing and shipping.
- I've looked at the diagnostic pre-print literature and there are eight papers looking at serological markers for COVID-19. Six of them are from China, one from Holland (Erasmus Univ), and one from Mount Sinai in NYC. Efforts are focusing on looking at antibodies to the spike proteins and the nucleocapsid proteins. Both the Dutch and American groups noted that they can detect antibodies three days post symptom onset. The Dutch group did much more to validate their assay methodology. Standardization of reagents will still be an important thing to do in order to deploy this widely. However, the ability to do large scale serological testing is important to understand the background rate of infection. Right now sensitivity is not high enough to make this reliable for mass deployment.

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2020-03-24

There is some 'potentially' good news coming out of Italy. New cases of SARS-CoV-2 dropped for the third straight day. We will need to see if this trend continues before moving the optimism meter forward. However, this comports with an interesting Greek/Italian paper that models the Lombardy outbreak. The math can get dense at times and if you are interested here is the link to the abstract where you can get the full paper: https://www.medrxiv.org/content/10.1101/2020.03.17.20037689v1 The researchers extrapolate to Day Zero which they believe was January 21 and predicted based on the quarantine that was imposed earlier this month that cases would begin to decrease right about now.

According to their model, the Lombardy region should fade out in mid-May (see Figure 5 of the paper). This argues for a social distancing time line of 8 weeks or so. There are a number of other modeling papers in pre-print form and I've been trying to keep track of them; I found this one to be the most rigorous.

New York has obtained 750K doses of chloroquine, 70K doses of hydroxychloroquine, and 10K doses of azithromycin to treat hospitalized patients. I assume this will be a giant open label trial and there are some questions here. How well will patients be monitored so that we can get information on efficacy and potential safety issues? What is the appropriate dose for the anti-malarials in a clinical setting? China has a number of trials in progress with both chloroquine and hydroxychloroquine but I've not seen the data yet. What is worrisome are the large off label Rx in the wider US community. This has resulted in shortages and patients who are on these drugs for lupus or RA may not be able to obtain them. We need clinical data for SARS-CoV-2 sooner rather than later.

One thing that occurred to me yesterday was the possibility of looking at patients who are being treated with these drugs for existing health conditions (lupus and rheumatoid arthritis) to see if they offer chemoprotection against SARS-CoV-2. As some of you know, I was the principal project manager of a PhRMA funded observational medical outcomes project that began in 2005. One of the goals of the original business plan was to create a platform where observational data could be used across disparate data sets to look for both drug safety and efficacy signals. A lot of good work was done and the project lives on here: https://www.ohdsi.org/ They are having a virtual COVID-19 session this week and there is an active discussion on the forums (registration is required to participate). I don't know whether there is any data from Italy.

NEWLY REGISTERED CLINIAL TRIALS

- University of Minnesota have registered trials for losartan on patients requiring and not requiring hospitalization for SARS-CoV-2 NCT04312009 & NCT04311177 Losartan has been identified in several AI screening efforts as a potential therapeutic.
- OncoImmune has registered a trial for CD24Fc, an immunomodulator that suppresses cytokines. It has undergone Phase 1 & 2 studies for other indications. Trial will be at Univ of Maryland. NCT04317040
- NeuroRx has registered a trial for IV Aviptadil, a synthetic form of Vasoactive Intestinal Polypeptide. Nonclinical studies demonstrate that VIP is highly concentrated in the lung, where it prevents NMDA-induced caspase-3 activation in the lung, inhibits IL6 and TNFa production, protects against HCl-induced pulmonary edema, These and other effects have been observed in numerous animal model systems of lung injury in mice, rats, guinea pigs, sheep, swine, and dogs. In these models, Aviptadil restores barrier function at the endothelial/alveolar interface and thereby protects the lung and other organs from failure. The drug has been approved in Europe and has a lengthy history of safety in CTs. Trials scheduled for New York City and Haifa Israel. NCT04311697
- A Chinese study looking at a traditional compound Fuzheng Huayu for the treatment of pulmonary fibrosis is registered. It will be co-administered with N-acetyl cysteine. NCT04279197

CLINICAL TRIAL RESULTS

- A small scale Chinese study showed that lopinavir/ritonavir or arbidol did not provide clinical benefit in adult patients hospitalized with mild/moderate SARS-CoV-2 https://www.medrxiv.org/content/10.1101/2020.03.19.20038984v1

DRUG DEVELOPMENT

- No New Papers Today

DIAGNOSTIC DEVELOPMENT

- There is an interesting pre-print from a Chinese group that identifies a series of biochemical markers that might be useful in identifying severe cases among SARS-CoV-2 patients. Serum urea, creatinine (CREA) and cystatin C (CysC) concentrations in severe COVID-19 patients were significantly higher than those in mild COVID-19 patients ($P<0.001$), and there were also significant differences in serum direct bilirubin (DBIL), cholinesterase (CHE) and lactate dehydrogenase (LDH) concentrations between severe and mild COVID-19 patients ($P<0.05$). Serum urea, CREA, CysC, DBIL, CHE and LDH could be used to distinguish severe COVID-19 cases from mild COVID-19 cases. In particular, serum biomarkers, including urea, CREA, CysC, which reflect glomerular filtration function, may have some significance as potential indicators for the early diagnosis of severe COVID-19 and to distinguish it from mild COVID-19. https://www.medrxiv.org/content/10.1101/2020.03.19.20034447v1
- https://www.sciencemag.org/news/2020/03/new-blood-tests-antibodies-could-show-true-scale-coronavirus-pandemic is a nice interview with the Mt. Sinai researcher who has a pre-print on a potential diagnostic test for SARS-CoV-2

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2020-03-25

Perhaps the big news for today is the press articles on Oracle working to set up a platform to collect uncontrolled clinical data from chloroquine and hydroxychloroquine treatments of SARS-Cov-2. The company has not issued any public statement about this so details about what type of data will be collected are unknown at this time (https://www.washingtonpost.com/politics/oracle-to-partner-with-trump-administration-to-collect-data-on-use-of-antimalarial-drugs-to-treat-covid-19/2020/03/24/ecbb8b76-6de2-11ea-b148-e4ce3fbd85b5_story.html & https://www.nytimes.com/2020/03/24/us/politics/trump-oracle-coronavirus-chloroquine.html?smid=em-share There has been no public statement from Oracle that I can find.). WHO previously announced an effort for these drugs and seven countries have announced participation.

Personally, I have some reservations about the Oracle project. Will this simply encourage wide-spread use of these drugs without collecting AEs or good dosing information (I've not seen any paper so far that discusses the latter).

NEWLY REGISTERED CLINIAL TRIALS

- An Italian trial using baricitinib, an anti-Janus kinase inhibitor (anti-JAK) acting against JAK1 and JAK2. The drug was found capable to reduce or interrupt the passage of the virus into target cells, and to inhibit the JAK1- and JAK2-mediated cytokine release. The drug was licensed for the treatment of rheumatoid arthritis at the daily dose of 4 mg/orally, with excellent results in terms of clinical response and a good safety profile. Since baricitinib does not interact with antivirals due to its prevalent renal elimination, it may be used in combination.The evidence on the advantageous action of baricitinib on viral entry and cytokine outbreak constituted the rationale to perform a trial on patients with mild to moderate COVID-19 infection receiving baricitinib combined with antiviral therapy. NCT04320277

CLINICAL TRIAL RESULTS

- Not a drug trial, but Chinese researchers looked at pooled epidemiological data from seven countries to establish the latency of infection. "Findings In total, 1155 cases from China, Japan, Singapore, South Korea, Vietnam, Germany and Malaysia were included for the final analysis. The mean and standard deviation were 7.44 days and 4.39 days for incubation period, 2.52 days and 3.95 days for the upper limit of latent period, 6.70 days and 5.20 days for serial interval, and -0.19 day (i.e., 0.19 day before symptom onset of infector) and 3.32 days for time point of exposure. R0 was estimated to be 1.70 and 1.78 based on two different formulas. For 39 (6.64%) cases, the incubation periods were longer than 14 days. In 102 (43.78%) infector-infectee pairs, transmission occurred before the symptom onsets of infectors. In 27 (3.92%) infector-infectee pairs, symptom onsets of infectees occurred before those of infectors. Stratified analysis showed that incubation period and serial interval were consistently longer for those with less severe disease and for those whose primary cases had less severe disease. Asymptomatic transmission was also observed. Interpretation This study obtained robust estimates of several key epidemiological parameters of COVID-19. The findings support current practice of 14-day quarantine of persons with potential exposure, but also suggest that longer monitoring periods might be needed for selected groups."
  https://www.medrxiv.org/content/10.1101/2020.03.21.20040329v1
- The Wuhan investigators looked at comorbidities and viral clearance as an end point. "patients at old age, males, and/or having diseases associated with high expression of ACE2 will have worse prognosis during a COVID-19 infections."
  https://www.medrxiv.org/content/10.1101/2020.03.22.20040774v1
- Here is an interesting pre-print from China on the environmental effects of temperature and humidity on the SARS-CoV-2 outbreak. They note that humidity seems not have an impact but that either very low or higher temperatures saw fewer transmission cases. Much more data is needed from other regions to confirm this.
  https://www.medrxiv.org/content/10.1101/2020.03.22.20038919v1
- This is really a very small study on the utility of danoprevir/ritonavir for SARS-CoV-2. Only 11 patients were treated over a 4-12 day course of therapy. All recovered based on virus gene sampling, normal body temperature, and lung imaging. As I've noted before many more trials

need to be done on all kinds of repurposed drugs. https://www.medrxiv.org/content/10.1101/2020.03.22.20034041v1

- Here is a bit of good news from China. A humanized antibody against CD147 was prepared (host expressed CD147 appears to bind the SARS-CoV-2 spike protein); meplazumab was administer IV on days 1, 2, & 5. No adverse events were noticed and patients on therapy significantly improved and were discharged. https://www.medrxiv.org/content/10.1101/2020.03.21.20040691v1 It was another small trial but points out the utility of MAb treatment of SARS-CoV-2. We need to get more of these products into the clinic.

DRUG DEVELOPMENT

- I didn't see any new papers today.

DIAGNOSTIC DEVELOPMENT

- Biomerica a Irvine CA company has begun shipping a 10-minute serological test for COVID-19 to sites outside the US. They are seeking an emergency exemption from FDA for use here. It uses only blood from a finger prick and is priced at $10/test. It would be great if this can be validated for use as it appears to address the widespread testing conundrum. https://biomerica.com/news/biomericacovid19.pdf

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2020-03-26

Discussions about the usefulness of chloroquine and hydroxychloroquine continue. Derek Lowe's always useful blog has a summary of some of the trial results: https://blogs.sciencemag.org/pipeline/archives/2020/03/24/the-latest-coronavirus-clinical-trials The good thing is there has been an uptick in clinical trial registration for each of the drugs with and without azithromycin. I'm not going to list all those trials unless there is something interesting as I note with the Spanish and Columbia University prophylaxis trials. It is uncertain how quickly data from these trial can be analyzed and reported on in terms of helping address the current pandemic.

The FDA added hydroxychloroquine sulfate to category 1 under the Interim Policy on Compounding Using Bulk Drug Substances Under Section 503B of the Federal Food, Drug, and Cosmetic Act. The FDA does not intend to object to registered outsourcing facilities using hydroxychloroquine (or chloroquine phosphate, which was already on category 1), to compound human drugs provided the drugs meet other conditions and requirements in the FD&C Act.

NEWLY REGISTERED CLINIAL TRIALS

- This is an Italian retrospective trial designed to answer questions about whether patients on ACE inhibitors are at a greater risk for serious disease progression. Study design Patients will be divided in two groups, a) controls: individuals who did not develop severe COVID-19 respiratory

disease (including individuals who recovered from the infection) and b) cases: individuals who developed severe COVID-19 disease (including fatal events). Association between use of ACE-I or ARB and severity of COVID-19 will be assessed by using of multivariable logistic regression analysis. Data on potential confounders will be obtained by medical records: age, sex, time intervals from hospital admission to worse manifestation of COVID-19 and to eventual death or recovering, smoking, body mass index, history of myocardial infarction, diabetes, hypertension, cancer, respiratory disease, other morbidities, creatinine, insulin, glomerular filtration rate together with use of Tocilizumab, anti-aldosterone agents, diuretics, Kaletra, cortisone, Remdesevir, Chloroquine, Sacubitril or Valsartan. NCT04318418

- A Spanish study will look at test and treat along with prophylactic use of chloroquine for all contacts. The strategy entails decentralized COVID-19 testing and starting antiviral darunavir/cobicistat plus chloroquine treatment immediately in all who are found to be infected. As viral loads decline to undetectable levels, the probability of onward transmission is reduced to very low levels. Such evaluation will require prospective surveillance to assess the population-level effect of transmission prevention. This is the first time I've seen a dosing regimen. Drug: Antiviral treatment and prophylaxis: darunavir 800 mg / cobicistat 150 mg tablets (oral, 1 tablet q24h, taking for 7 days) and hydroxychloroquine (200mg tablets) 800mg on day 1, and 400mg on days 2,3,4, 5, 6 and 7.

  Contacts will be offered a prophylactic regimen of hydroxychloroquine (200mg tablets) 800mg on day 1, and 400mg on days 2,3,4. NCT04304053

- Columbia University is also undertaking a prophylaxis study of hydroxychloroquine in New York City. Dosage: Two tablets (400mg) twice daily on day 1; for days 2-5, they will be instructed to take one tablet (200mg) twice daily. NCT04318444
- A Danish study has been registered to look at camostat, one of the drugs identified as an Mpro inhibitor. NCT04321096

CLINICAL TRIAL RESULTS

- I didn't see anything new other than the link from Derek Lowe's blog already mentioned.

DRUG DEVELOPMENT

- A Chinese drug discovery group used a Free Energy Perturbation approach to looking at drugs that that might block the viral proteinase Mpro. They screened the FDA-approved drugs database and fifteen out of twenty-five drugs validated in vitro exhibited considerable inhibitory potencies towards Mpro. The most potent Mpro inhibitor dipyridamole potentially NF-κB signaling pathway and inflammatory responses, and has just finished the first round clinical trials. I'll refer you to the paper for the full list of drugs but note that montelukast sodium had the same potency as chloroquine in this modeling. How long will it be before it disappears from pharmacy shelves. https://www.biorxiv.org/content/10.1101/2020.03.23.004580v1
- A Turkish research group used a guide docking approach to identify potential inhibitors of Mpro. These numerical calculations showed that the following 6 compounds can be considered as

COVID-19 Main Protease inhibitors: Lasinavir, Brecanavir, Telinavir, Rotigaptide, 1,3-Bis-(2-ethoxycarbonylchromon-5-yloxy)-2-(lysyloxy)propane and Pimelautide. https://chemrxiv.org/articles/Screening_of_Clinically_Approved_and_Investigation_Drugs_as_Potential_Inhibitors_of_COVID-19_Main_Protease_A_Virtual_Drug_Repurposing_Study/12032712

- I post this link with trepidation as it deals with challenging human subjects in a vaccine trial with the infectious agent: https://dash.harvard.edu/handle/1/42639016 (click on the link to open the full paper). The problem has been a failure of imagination. We know how to make vaccines against a wide variety of bacterial and viral infectious agents. There are new design platforms that have been developed in the past several years based on DNA and mRNA antigen carriers. We also have a variety of cell culture approaches to generating antigens at scale that would negate the need for an egg-based production process as used for seasonal flu. All of these can be piloted so that we would know beforehand whether they work in humans. Right now there are only two vaccine trials going on the Moderna mRNA and a Chinese DNA; neither approach to my knowledge has been tried in humans. I've noted in the past to some of you that the Zika outbreak could have better informed us as to possible approaches. Given the unknown age-related mortality of a new pathogen, I don't think a challenge test is ethical. Think about doing something like this with Ebola or HIV where there have been experimental vaccine trials; what IRB would approve this? I will have more to say about vaccine development in a future post.

DIAGNOSTIC DEVELOPMENT

- A UC Irvine group reports on the serological cross-reactivity between common human coronoaviruses and SARS-CoV-2. This has implication for development and validation of a serology test as well as potentially informing vaccine developers. https://www.biorxiv.org/content/10.1101/2020.03.24.006544v1

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2020-03-27

Looks like it's information overload today! A number of new trials have been registered and more modeling papers published. There has been some good activity from the OHSDI group that I will summarize in a future email.

Here is a fun start for today's communication and apologies if it is behind a paywall. The Washington Post has a nice story of the history of Purell: https://www.washingtonpost.com/lifestyle/style/the-power-of-purell-compels-you/2020/03/26/41243960-6dde-11ea-b148-e4ce3fbd85b5_story.html I mixed up a batch of DIY hand sanitizer when all the bottles of Purell disappeared from the shelves right after the outbreak. The 1/3 aloe vera, 2/3 isopropyl alcohol meets the specs but it is not a gel as I am missing the polymers that GOJO add to their commercial preparation. Any port in a storm!.

One of the big problems in dealing with SARS-CoV-2 is the lack of knowledge about the background rate of infection. Policies in some countries were driven by a model from the Imperial College of London which discussed very high levels of mortality. This seems to have been the worst-case scenario but in the absence of good epidemiological numbers, political leaders face a quandary in regard to 'social distancing' policies. Certainly in hard hit areas where hospitals are stretched, such policies were

warranted. Here is a pre-print from an Italian group that argues for a higher level of infected individuals: https://www.medrxiv.org/content/10.1101/2020.03.25.20043562v1

Along these same lines, here is a paper using data from Santa Clara County in CA: https://www.medrxiv.org/content/10.1101/2020.03.24.20043067v1 The inferred number of infections for March 17 is 6,500, and the lower and upper bounds are 1,400 and26,000, respectively. These estimates provide a prevalence of 0.34%, with bounds of 0.08% to 1.36%(Table 1). If the shelter-in-place order worked, this would be the expected maximum prevalence in the area, until people recover. Unfortunately, we will not know until about March 27-31 if this is the case, at which point we expect the number of hospitalizations to plateau.

Here's another model for estimating progression on the US East and West Coasts. Our computation results predict that the number of new cases would peak around mid-April and begin to abate by July, and that the number of cases of COVID-19 might be significantly mitigated by having greater numbers of functional testing kits available for screening. The model also showed how small changes in variables can make large differences in outcomes and highlights the importance of healthcare preparedness during pandemics. https://www.medrxiv.org/content/10.1101/2020.03.24.20043026v1

NEWLY REGISTERED CLINIAL TRIALS

- A Chinese trial for the compassionate use of DAS181, an inhaled sialidase, is recruiting patients in Wuhan. NCT04324489
- A French trial examining the use of Naproxen in the treatment of critically ill patients is registered. The symptoms of respiratory distress caused by COVID-19 may be reduced by drugs combining anti-inflammatory and antiviral effects. This dual effect may simultaneously protect severely-ill patients and reduce the viral load, therefore limiting virus dissemination We want to demonstrate the superiority of naproxen (anti-inflamatory drug) treatment addition to standard of care compared to standard of care in term of 30-day mortality. NCT04325633

CLINICAL TRIAL RESULTS

- This observational trial from China looks at the effect of anti-hypertensive angiotensin II blockers (ARB) on disease severity. SARS-CoV-2 uses the membrane protein angiotensin I converting enzyme 2 as a cell entry recptor. Patients with hypertension comorbidity, the risk of COVID-19-S (severe disease) was significantly decreased in patients who took ARB drugs prior to hospitalization compared to patients who took no drugs. https://www.medrxiv.org/content/10.1101/2020.03.20.20039586v1
- There is a registered Italian trial that was just posted that will do a similar analysis. NCT04318418
- Spanish trial looking a dexamethasone in mechanically venilated adult patients. NCT04325061
- Here is an Italian study for a Phase 2/3, Randomized, Open-label, Parallel Group, 3-arm, Multicenter Study Investigating the Efficacy and Safety of Intravenous Administrations of Emapalumab, an Anti-interferon Gamma (Anti-IFNγ) Monoclonal Antibody, and Anakinra, an Interleukin-1(IL-1) Receptor Antagonist, Versus Standard of Care, in Reducing Hyper-inflammation and Respiratory Distress in Patients With SARS-CoV-2 Infection. NCT04324021

- First new vaccine trial in a week as a British group is launching a multi-center trial to determine efficacy, safety and immunogenicity of the candidate Coronavirus Disease (COVID-19) vaccine. The vaccines are produced using a safe version of an adenovirus; another virus that can cause a common cold-like illness. The adenovirus has been modified so that it cannot reproduce within the body, and the genetic code to provide instructions for making the coronavirus Spike protein has been added, enabling the adenovirus to produce this protein after vaccination. That results in the formation of antibodies to the Spike protein, which is found on the surface of coronaviruses. In someone who has been vaccinated, antibodies to the Spike can bind to the coronavirus and stop it from causing an infection. ChAdOx1 nCoV-19 in UK healthy adult volunteers aged 18-55 years. The vaccine will be administered intramuscularly (IM). NCT04324606
- A proposed Italian study to look at colchicine has been registered. Colchicine, an old drug used in auto-inflammatory disorders (i.e., Familiar Mediterranean Fever and Bechet disease) and in gout, counteracts the assembly of the NLRP3 inflammasome, thereby reducing the release of IL-1b and an array of other interleukins, including IL-6, that are formed in response to danger signals. Recently, colchicine has been successfully used in two cases of life-threatening post-transplant capillary leak syndrome. These patients had required mechanically ventilation for weeks and hemodialysis, before receiving colchicine, which abruptly restored normal respiratory function and diuresis over 48 hrs NCT04322565 A similar trial in Montreal has been registered. NCT04322682

DRUG DEVELOPMENT

- A Taiwan group looked at potential compounds that might block the entry via the angiotensin converting enzyme process. They identified theaflavin, a polyphenol found in black tea, as a potentially useful compound based on docking studies. (aside: does this have any bioavailability in the lung? This is unclear and more work needs to be done here) https://www.biorxiv.org/content/10.1101/2020.03.26.009803v1

DIAGNOSTIC DEVELOPMENT

- Abbott Laboratories is immediately shipping 150,000 Abbott RealTi*m*e SARS-CoV-2 EUA tests to existing customers in the U.S. The tests are used on the company's *m*2000™ RealTi*m*e System. Abbott will be working with health systems and government authorities to deploy additional *m*2000 systems where they are needed. The company’s goal is to scale this up to 1M test kits per week.
- A restatement of the obvious, a British group points out the immediate need for large-scale serological surveys to assess the stage of the SARS-CoV-2 epidemic. https://www.medrxiv.org/content/10.1101/2020.03.24.20042291v1

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2020-03-28

It's the weekend and there is not much to report. A couple of day ago I mentioned the fine work that OHDSI was doing in setting up some observational queries. I saw one post that they will have access to deidentified data from South Korea which has a nationwide EMR system. Rather than provide synopses, I will provide you the links to the first two days of the study-a-thon (I haven't had the time to go through everything). There is some interesting stuff here.

https://forums.ohdsi.org/t/day-1-report-ohdsicovid19-study-a-thon/10193

https://forums.ohdsi.org/t/day-2-pm-update-ohdsicovid19-study-a-thon/10218

It's not clear to me what the optimal treatment approach is for those who have progressed to full blown pneumonia. We know from seasonal flu that antiviral therapy has to be started quickly in order to see a clinical effect. Is the same thing true with SARS-CoV-2? The scant pre-print literature on chloroquine/hydroxychloroquine points to early intervention and not patients who have progressed and are in the ICU. There are some inhaled corticosteroid trials underway for this latter group along with IL-6 blocking agents. Perhaps those are the most promising approaches until we have some MAbs to use.

I was musing in the middle of the night as one who has had mild asthma over the years, mainly a result of spring tree pollen (particularly oak which is soon to come to my neighborhood). I wonder if bronchodilators might be useful in this setting. Prior to its withdrawal from the market a decade ago, I was using inhaled sodium cromolyn, a mast cell stabilizer with a very good safety profile, and it worked for me extremely well. It went generic and was overtaken by the inhaled corticosteroids with and without a long acting beta agonist. Other than curiosity, I have no idea whether it will work in this setting.

The one good notice below is the emergency use approval of a serological test.

NEWLY REGISTERED CLINIAL TRIALS

- Here is a Chinese trial set up to examine the preventive effect of recombinant human interferon alpha nasal drops on the infection of 2019 new coronavirus in medical staff. The low risk group will be given drops four times a day and the high risk will also get a subcutaneous injection of thymosin-α weekly. NCT04320238
- An Italian group has registered a trial to look at escin (a mixture of saponins with anti-inflammatory, vasoconstrictor and vasoprotective effects found in Aesculus hippocastanum. Aescin is the main active component in horse chestnut, and is responsible for most of its medicinal properties.) as an adjunct to traditional drug therapy. NCT04322344
- Another Italian study. Acute lung injury represents the most severe form of the viral infection sustained by coronavirus disease 2019 (Covid-19) also named as SARS-CoV-2, a new virus emerged in December 2019 in Wuhan (China). The diagnosis is clinical and patients develop flu-like syndrome with fever and cough; patients with clinical symptoms can perform a swab test for diagnosis of positivity to Covid-19. Even if diagnosis and treatment are well described, to date, this viral pandemic infection induces an increased mortality in the world. The aim of the present

project is to evaluate specific biomarkers that could be used for patient stratification and for tailor therapy in COVID-19 infected patients. NCT04322513

CLINICAL TRIAL RESULTS

- Didn't see anything new but it's Saturday and perhaps that is why things are slow.

DRUG DEVELOPMENT

A group at Immuneering Corp, a Cambridge MA company, used two different computational tools to identify existing FDA drugs that could block virus entry by binding to ACE2 or TMPRSS2. The second approach was to search for compounds that might induce gene expression signals that counteract disease-associated signals. The first screen Top results included several ACE inhibitors, a beta-lactam antibiotic, two antiviral agents (Fosamprenavir and Emricasan) and glutathione. The second screen came up with Vitamin E, ruxolitinib, and glutamine. They suggest that trials of glutathione & glutamine might be warranted.
https://chemrxiv.org/articles/Advanced_Bioinformatics_Rapidly_Identifies_Existing_Therapeutics_for_Patients_with_Coronavirus_Disease_-_2019_COVID-19_/12037416

DIAGNOSTIC DEVELOPMENT

- This is the first announcement I've seen of a serological test approved for emergency use in the US: http://investor.henryschein.com/news-releases/news-release-details/henry-schein-announces-availability-coronavirus-2019-covid-19