I hope everyone had a wonderful weekend as we approach Thanksgiving.

Today I have focused on vaccinations highlighted by an excellent article in Health Affairs which I think puts where we are and where we need to go moving forward. I also review the differences between efficacy and effectiveness. See my comments below.

On the COVID news front, Pfizer vaccine has filed a EUA, AstraZeneca reported the initial results of their vaccine. Baricitinib/Remdesivir combo (ACTT-2 trial) and Regeneron's monoclonal received FDA EUA. In addition to the Health Affairs article, I also included a pre-publication on a very interesting nasal spray delivery and formulation to see if it works prophylactically and/or prevent disease transmission. The last review is documenting delirium as a common presenting symptom of SARS-CoV-2 infection especially in the elderly.

COVID-19 News

Pfizer has filed for EUA for its vaccine:

The vaccine, BNT162b2 is an mRNA-based platform which in Phase II trials found a 95% efficacy in general and 94% efficacy in individuals over age 65. FDA will hold a meeting of its Vaccine and Related Biological Products Advisory meeting on December 10, 2020. See Health Affairs article below.

Baricitinib/Remdesivir combo received FDA EUA:

Released data shows 1,033 patients with moderate or severe COVID-19: a total of 515 of whom received baricitinib with remdesivir and 518 who received placebo with remdesivir who were followed for 29 days. Baricitinib is a JAK inhibitor approved for severe rheumatoid arthritis.

Median time to recovery was 7 days for the intervention group compared with 8 days for the control group. Odds of progressing to death or being ventilated were lower and odds of clinical improvement at day 15 were higher for patients receiving the intervention compared with placebo.

Some exclusion [from ClinicalTrials.gov] included convalescent plasma, received >/= 20 mg/day of prednisone or equivalent for >/=14 consecutive days in the 4 weeks prior to screening, received monoclonal antibodies targeting cytokines (e.g., TNF inhibitors, anti-interleukin-1 [IL-1], anti-IL-6 [tocilizumab or sarilumab]), or T-cells (e.g., abatacept) in the 4 weeks prior to screening, or received small molecule tyrosine kinase inhibitors (e.g. baricitinib, imatibib, genfinitib), in the 1 week prior to screening.

Comment: Interesting study. We do not know results if baricitinib was used alone and from FDA press release unclear if patients were allowed to have steroids as well. Is remdesivir+baricitinib better than remdesivir+steroids?

Regeneron:

Regeneron's monoclonal has just received EUA. Regeneron's monoclonals combines two lab-made antibodies (casirivimab plus imdevimab) for use treating mild to moderate Covid-19 patients 12 years of age and older, including people older than 65 years.

The FDA said its authorization was based on a study of about 800 people. In the study, 3% of subjects taking Regeneron's drug and who were at high risk of severe disease had to be hospitalized or visit emergency rooms, compared with 9% of patients who received a placebo.

Comment: The Eli Lilly and Regeneron drugs are the first to show promising results in treating patients who have not yet been hospitalized. These therapeutics are welcome additions and designed to prevent progression and hospitalizations in high-risk individuals.

AstraZeneca vaccine

Initial report from the viral vector vaccine (adenovirus) shows 90% efficacy, but safety checks are ongoing. If safety looks good this may be the next vaccine to apply for EUA. Like the mRNA vaccines this requires 2 doses.

Literature Review

Clinical Outcomes of A COVID-19 Vaccine: Implementation Over Efficacy

Health Affairs published online November 19, 2020

doi: 10.1377/hlthaff.2020.02054

The authors examine how different definitions and thresholds of vaccine efficacy, coupled with different levels of implementation effectiveness and background epidemic severity, translate into outcomes including cumulative infections, hospitalizations, and deaths. They use a mathematical simulation of vaccination and factors related to implementation that could impact the success of vaccination programs beyond a vaccine's efficacy as determined in phase III clinical trials. They found the benefits of a vaccine will decline substantially in the event of manufacturing or deployment delays, decrease vaccine acceptance, or more widespread disease and severity. Their findings highlight the urgent need for health officials to invest greater financial resources and attention to vaccine production and distribution programs, to promote public confidence in COVID-19 vaccines, and to encourage continued adherence to other mitigation approaches, even after a vaccine becomes available.

Comment: Pfizer and Moderna both announced the results of phase III studies showing ~95% efficacy. Pfizer is applying to the FDA for EUA. Moderna will not be far behind. My guess is that both vaccines will be reviewed at the December 10th meeting. A 95 percent efficacy is certainly great news that a vaccine works well under optimal conditions in preventing symptomatic disease, but the numbers do not tell us how well the vaccine will bring down Covid-19 across the United States. Efficacy and effectiveness are related, but they are not the same. Efficacy is derived from clinical trials while effectiveness is how well the vaccine works out in the real world. The clinical trials are specifically designed to see whether vaccines protect people from getting sick from Covid-19. If volunteers developed symptoms like a fever or cough, they were then tested for SARS-CoV-2. There is substantial evidence that ~40% of infected persons have no or minimal symptoms and can transmit infection to others. So, it is possible that several people who got vaccinated in the clinical trials got infected, too, without ever realizing it. This will not be reflected in the 95 percent efficacy rate. Therefore, if people get vaccinated and disease is still spreading in their community and then stop wearing masks and other mitigation measures, there is still a chance of spreading the SARS-CoV-2 to others. We do not know if the vaccine reduces all acquisition of infection (asymptomatic). Do persons still get infected after vaccination and if so, are they still infectious to others? How long will immunity last? How well do these vaccines work in different populations and age

groups? On an individual level - do I still need to wear a mask after vaccination? Until we find out I say yes.

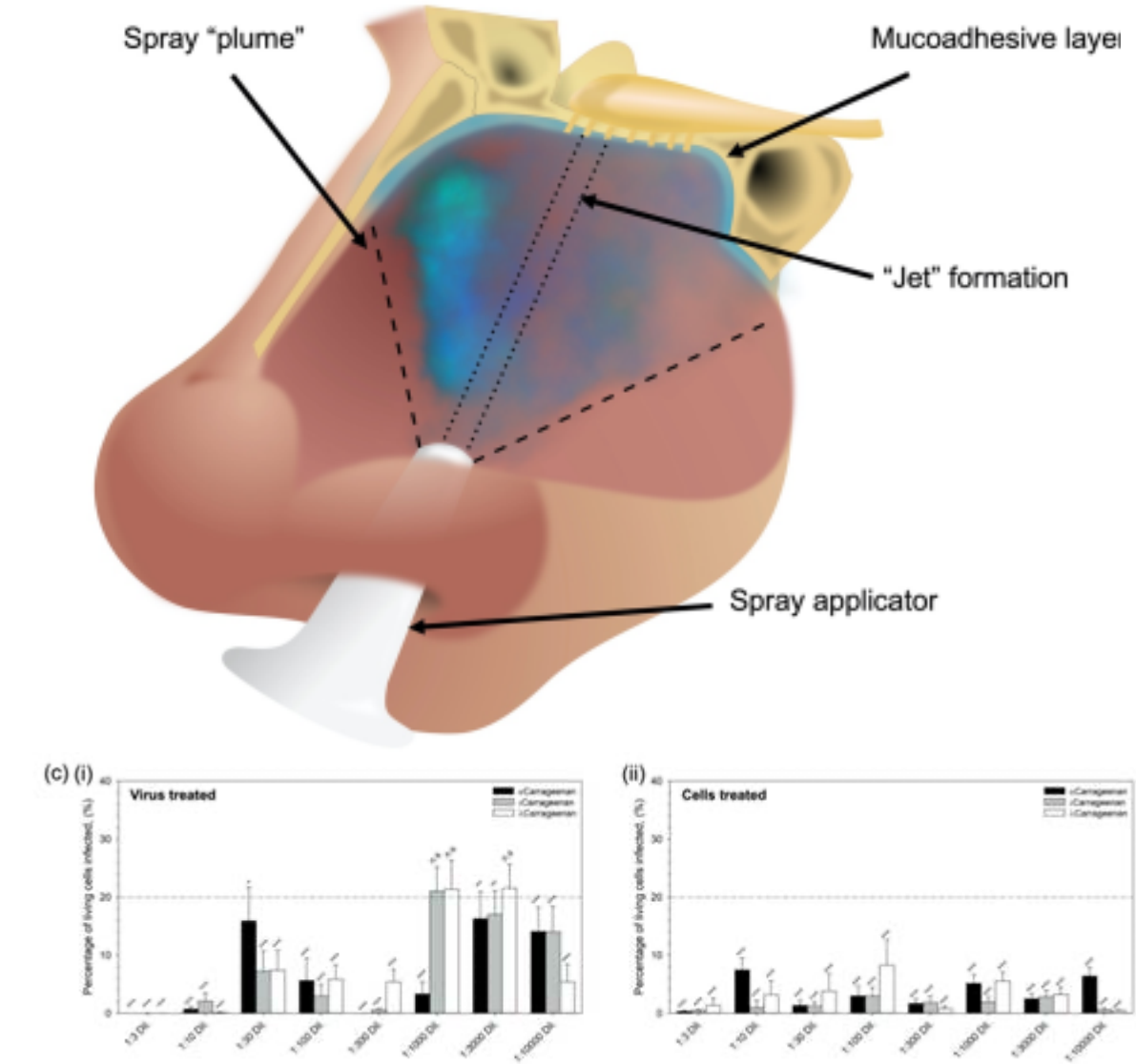
Vaccines do not protect by themselves unless people in large numbers agree to be vaccinated. In the case of ongoing community spread, population-based effects will be highly dependent on vaccine coverage. It is estimated with 95% vaccine efficacy we need ~70% of the population to be immunized to achieve true herd immunity. This is unlikely to occur until ~ May 2021 assuming people get vaccinated. The study reviewed above from Health Affairs highlights that the deployment mattered just as much as the efficacy. Have we done enough to prepare for the massive distribution of the vaccine in the months to come and have we done enough to convince the public on the safety importance of vaccination?

Formulation of a Composite Nasal Spray Enabling Enhanced Surface Coverage Andprophylaxis of SARS-COV-2

bioRxiv published online November 18, 2020
doi.org/10.1101/2020.11.18388645

This pre-publication study focuses on a nasal applicant with the capacity to combat such issues, by focusing on the SARS-CoV-2 virus. Formulation of a spray containing polysaccharides known for their mucoadhesive properties was undertaken and characterized for their mechanical, spray patterns, and antiviral properties. Spray systems demonstrated highly potent antiviral capacities, resulting in complete inhibition of the virus.

SARS-CoV-2 has been found to target the ciliated and goblet cells, where subsequent viral shedding results in extensive viral loads, especially within the upper respiratory tract. Respired air is primarily routed through the nose. Even though the nasal passages present the highest resistance to airflow, on average *ca.* 10,000 L of air is inhaled by a healthy human per day. Only once this pathway becomes overloaded does the body switch to respiratory through the mouth. The airborne risk imposed not only through ventilation systems and crowds, but re-suspension of the virus from inanimate objects, including personal protective equipment, vociferates the need for new and novel devices that not only prevent contraction, but stop spread thereafter. This study addressed such issues, by specifically engineering spray formulations which target the nasal passages.



This study demonstrated the formulation of a potent antiviral nasal spray, with not only prophylactic capacity, but the ability to prevent viral transmission. Its ability to completely inhibit infection is derived from the chemistry (sulphated polymer backbone) of the active polymer, ɣ carrageenan. Spray characteristics were engineered through the production of a composite, where a set of design rules were understood to allow for manipulation over the material behaviors: spray coverage, viscosity and yielding behavior.

Comment: I found this study more of a proof of concept, but it follows several publications looking at antiseptics, mouthwashes etc. that have antiviral activity. The activity of these agents work and how they are delivered are of interest and more importantly will they work. This paper has not gone through peer review yet. A colleague from Johns Hopkins has contacted me and with his permission I am sharing a proposal that HOCl could potentially be used as an inhaled treatment to reduce viral load and may potentially reduce or eliminate the progression of disease. Their findings were also based on previous studies that demonstrated that low concentrations of HOCl are effective and safe as a nasal irrigation

against nasal infections including viruses. As you can see, they are looking to the FDA to grant a research IND approval, so human studies could be conducted very quickly and safely. If any of you are interested, please contact me and I can put you in touch with Dr. Stonemetz.

Delirium in Older Patients With COVID-19 Presenting to the Emergency Department

JAMA Netw Op published online November 19, 2020
doi:10.1001/jamanetworkopen.2020.29540

This multicenter cohort study was conducted at 7 sites in the US. Participants included consecutive older adults with COVID-19 presenting to the ED. A total of 817 older patients with COVID-19 were included, of whom 386 (47%) were male, 493 (62%) were White, 215 (27%) were Black, and 54 (7%) were Hispanic or Latinx. The mean (SD)age of patients was 77.7 (8.2) years. Of included patients, 226 (28%) had delirium at presentation, and delirium was the sixth most common of all presenting symptoms and signs. Among the patients with delirium, 37 (16%) had delirium as a primary symptom and 84 (37%) had no typical COVID-19 symptoms or signs, such as fever or shortness of breath. Factors associated with delirium were age older than 75 years (adjusted relative risk [aRR], 1.51; 95% CI, 1.17-1.95), living in a nursing home or assisted living (aRR, 1.23; 95% CI, 0.98-1.55), prior use of psychoactive medication (aRR, 1.42; 95%CI, 1.11-1.81), vision impairment (aRR, 1.98; 95% CI, 1.54-2.54), hearing impairment (aRR, 1.10; 95% CI0.78-1.55), stroke (aRR, 1.47; 95% CI, 1.15-1.88), and Parkinson disease (aRR, 1.88; 95% CI, 1.30-2.58).Delirium was associated with intensive care unit stay (aRR, 1.67; 95% CI, 1.30-2.15) and death (aRR, 1.24; 95% CI, 1.00-1.55)

Comment: In this cohort study of older adults with COVID-19 presenting to US emergency departments, delirium was common and often was seen without other typical symptoms or signs. In addition, delirium was associated with poor hospital outcomes and death. These findings suggest that older adults with COVID-19 may present to the ED with delirium and that delirium alone should be considered an important presenting symptom of COVID-19. We can now add delirium to the long list of COVID-19 related symptoms especially in the elderly. It should be mentioned, however, a large proportion of included patients were from assisted living facilities or nursing homes (36%) and/or had previously been diagnosed with dementia.

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November 20, 2020

To Whom It May Concern:

Hypochlorous Acid as an Effective Inhaled Antiviral Treatment

According to our Epidemiologists here at Johns Hopkins, "We are still in the midst" of the pandemic. The global COVID-19 pandemic has engulfed the citizens of all nations around the globe resulting in millions of deaths while impacting both global commerce and increasing national security concerns. We believe that advanced and science-based solutions must be deployed in order to help curtail the pandemic wave.

Over the last few decades, researchers at Spectrum Antimicrobials in the United States have captured the power of the human immune system to manufacture the first stable drug formulation of HOCl to combat viral and bacterial infections including those caused by COVID-19. The same drug has been made available which is supported with significant safety studies for rapid disinfection of hard surfaces.

HOCl, a weak acid of chlorine is produced by human immune systems, where it is produced by our defensive cells (phagocytes) to attack foreign bodies at a cellular level. Once produced, it is extremely effective at killing bacteria, spores and viruses. It rapidly degrades to harmless ions. HOCl has been recognized as a potent antimicrobial for decades, however, the challenge was the ability to produce this product in a shelf-stable formulation at a commercially reasonable cost. HOCl has been well researched, published and later cleared by FDA in different therapeutic areas including reduction of topical inflammation and topical pain as well as disinfection of food and food preparation areas. However, none of the above-mentioned products have been able to provide stability at lower concentrations for safe use of the product on humans. Spectrum Antimicrobials has developed unique and patented formulations to provide rapid disinfection in presence of soil and other organic matter, at concentrations of 0.032%.

This chemistry is now being utilized and formulated as a surface disinfectant, comprising of more than 99.9% water and 0.032% HOCl (hypochlorous acid), which is more than an order of magnitude below concentrations identified by WHO and other medical organization to cause any safety concerns. The product's active ingredient has a long history of use and clearance by The U.S. Food and Drug Administration as safe for use in wound care and for sanitization of food products amongst other indications.

In its stable form, a key feature of HOCl which has been well studied and published is its ability to pose non-selective antiviral and antibacterial effect against a broad range of viruses and bacteria, without inducing further microbial resistance. Studies to date show HOCl does not rely on a single mode of action to block or eradicate viruses and bacteria and further confirms it does not induce resistance amongst target viruses and bacteria.

Covid-19 virus (SARS CoV2) has an envelope or outer coating that is composed of a lipid layer (fatty substance). This is the virus's weak point since breaching the envelope results in complete loss of infectivity ("kills" the virus), and this can be accomplished by appropriate disinfectant chemistry. Spectricept has been independently tested against a range of bacteria and other microorganisms that are known to be difficult to "kill". Spectricept has demonstrated to be highly effective against corona virus when tested at a third party laboratory in the U.S. Spectricept is the only HOCl based solution to date capable of demonstrating the required shelf-life and stability while also capable of providing consistent antimicrobial activity in presence of soil and serum load.

We now know that this virus remains in extremely high concentrations within the nasal passages, and is likely to reside there for a few days before systemic infections appear. There is evidence that once attached to the ACE-2 Receptors, the

virus begins to 'up-regulate' the receptors, resulting in an increase in number of receptors, and hence increased opportunity for a greater viral load to infect the patient. Recently, we have also learned that there is essentially a dose-dependent response, and if the viral load can be lessened (wearing masks), more patients remain asymptomatic and do not seem to convert to the fulminant systemic disease.

Based on these realizations, the Advisory Board at Spectrum proposed that HOCl could potentially be used as an inhaled treatment to reduce viral load, and may potentially reduce or eliminate the progression of disease. Their findings were also based on previous studies that demonstrated that low concentrations of HOCl are effective and safe as a nasal irrigation against nasal infections including viruses. Consequently we requested that Spectrum create a specific formulation of HOCl that would be the safest platform for inhalation and that product is known internally to the company as Spectricept 115. A nasal irrigation formulation is soon to be released as well.

Spectricept platform formulations have been subjected to full biocompatibility testing in compliance with the ISO 10993 series of standards. Spectricept has successfully passed the following safety studies conducted at a certified third-party laboratory.

- *Cytotoxicity; Cells did not show any toxicity*
- *Hemolysis; blood cells did not show any toxicity*
- *Skin irritation; Exposure to animal skin showed no irritation*
- *Skin sensitization; Repeated exposure to animal skin showed no signs of sensitization*
- *Systemic injection; direct injection into animal showed no sign of systemic toxicity*
- *Pyrogenicity; direct injection into blood stream of animal showed no increase in body temperature*

In conclusion, based on the scientific information provided by Spectrum, the Spectricept solution has shown to be a highly effective disinfectant (antiviral and antimicrobial) and it has been shown to be biocompatible at the concentration levels referenced herein. As such, I would recommend that Spectricept should be considered and evaluated by authorities as an ideal potential candidate for use as a first line of defense against Covid-19 as an inhaled therapy. If FDA would grant a research IND approval, human studies could be conducted very quickly and safely.

As an additional personal note, I am using the main active compound for self-inhalation as a nebulized treatment in an attempt to prevent the contact of Covid. I personally feel this has protected me over the past few months given my frequent exposure to Covid patients. Finally, with the disappointing news coming our way regarding lasting immunity, I feel this might represent the only true opportunity to keep this virus at bay. I am more than happy to provide additional information if necessary.

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