THE ALCIVAX

Alcimed analyzes the cornucopia of COVID vaccine interim data to understand what we have to precisely be thankful for.

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A Cornucopia of Vaccines: What we know

Just two weeks after the announcement of extremely good interim data from the Pfizer trials, two more COVID vaccines have exceeded preliminary expectations. As these are just interim reports, it is important to pause analyze the trial designs and evaluate what we really know at this point.
Let's start with the three vaccine candidates with Phase 3 interim results:

	Pfizer BIONTECH	moderna	AstraZeneca
	• mRNA vaccine • 2 doses, 3 weeks apart • Ships at -94 degrees F	• mRNA vaccine • 2 doses, 4 weeks apart • Ships at -4 degreed F	• Adenovirus vector vaccine • 2 doses, 4 weeks apart • Ships refrigerated
Efficacy	90%	90%	70%
Trial Size	44,000 participants	30,000 participants	23,000 participants
Population	No data in the elderly or children	No data in the elderly or children	No data in children
Protection	Prevents symptomatic infection	Prevents symptomatic infection	Prevents symptomatic infection
Duration	Duration of protection TBD	Duration of protection TBD	Duration of protection TBD
Price tag	$20 per dose	$10-50 per dose	$3-4 per dose

The biggest outstanding question in COVID vaccines is the difference in efficacy between the three options. Is the split between the efficacy driven by the vaccine platform? So is mRNA technology really better? Or is there something more puzzling about the Astrazenca trial design?

The Astrazeneca trial has two arms, one arm is given 2 full doses 1 month apart resulted in 62% efficacy, while a second arm of the trial gave subjects 1 half dose and then 1 full dose after a month, resulting in 90% efficacy. The two arms average out to be the 70%. What is baffling is why the efficacy increases with a lower dose of vaccine. While this may still be an anomaly, the vaccine may be inducing an immune response to the viral vector itself, which may interfere with the bodies ability to make an immune response to the SARS-CoV-2 spike protein, but these theories will need to be analyzed with more trial data.

Lastly, one of the most important things we have learned with this interim data, is mRNA vaccine technologies are officially on the map and may very well alter the vaccine landscape permanently. The speed at which they can be developed and adapted has always been impressive, but whether they can mount their logistical hurdles such as their extreme cold chain needs remains to be seen.

Either way, it looks like we do have some good vaccine news to be thankful for.

The Current Strain

Much like the flu, coronaviruses mutate as the pass through a population. This raises concerns about whether arising mutations would eventually make the vaccine less effective. A recent paper in Science suggests no.

The current predominant strain of SARS-CoV-2 is D614G. This mutation involves the spike protein, which is responsible for getting SARS-CoV-2 into cells and is also the target of the COVID vaccines. The D614G mutation began circulating in Europe in February, was more transmissble, and was the primary strain transmitted in early phases of the US outbreak.

These new studies show important characteristics of the mutation. The mutant strain replicates faster and is more transmissble than the original strain from China. While not causing more severe disease, its easy replication in the nasal passages does bolster its airborne transmission.

The mutation does however also make it more susceptible to antibody neutralization, which means that it is more likely to be subdued by the vaccine, than the original strain. Studies confirm that the current vaccines can neutralize D614G infections.

The Next Strain

The remaining concern for mutations disrupting vaccine efficiency is zoonotic transfer. A new strain of SARS-CoV-2 has emerged from human to mink transmission. Infected minks have transmitted the mutated virus to humans 12 times according to the WHO. 15 million minks in Denmark are slated for culling to attempt to control the infection.

Preliminary studies suggest that the mutated strain from minks is less susceptible to antibody neutralization. There may also be other zoonotic reserviors of SARS-CoV-2 that could continue to link in the animal population while active spread in the human population subsides, leaving open the possibility of SARS-CoV-2 reemergence should animal to human transmission reoccur. This warrants the development of CoV surveillance programs world wide.

The Fight over Remdesivir

While the interim data on vaccines has all been positive, the new data on the only approved antiviral, Gilead's remdesivir has not been based on a global WHO sponsored clinical trial, leading the WHO to not recommend its use in hospitalized COVID patients. In previous clinical trials, sponsored by the NIH, remdesivir shortedrecovery time by 31%.

In the WHO's Solidarity trial, remdesivir provides no mortality benefit, does not reduce the need for ventilation, indicating that it is not helping the sickest of patients. From the WHO's perspective this raises some cost-effectiveness questions and has led to the negative recommendation. Between the price and the need to administer remdesivir intravenously, the WHO has raised questions about whether it is worth the effort. This is in contrast the dexamethasone, a cheap oral steroid that has a clear mortality benefit in severe COVID patients.

In early October, the EU penned a $1.2 B deal with Gilead for 500,000 doses of remdesivir, but the WHO trial data was not disclosed. No word yet if the terms of the EU deal will be renegotiated in the wake of the WHO's negative recommendation.

The Search for Treatments Continues

The lab from the University of North Carolina that helped to develop remdesivir, is working on a new SARS-CoV-2 antiviral, EIDD-2801, licensed to Merck and Ridgeback Biotherapeutics is now in Phase 2/3 trials and can be used orally, which could be a great help to treating non-hopsitalized COVID patients. Merck also made a deal this week to purchase OncoImmune to add their CD24Fc protein therapy to its COVID pipeline. Interim Phase 3 data, shows a 50% reduction in mortality for severe COVID patients requiring oxygen.

On the antibody front, Regeneron's antibody cocktail, has been given FDA emergency use authorization, just 3 weeks after Eli Lily's COVID antibody therapy got the same EUA nod from the FDA. A $450 M deal with Operation Warp Speed means that 30,000 doses of the cocktail shipped as soon as the EUA was issued by the FDA for treating mild to moderate COVID. Regeneron is hoping to ship another 270,000 doses before February. Similarly, the Eli Lily antibody cocktail, bamlanivimab, should be used within 10 days of developing COVID symptoms and are not approved for use in hospitalized COVID patients.

Where Did it Come From?

Based on current reports, the first cases of "pneumonia of unknown origin" were officially reported in early December 2019 in Wuhan China. The WHO has recently launched an initiative to isolate the origins of the SARS-CoV-2 virus. Here is what we know so far:

- The study kicked off on October 30th with an international group of researchers and study protocols are under development.
- The origin search will start in Wuhan, scanning hospital records for earlier cases.
- SARS-CoV-2, like other outbreak strains of coronavirus (SARS, MERS) likely transfer from bats to humans through an intermediate species such as a civets or racoon dogs, which was the case for SARS in 2002.
- While in Wuhan, researchers will take a closer look at the Huanan markets where several early patients were known to have eaten.
- An early report of frozen meat samples from that market did not contain traces of SARS-CoV-2
- WeChat, China's social media platform, shows indications of increased discussion of coughs, colds, and shortness of breath as early as mid-November.
- The WHO is quick to remind the public that the first place pandemic is detected is not always its place of origin, as retrospective evidence of SARS-CoV in sewer samples from Spain from March 2019 in a non-peer reviewed report.

Vaccine Locators

Geographic information system (GIS) mapping software is joining the fight to distribute COVID vaccines once they become available. Esri is working with local governments in the US to use GIS technology to plan their vaccine distribution plans. Location intelligence was used for drive up Flu campaigns in the US Midwest resulting in a three fold increase in the number of people vaccinated in a single day. The ArCGIS Survey123 system allows residents to preregister for vaccinations, and when combined with traffic patterns, adjust staffing schedules, map out hard to reach communities, and encourage community engagement.

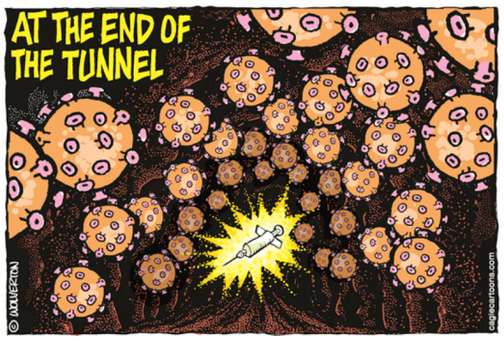

Image Credit: Monte Wolverton

All Joking Aside

Image: Peter Kramer/NBC

COVID has forced people to get fairly creative in reimagining large public events, such as concerts and sporting events. The newest innovation is a parade with no parade route. The Macy's Day Thanksgiving Parade normally covering 2.5 miles of NYC will only cover the block right in front world famous department store.

Can you commit assault by COVID? Perhaps! In the US, a man was charged with assault for breathing on people without a mask at a protest in Virginia. Just a misdemeanor, but does raise some questions about the criminality that can be assigned to necessary bodily functions.

Image Credit: NBC News

Happy COVID Thanksgiving! What are you thankful for?

Good Food!

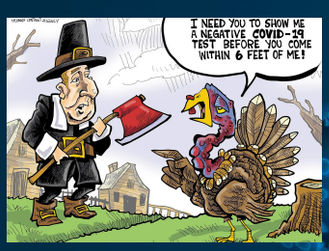

Image Credit: Phil Hands

Making New Friends!

Image Credit: Koterba

Family Gatherings!

Image Credit: Dave Whamond

2021 Is Coming!

Image Credit: Darkow

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