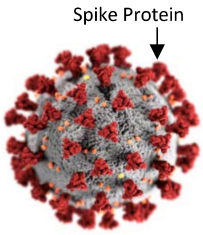
What You Need to Know…
COVID-19 Vaccine Development

Pfizer's successful Phase III COVID-19 trial results highlight the power of human ingenuity, scientific innovation, and teamwork. With more vaccine trial results imminent, the following Q&A discussion is intended to give you and your colleagues, families, and friends some important context and deeper understanding of certain issues as you contemplate investment, lifestyle, health, and other choices.

SS: Before we take a look at the implications of Pfizer's exciting news, let's discuss some of the mechanics of vaccines and the development process. The primary mechanism by which the human body can fight a virus is training the immune system to respond. How do you "train" an immune system to recognize and combat the COVID-19 strain of coronavirus?



Source: cdc.gov

AW: There are several ways to elicit an immune response to coronavirus. At a basic level they all involve getting parts of the virus into the body and triggering the immune system to respond. All of the leading vaccine programs target the spike protein. Vaccines are designed to provoke the body to generate antibodies to the spike protein, thereby stopping the virus from entering a cell.

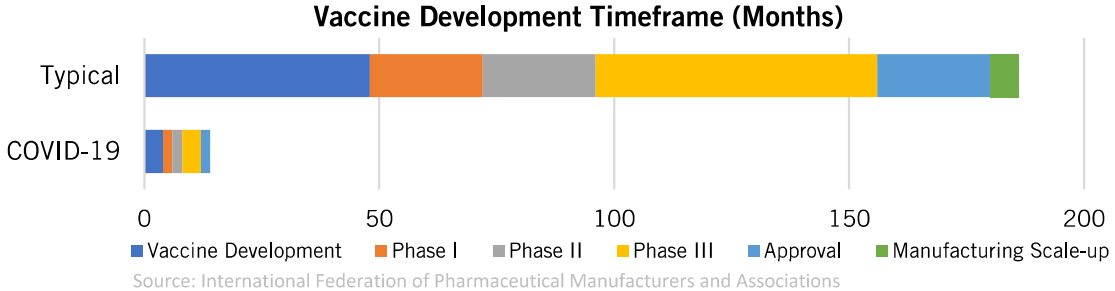
SS: What are the most common vaccine approaches and which are the current COVID-19 front-runners?

AW: There are four main types of vaccines: 1) Inactivated/Weakened Virus, 2) Viral Vector, 3) Nucleic Acid (DNA/RNA), and 4) Protein-Based. Some of the methods being tested for COVID-19 have been used for other vaccines in the past, but two of the leading programs – Pfizer and Moderna – are using a novel (RNA) approach. A full description of each vaccine approach, including the pros/cons, existing examples, and companies testing each approach for COVID-19, is provided in Appendix II.

SS: How has the development of the COVID-19 vaccine differed from the normal vaccine development process, and are there any risks associated with this?

AW: The development timeline for the COVID-19 vaccine has been significantly shortened. What would normally take about 10 years from start to finish has been compressed into just 12 months. Some of this compression comes with financial risk. For example, building manufacturing capacity usually occurs at the end of the development process. For COVID-19, dedicated manufacturing facilities were completed just seven months after finding ourselves amidst a pandemic. Some of the changes come with unknown risks. For example, several years would normally be spent making sure you optimise the antigen up front before entering the clinic for trials – for COVID-19, this has been compressed to several months.

First generation vaccines may not be perfect, but if they are safe and lessen the severity of the disease to any extent, then that is a good start given the circumstances of a pandemic. Pfizer's recent news suggests that we may be in the unexpectedly positive situation of not trading off effectiveness for speed, as preliminary results show efficacy around 90% - much better than early estimates.



Source: International Federation of Pharmaceutical Manufacturers and Associations

SS: Prior to the recent Pfizer announcement, efficacy rates for various trials were hovering around 50-60%. This might turn out to be irrelevant, but those numbers sound pretty terrible. Should we be worried? Do vaccines typically improve over time?

AW: As mentioned above, early indications suggest that the Pfizer vaccine may be as high as 90% but the wider range of COVID-19 vaccines in trials were initially expected to have efficacy of just 50% or better. While a target of 50% sounds low, it is a good start for a vaccine developed against a virus characterized only nine months ago. An ideal vaccine would stop infection in everyone vaccinated but there are other points to consider. A vaccine that reduces the severity of the disease resulting in decreased mortality and fewer hospitalizations can still be considered a success. The flu vaccine, as a reference point, has an efficacy rate between 30-80% depending on the year and viral strain.

SS: The flu vaccine must be reinvented each year depending on the different genetic variants that are dominant that year. Could this happen with the coronavirus?

AW: The simple answer is we do not know. The data so far would indicate that the coronavirus mutates far less frequently than the flu. While mutations have occurred, so far they have not been clinically relevant and should not affect vaccine efficacy.

SS: What are some of the shortcomings of typical vaccine clinical trials, and what is the read-across for COVID-19 trials?

AW: Clinical trials for vaccines are typically robust but do face some shortcomings related to minority representation (race, ethnicity, etc.) and age cohorts. Smaller trials and less follow-up for COVID-19 vaccines (due to the shortened timeline) could have amplified safety implications longer term. As an example, there are questions about the efficacy among different ethnic and racial groups, age groups, individuals with varying genetic makeup, etc. Certain minority communities also represent higher risk populations than average – we do not fully understand (yet) how well the vaccine will perform for these individuals. Distrust due to the condensed timeline and politicized nature of the discourse surrounding the COVID-19 vaccine may lead to additional challenges down the line, compounded by the impact of social media and controversial viewpoints from anti-vaxxers (right to choose, purported linkage to autism, etc.).

SS: How soon after the vaccine is launched should we expect to see side effects and perhaps regulatory action?

AW: It has been over two decades since we have seen an example of a vaccine withdrawal. In 1998 there were two. One was for financial reasons (a Lyme disease vaccine that was not selling) and one was for side effects (Rotashield – prevents gastroenteritis) one year after approval. In 2015 the Dengue vaccine faced limited withdrawal globally. On average it takes five years between approval and first label modification (for safety, contraindications, excluding groups, etc.). Withdrawal of approval due to safety concerns is rare. At this stage it is too early to tell what side effects might emerge from the COVID-19 vaccine – a situation that is really limited to a crisis period, as this is typically addressed during the lengthy clinical trials. Early results from Pfizer show no major safety concerns – we will see how that evolves as testing widens.

SS: When will most "regular" people have access to a mass-marketed vaccine?

AW: This is still somewhat of an unknown, particularly due to the dichotomy of some recent clinical trials being paused while Pfizer's news accelerates hope. Our best guess at this stage is that a vaccine will likely be approved in late 2020 or early 2021 and available for mass vaccination at some point during the second half of 2021. The type of vaccine that is ultimately approved for public use will have logistical implications (and possibly hurdles to mass adoption) including storage/transport temperatures, the number of doses required per patient, the speed at which doses can be prepared/made available, etc.

As an example, while markets rallied at the news of Pfizer's promising vaccine, experts suggest it will not be easy to distribute and administer widely as it requires transport and storage at temperatures of -94°F/-70°C or colder. Even sophisticated hospitals in developed nations will be challenged to accommodate the complex, ultra-cold storage requirements. Regular doctors' offices, clinics, and pharmacies – plus hospitals

in more rural areas or less developed nations – will face even bigger (and potentially insurmountable) issues. Additionally, the Pfizer vaccine requires a two-dose schedule, meaning individuals would have to make two separate visits to a doctor, clinic, or hospital setting in order for the vaccine to be effective.

While the public is now hyper-focused on Pfizer's progress, it is important to note that once one vaccine is approved, other companies will continue their development efforts in search of a "better" vaccine for the future. As an example, Moderna – one of the other front-runners that is also exploring the RNA-style vaccine – has said that its vaccine does not need to be stored at such low temperatures, which could be helpful, but we are still awaiting test results regarding safety and efficacy.

SS: Are there any concerns about vaccine durability for COVID-19?

AW: This is one of the more important questions that remains unanswered. Will the durability be "flu like" where we must receive a vaccination annually, "mumps like" where the durability generally lasts a lifetime, or somewhere in between? Measurement of antibody levels fall off quite quickly after recovering from COVID-19. At this stage we do not know what level of antibodies is enough to provide protection nor do we know if the immune system has been "trained" and will respond if challenged with COVID-19 again. What we do know is that all of the vaccine front-runners generate an antibody response similar to that seen in patients that have recovered from COVID-19.

SS: What are the investment implications of the accelerated vaccine development timeline prompted by the COVID-19 outbreak and Pfizer's promising Phase III results?

AW: At the highest level, moving toward a "solution" to the COVID-19 pandemic instills confidence in society, companies, and investors to begin planning for a return to normalcy. Speaking generally, we believe societal normalcy is still 18+ months out (sometime in 2022) when a successful vaccine has been widely distributed – but confidence that we are making progress puts the recovery wheels in motion.

Demonstrable progress toward normalcy also reduces the tail risk in many cyclical and highly leveraged businesses – and highlights the value and importance of innovation. In health care specifically, companies temporarily set aside their commercial ambitions for societal good but simultaneously demonstrated their ability to pivot and innovate, condensing a decade-long timeline into just months! When most people think about the word innovation, they think about technology and AI – but we believe that the pace of scientific innovation, coupled with enhanced processing power, will shape the future of the health care industry and drug development processes.

Finally, we have seen a notable shift toward e-commerce and the purchase of tangible goods over the past nine months as people were stuck in their homes and searching for items to bring safety and comfort. Many dipped into savings accounts, borrowed on credit cards, and spent government stimulus checks. With the shift back toward societal normalcy will come an aggressive shift in consumer behavior, including spending on services and experiences. The fragility and unpredictability of life has come under the spotlight and many have been reminded of the importance of living life to the fullest and experiencing all that the world has to offer, while those opportunities exist. Many companies in the travel, leisure, and hospitality industries are positioned to capitalize on this, but they must have fortified balance sheets to withstand the challenging interim transition period and possible air pocket during the winter months.

We look forward to tracking progress against these trends and hypotheses and applying our time-tested, long-term oriented, private equity approach to public equities to find productive investment opportunities.

APPENDIX I: GLOSSARY OF COMMONLY USED TERMS

Antibody: A blood protein produced in response to, and counteracting, a specific antigen. Since early on in the COVID-19 pandemic, much of the discussion has focused on antibodies as both a trigger to determine who might have had the virus without knowing earlier in the year and also as the key to certain potential treatments and/or vaccine development efforts. Doctors and scientists are still trying to pinpoint how long antibodies linger in COVID-19 patients and whether they promote any degree of immunity.

Antigen: A toxin or other foreign substance which induces an immune response in the body, especially the production of antibodies. Viruses and bacteria are both types of antigens – sometimes an antigen can be helpful (as in the context of vaccine development) and sometimes it is the cause of the illness itself.

Blood protein: Proteins found in the blood that serve a variety of functions including the transport of vitamins, minerals, hormones, and other materials that contribute to the functioning of the immune system. Perhaps the best known is hemoglobin.

Contraindication: A condition or factor that serves as a reason to withhold a certain medical treatment due to the harm that it would cause the patient. Over time, we may discover a contraindication related to the COVID-19 virus that could contribute to regulatory action or a vaccine pull-back. In typical vaccine development timelines, sufficient testing periods are built in before approval to uncover these issues.

Efficacy: The capacity for producing a desired result or effect; effectiveness. The efficacy rate of the COVID-19 vaccines being tested have been at the center of certain discussions about the speed at which companies are moving through the development process and the exceptions that are made for vaccines to be approved during a pandemic. While higher efficacy rates are better, 50% efficacy is better than nothing, given the circumstances.

Immune response: How your body recognizes and defends itself against bacteria, viruses, and substances that appear foreign and harmful. One of the big questions during any vaccine development process is which style of vaccine will produce the most reliable and robust immune response.

Spike protein: A protein that protrudes from the envelope of some viruses (such as a coronavirus) and facilitates entry of the virus particle into a host cell. Like a key in a lock, the spike protein opens the door. The spike protein is the focal point for all current COVID-19 vaccine front-runners – the goal is to generate an immune response to that protein such that the virus is blocked from entering healthy cells.

Vaccine durability: The length of time immunity lasts in people who have received a full vaccine regimen. It is still unknown whether the COVID-19 vaccine (or contracting COVID-19) will deliver long-term immunity or whether, like the flu vaccine, the impact will be a shorter-term immune response.

APPENDIX II: OVERVIEW OF COMMON VACCINE DEVELOPMENT APPROACHES

Types of vaccines	Live Attenuated Virus	Inactivated Virus	Viral Vector	Nucleic Acid (DNA & RNA)	Protein-Based (Subunit)
How it works	This is a weakened version of the actual virus.	An inactivated vaccine uses the whole virus after it has been killed with heat or chemicals.	This approach takes a harmless virus and uses it to deliver viral genes to build immunity.	This vaccine uses DNA or RNA molecules to teach the immune system to target key viral proteins.	This vaccine uses a piece of a virus' surface to focus your immune system on a single target.
Pros	Stimulates robust immune response without causing serious disease.	Safe because the virus is already dead and easy to make.	Live viruses tend to elicit stronger immune responses than dead viruses or subunit vaccines.	Easy and quick to design.	Focuses immune response on the most important part of the virus for protection; cannot cause infection.
Cons	May not be safe for those with compromised immune systems.	Not as effective as live virus. Some previous inactivated vaccines have made the disease worse; safety needs to be shown in clinical trials.	Important to pick a viral vector that is truly safe. An immune response to the viral vector could make the vaccine less effective.	Never been done before. There are no licensed DNA or RNA vaccines currently in use.	May not stimulate a strong response, other chemicals may need to be added to boost long-term immunity.
Existing examples	• Measles, Mumps, & Rubella • Chickenpox	• Polio	• Ebola • Veterinary medicine	• None	• Pertussis • Hepatitis B • HPV (Human papillomavirus)
Groups testing for COVID-19 vaccine	• Codagenix • Indian Immunilogicals Ltd.	• Sinovac • Sinopharm	• Univ. of Oxford/ AstraZeneca • CanSino Biologics • Johnson & Johnson	<u>RNA</u> • Pfizer/ BioNTech • Moderna <u>DNA</u> • Inovio	• Novavax • AdaptVac

Source: CDC; NIAID; FDA. Michelle Guerrero & Jonathan Wosen / U-T

Important Considerations & Assumptions

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