Not all vaccines are created equal

By Carlos E. Soto-Albors M.D.

In the past, flu vaccines were produced by injecting a fertilized egg with a live virus.

These viruses replicated in this egg culture media, and were killed to produce an inactivated virus. This required millions of eggs. Developing a vaccine would take years, not to mention cost because they were developed following the traditional phase 1- to phase 3 approach. Since not all vaccines would show efficacy or safety, they were abandoned before being produced and manufactured.

Due to advances in immunology, genetics, genetic engineering in the last few years, technology has improved to the point where they could be cultured in mammalian cells or insect cells.

Most recently mRNA or DNA technology started to advance so that vaccines would be produced by injecting an mRNA strand with the genetic information, so that the individual would produce the antigen. (more about this later).

Around the end of 2019, a novel coronavirus, subsequently called Covid 19, a Sars CoV2 virus originated in the Wuhan region, in China, and because of global travel it spread rapidly to Italy, Spain, USA and eventually the rest of the world, quickly becoming a pandemic, unlike anything else seen since the Spanish Flu pandemic of 1918.

By March 27, 2020, there were 509,164 confirmed cases, and 23,328 deaths.

We all know how those figures have grown exponentially, by the time I am writing this article, there are 58 million confirmed cases and 1.38 million deaths in 217 countries.

So early on, by January 2020, it was clear that prompt, decisive action and innovation was imperative in order to develop vaccines that would be safe in the shortest period of time.

One such advance was that by January 2020, the genetic sequence of the virus had become available, enabling vaccine manufacturers to start the race against this deadly virus.

To accelerate the distribution if the vaccines are effective and safe , several entities advanced or granted funds to pharmaceutical companies, among them Operation Warp Speed , CEPI (Coalition for Epidemic Preparedness) and Gavi (Global Alliance for Vaccines and immunizations), so vaccines are being manufactured at the same time the clinical trials are ongoing so that if proven to be safe and if efficacy is present, they can begin distribution of the vaccines, as soon as they are authorized or approved, and there is no need to wait for approval and then starting to manufacture them like it had been done in the past.

There is also the Covax facility, a global risk sharing mechanism for pooled procurement and equitable distribution of eventual Covid-19 vaccines, to date they have raised 2 billion dollars.

So there are at least four main platforms for the vaccines under investigation and on clinical trials.

1) Traditional approach
   Inactivated virus
2) Live virus (not common)
3) Recombinant spike protein platforms
   Platforms that have resulted in licensed vaccines

   Recombinant spike protein platforms
   Platforms yet to result in a licensed vaccine
4) RNA or DNA vaccines.

The main two mRNA vaccines that at this time are further along currently are Pfizer and Moderna and although they are both mRNA vaccines, there are some differences.

Both appear to have similar safety and efficacy at the moment.

RNA vaccines - an mRNA (messenger RNA) strand codes for a disease specific antigen, in this case the coronavirus spike protein.

Once the mRNA is inside the body's cells, the cells use the genetic information to produce the antigen, which is then displaced on the cell surface and recognized by the immune system.

Moderna

Safety- Adverse events – (AE) mild to moderate.

After the first dose - 2.7 % - injection at pain site.

After the second dose - 9.7 % fatigue, 8.9 % myalgia, 5.2 % arthralgia, 4.5 % headache, fever

In theory, we do not know if there are any long term side effects since neither of them have had years of being used and the platform using mRNA strand technology has never being approved or licensed.

One of the safety concerns with the mRNA vaccines are that due to the injection of mRNA can they cause inflammation or an autoimmune reaction down the road. Although theoretical, these are some of the unknown long term side effects as of now.

Cold Chain Storage and distribution.

Moderna – the vaccine has to be kept at -20 degrees Celsius or – 4 degrees Fahrenheit (similar to chicken pox vaccine).

Once thawed – Moderna states that it's vaccine can be kept refrigerated for 30 days.

Recently Moderna released its Phase 3 study results, they enrolled 30,000 patients, in a double blind placebo controlled study, where 15,000 were given a placebo, and thus received two doses and 15,000 participants received two doses of the vaccine.

First interim analysis of the phase 3 trial was based on 95 cases of Covid-19, where 90 cases of Covid-19 were observed in the placebo group, and 5 were observed in the mRNA vaccine group.

Based on the above they stated a vaccine efficacy of 94.5 %.

How to calculate vaccine efficacy as per CDC.

Vaccine Efficacy formula;

VE= ARU- ARV / ARU x 100 % .

ARU- Attack rate of unvaccinated people

ARV – Attack rate of vaccinated people

So in the analysis above by Moderna – Vaccine efficacy : VE = 90-5 /90 or 85/90 = 85/90= .944 x 100 % = 94.4%

Pfizer -

Pfizer – is another mRNA vaccine, using an mRNA strand in a similar mechanism of action as described above for Moderna.

It just reported last week, its latest analysis.

There were 43,000 participants, of those there were 162 cases of Covid-19 the placebo group, and 8 cases of Covid-19 among those vaccinated.

Therefore using the same Vaccine Efficacy formula as described above – the efficacy rate for the Pfizer vaccine was 95%.

This means that both mRNA vaccines are very similar in their vaccine efficacy.

Pfizer

Cold Chain Storage and Distribution

Here is where there is a big difference among the two vaccines just mentioned.

Pfizer vaccine –also using the mRNA strand technology has to be kept at minus 75 degrees Celsius or minus 94 degrees Fahrenheit.

Doctor offices or Pharmacies do not have freezers that go to such a low temperature.

So storage, distribution, transportation of their vaccine is going to be a challenge and it may not be a good candidate to reach individuals across the US, and more importantly it will be a challenge across the globe. Pfizer has stated that it is now working on this issue.

Pfizer stated that it plans to produce globally 50 million doses by 2020 and 1.3 billion in 2021.

Next we will discuss the other vaccines starting with the recombinant protein ones.

Recombinant Protein Vaccines

Novavax - Covid – 19 NVX –COV 2373

This is a recombinant protein vaccine, its immunogenicity is achieved in an insect cell, where genes cloned into Baculovirus infects sf9 insect cells, and the antigen, the Coronavirus spike protein is then expressed and purified as multinumeric nanoparticles.

Vaccine also contains an adjuvant which improves (boost's) the immune response and by doing so enables vaccine dose sparing.

The adjuvant in Novavavax is Matrix – M, which is composed of saponin extracted from the Quillaja saponaria Molina bark together with cholesterol and phospholipids.

This adjuvant increases neutralizing antibodies and long lasting memory B cells and recruits and increase the frequency of Cd 4 and CD8 Tcells that enhances T cell immunity.

By adding the adjuvant, it makes it possible to lower the vaccine dose needed which then increases supply and manufacturing capacity.

During its phase 1 study, the vaccine was given to 131 adults (18-59).

It was well tolerated – adverse events were mild, and there were no serious adverse events.

All patients developed anti-spike Ig G antibodies after the first dose of the vaccine.

NVX-COV 2373 induced wild type neutralizing antibody titers in 100 % of participants, after the second dose.

Furthermore , the wild-type neutralizing titers seen after the second dose were much higher, and generated peak geometric mean titer(GMT) greater than 1:3,300 which were higher than the titers observed comparing them to convalescent sera from patients who had confirmed Covid-19 infection and higher than even those patients who had been hospitalized.

This Phase 1 study has been published in the New England Journal of Medicine.

Given the above safety and antibody responses, phase 2 was commenced, and the FDA allowed then to proceed to phase 3.

Stability and Cold chain

Novavax vaccine is stable – allowing handling in a liquid formula that can be stored at 2 degrees to 8 degrees Celsius so it can be stored and transported with existing infrastructure.

This differentiates the Novavax vaccine from the mRNA vaccines, Moderna and Pfizer) both of them requiring storage at colder temperatures , minus 20 degrees Celsius in the case of Moderna and minus 75 degrees Celsius in the case of the Pfizer vaccine.

Current status of Novavax vaccine

As of mid- November phase 3 has already started in the United Kingdom and the number of participants was just increased to 15,000 in the UK, and its designed to evaluate safety,efficacy and immunogenicity.

Phase 3 of the Novavax vaccine has been given the green light in the US and is expected to start at the end of November. Clinical trials will take place in the US and Mexico.

Recombinant Protein Vaccine

Sanofi/Glaxo Smith Kline

In this Covid-19 vaccine collaboration:

Sanofi contributes its S-protein Covid-19 antigen which is based on recombinant DNA technology, and GSK contributes its proven pandemic adjuvant technology.

Sanofi is leading the phase – one/two study which will be followed by a Phase 3 study by the end of 2020, if the data is positive, they will request authorization and approval in the first half of 2021.

Recombinant Vector Vaccine – with Adenovirus

Johnson and Johnson/Janssen - Covid-19 vaccine

Ad.26COV2.S - this vaccine uses a human adenovirus to express the spike protein in cells. It does so by delivering DNA that contains instructions for building a copy of the coronavirus spike protein.

Adenovirus are a group of viruses that cause the common cold, but here the adenovirus has been modified so it can no longer cause disease .

The adenovirus is the vector.

Stability - vaccine is stable around minus 4 degrees Fahrenheit and can last up to three months at 35-46 degrees. (Standard refrigeration).

So far the plan is that this vaccine will require only one dose, all the others we have mentioned so far are administered via two doses, an initial one and a second one is given 14 days later.

If the efficacy of this vaccine is at least equal to the other ones, this will definitely be an advantage.

Adenovirus – vector based vaccine

Astra Zeneca - its vaccine is AZD 1222 and is in collaboration with the University of Oxford.

AZD 1222 is a replication deficient chimpanzee viral vector based on a weakened adenovirus.

Astra – Zeneca- when it finished phase 2, it reported the following.

Data was from 560 adults, of which 240 were > 70 years old. Safety so far for this latter group and response was similar to the 18-55 y/o group.

Until last week their phase 3 was not done yet, so the vaccine efficacy was not known.

Stability is similar to the vaccine from Johnson and Johnson, so it does not require ultralow freezing.

Like the other vaccines, it requires two doses.

As of this writing, on Nov 23, 2020, Astra- Zeneca just released a report of the interim analysis of its AZD 1222 in their phase 3 clinical trial.

They reported that the overall vaccine efficacy was 70%. There were 131 Covid-19 cases in the analysis. Clinical trials were conducted in the United Kingdom and Brazil.

One dosing regimen had a larger group of participants (n=8,895), and the vaccine efficacy rate was 62 %, they were given two full dose on month apart.

Interestingly in a smaller group of participants (n= 2,741), the vaccine efficacy was 90 %. Those participants received initially a half dose, followed by a full dose one month apart.

That is how the combined average efficacy from the two groups resulted in an average efficacy of 70 %.

They did not mention why they think there is such a discrepancy from both groups.

They will continue to analyze the data as more participants complete the phase 3 trial and if safe and effective they plan to file for authorization.

Conclusion:

We have looked at the six vaccines that are further ahead in the trials, and we have seen that there are basically three different platforms for the six vaccines.

The vaccines from Pfizer and Moderna were the first two to complete an interim analysis of their phase 3 trials. Both vaccines use the mRNA platform which is a new platform that on initial results, both vaccines showed vaccine efficacy rates of 94.5 % and 95% respectively.

Both efficacy rates are very good news, since Covid-19 is a pandemic that has affected some many worldwide and it appears to be highly contagious, the FDA had stated that they would consider vaccines with a 50% or higher efficacy rates for EUA (Emergency Use Authorization) as long as they were safe and met all the criteria of placebo controlled randomized trials with a large number of participants, and participant diversity.

So it was a nice surprise when the first two to report efficacy rates were in the 94.5 % and 95 %. While this is great news, both of them have a challenge of requiring very cold temperatures, for storage, transport and distribution.

The Pfizer vaccine requires by far the coldest temperature (at – 70 degrees Celsius) and it might affect how far this vaccine can be distributed worldwide.

Both vaccines are using an mRNA platform which is a new frontier, and although preliminary results are good, there has never been a licensed or approved vaccine

with this technology, so long term side effects or problems are for the moment unknown.

The recombinant protein vaccines , there are two in this group , Novavax and Sanofi , are on a platform that has been around for years , think Hep B etc, and the flu vaccine.

Of the two vaccines, Novavax had the best results on the neutralizing antibodies when phase 1 results were available.

Novavax does not have a licensed vaccine yet but recently (March 2020) completed a phase 3 trial for Nanoflu which met all its endpoints, with a good safety profile.

It's a vaccine for the seasonal flu that was done on persons over 65 years old, at the moment it is waiting to apply for a BLA and probable approval from the FDA , it was only delayed by the company to prioritize its Covid -19 vaccine.

But the platform for Nanoflu is the same as for their Covid –19 vaccine, a recombinant protein and Matrix- M as an adjuvant and given the safety profile of Nanoflu, there are high hopes for this vaccine.

Interestingly, Novavax has a small trial looking into administering their flu vaccine with their Covid-19 at the same time but this is preliminary.

Finally, Novavax based in Maryland, already has manufacturing facilities or contracts to manufacture in 7 different locations, including US, Japan, South Korea, Spain, Czech Republic and India for the moment. So if proven that it also has a good vaccine efficacy, they will be able to manufacture as many as 2 billion doses in 2021.

Sanofi is the other recombinant protein vaccine with an adjuvant, and they already have licensed vaccines with this platform, like Fluzone for the seasonal flu.

Sanofi has been making vaccines for years, and although their phase clinical trial has not started, it will probably in early December.

Adenovirus vector Vaccines.

There are two, Johnson and Johnson and Astra- Zeneca.

Of the two only Astra- Zeneca has recently released results of their phase 3 trial, but its efficacy was 62 % in one group and 90 % in the other for a combined 70%.

Hopefully they can do some adjustments to improve their efficacy rate.

Johnson and Johnson is the other one and as was discussed has the advantage of requiring one dose, and we are also waiting for efficacy rates.

To summarize I personally think we are in a much better place now at the end of 2020 than anyone would have expected, thanks to innovation , speed of vaccine development and thanks to the monetary assistance of the entities I already mentioned which really made this acceleration possible.

I think that by 2021, we have several vaccines with good efficacy rates and safety profiles, but we must remember there are over 7 billion people in the world now so several vaccines will be needed.

An unknown at the moment is how long will the immunity last, and we do not have answer for that yet, we can only hope that it is for a long time, so we can all get back to live our lives like we were before this pandemic.

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