NEUBERGER BERMAN

Neuberger Berman Equity Research Team

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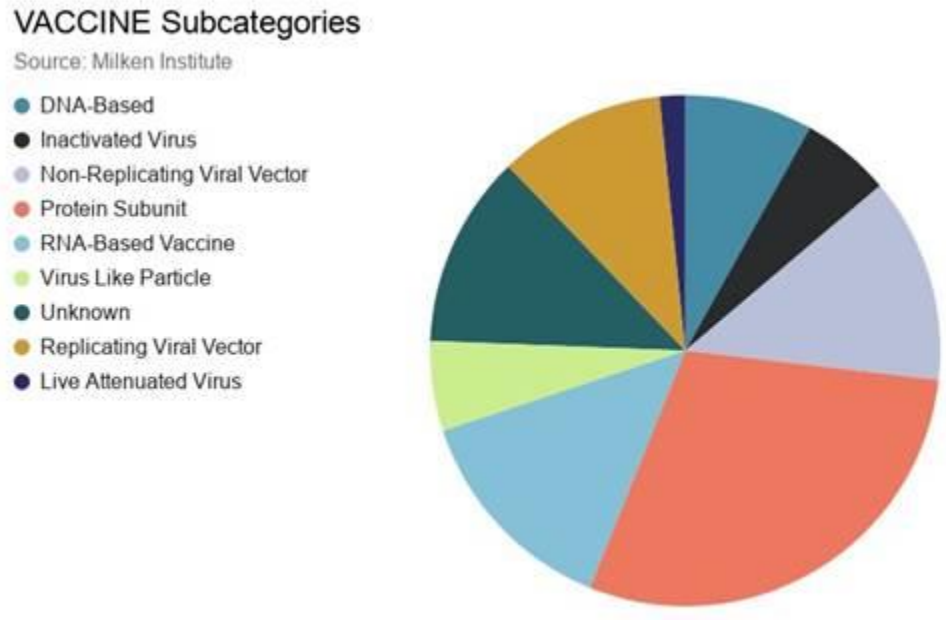
Science can win on the COVID-19 vaccine front...It's a matter of coordinating a multipronged approach across public and private players.

In a recent note, we focused on whether we would be ready for a second wave with regard to testing, both at the molecular and serological levels, and highlighted our views on therapies including direct antivirals, such as the FDA's recent Emergency Use Authorization for Remdesivir, as well as other agents that treat the clinical sequelae of infection with SARS-CoV2 (the virus that causes the COVID-19 disease). While advances in treatments will surely aid in fighting this pandemic, we believe a vaccine that provides lasting immunity against the virus is needed to put the pandemic behind us. In this update, we frame the development pathway for vaccines in the age of COVID-19, highlight the risks and rewards of moving at "warp speed," contemplate the rationality of compressed timelines, manufacturing scale, broad access and affordability, and offer our views on why many players can win, as well as on a plan B should vaccine approaches fail. To be clear, we firmly believe a coordinated effort between the public and private sectors will be required to meet the needs of the global community in addressing this pandemic, consisting of multiple, effective vaccine approaches, global supply and, importantly, access and affordability for the world's population.

What technologies are employed and who are the players? So many companies have thrown their hat into the proverbial ring in the race to develop a vaccine against SARS-CoV2, encouraging considering we will most likely need several vaccine options in order to address a diverse population and meet demand going forward. The chart below highlights the vaccine subcategories from a technology perspective and shows that out of the ~95 active vaccine programs, traditional recombinant protein subunit methods dominate given familiarity and potentially lower risk; unfortunately, they also may require protracted timelines and many intermediaries in order to manufacture substantial supply.



Source: Milken Institute as of May 15, 2020.

Recent advances in nucleic acid and viral vector-based methods have gained traction in the past few years, with mRNA, DNA and non-replicating viral vector programs outstripping traditional methods as a group. Today, they collectively represent the most advanced COVID-19 vaccine programs with advantages of flexible and rapid scale-up, broad immunity mechanisms and lower costs to manufacture. Most vaccines in clinical development to date target the spike protein of SARS-CoV2; the spike protein mediates viral entry into the host cell and

hence blocks its interaction with the human ACE-2 receptor, thereby preventing the virus from gaining entry and shutting down the viremia that results in COVID-19.

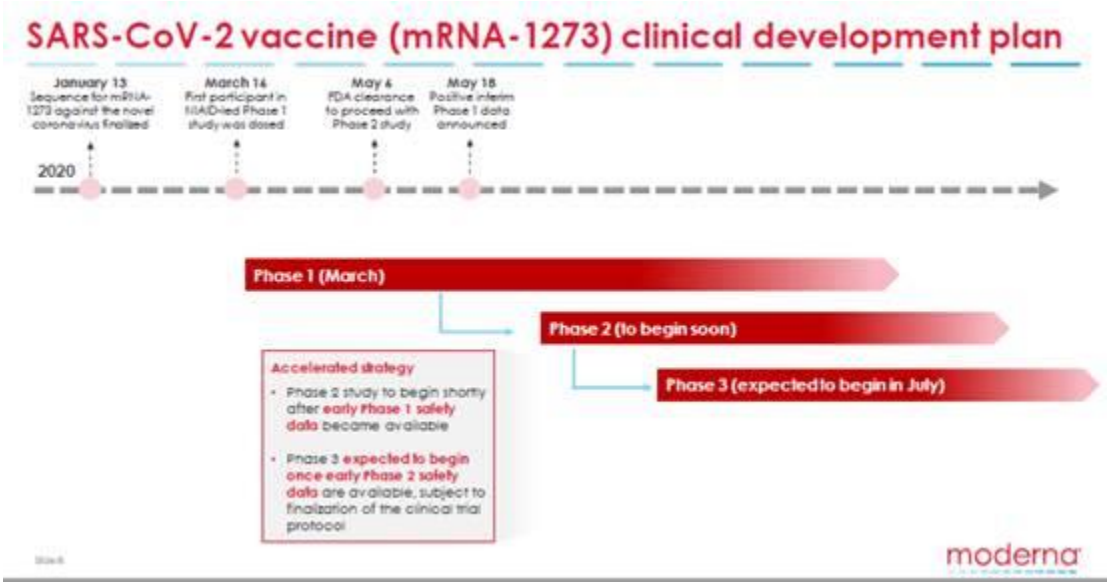
Interim results from the first mRNA-based vaccine from Moderna were recently announced: While the data was encouraging from the interim look of the Phase I study of mRNA-1273 in healthy volunteers, we still have a long way to go to bring a SARS-CoV2 vaccine to the masses by early to mid-2021.

What happened: On Monday, May 18, Moderna announced positive Phase I data from the mRNA-1273 SARS-CoV2 program in partnership with the National Institute of Allergy & Infectious Disease (NIAID). The punch line is that all patients seroconverted across all doses, producing binding antibodies against SARS-CoV2 and more importantly, the first eight out of 25 patients tested produced neutralizing antibodies at levels equal to or above those observed with convalescent plasma.

What does this mean? Moderna has passed the first hurdle in bringing a safe & efficacious vaccine to the market sometime in early 2021, earlier for healthcare providers, first responders, at risk workers etc. We are encouraged by the following data points:

- A dose-dependent response was observed across all doses as measured by total binding antibodies.
- Importantly, the antibody response was stronger post the second "boosting" dose, suggesting that both humoral (antibodies) and cellular (T cells) immunity was triggered.
- Data from the first 8 patients, four per dose cohort, demonstrated neutralizing antibodies in all 8 patients at levels equal to (at the lower dose) or far exceeding (at the high dose) that's seen in convalescent plasma exchange patients who had recovered post infusion.
- Tolerability data looks solid, safety looks good so far, but will require more patients before we have total comfort…….a good start nonetheless.
- Challenge study in mice is interesting to us, however it does not meet our bar given issues with the assay and the fact that modifications were made to the virus-ACE2 receptor binding interaction given differences between mice and humans. We await challenge studies in non-human primates which will likely provide more impactful information given similarities between species and translation to real world viral infections in humans with SARS-CoV2.

Clinical development timelines and manufacturing capacity? The Phase II program will begin imminently and include 600 patients, 300 aged 18 – 55 years and another 300 over the age of 55. The 25 microgram Phase I low dose has been dropped; a 50 microgram dose will be introduced in phase II as well as the 100 microgram dose used in Phase I. It appears the high dose of 250 micrograms will no longer be necessary given robustness of total antibody responses observed at the 100 microgram dose from Phase I. Moderna expects the Phase III to begin in July, post safety information from the phase II given broader age cohort and risk factors for the large, pivotal program.



Source: Moderna as of May 18, 2020.

Manufacturing and Supply: The Moderna Norwood facility is ramping production, and is producing millions of doses per month currently (an average implied dose between 25 and 100 micrograms), expanding to tens of millions of doses per month by mid-year. The partnership with Lonza should yield one billion doses per year beginning in mid-2021 with Moderna previously stating availability of ~100 million doses by end-of-year, or enough to vaccinate 50 million individuals from Norwood alone. Lonza supply is expected to come on line in the next few months although production commitments for 2020 were not disclosed.

In summary we view this interim data as a first step in the right direction and while not declaring victory just yet, we view the robustness of data from the first 25 healthy individuals keeping our optimism high.

Other Players with data in the next few weeks:

Below is a select list of additional COVID-19 vaccine developers that highlights technology platforms as well as experienced manufacturers/novel modalities furthest along in clinical development. In our view, multiple vaccine approaches may be needed in order to address the geographic diversity of the pandemic as various mechanisms of immunity may work better in specific populations.

Pfizer/BioNTech mRNA vaccines

- Pfizer/BioNTech's mRNA platform will employ a multipronged approach testing four vaccine candidates, all targeting the receptor binding domain of the spike protein. Current studies in Germany and the U.S. involving two vaccine candidates across 50 – 70 patients are ongoing, with data expected sometime in June.
- Benefits of mRNA vaccine technology include flexibility in design should the virus mutate more rapidly than currently postulated, lower manufacturing costs vs. protein subunit-based vaccines and established contracts with expert, large-scale manufacturers Lonza and Pfizer. Key risks beyond safety and efficacy include scalability of the delivery vehicle and the stability of the nanoparticle technology employed.

Viral vector technologies employed by JNJ and Oxford University have demonstrated efficacy in the past (Ebola and MERS) and are easily scalable.

- We are growing more optimistic for JNJ's adenoviral-26 vector approach to the SARS-CoV2 vaccine, with clinical trials slated to start in September 2020. Data from the phase I study will likely be reported by year-end, followed by a rapid initiation of a broad phase II/III program while simultaneously filing for emergency use authorization (EUA) should efficacy and safety be established.
- While some are disappointed with the long lead times, JNJ believes it would have supply of over one billion doses globally in early 2021 through partnership with Emergent BioSolutions, with a commitment to manufacturing doses at risk.
- Regarding the Oxford University/AstraZeneca collaboration that employs a chimpanzee adenoviral vector system, we are cautiously optimistic given success from previous MERS viral studies, which appeared to demonstrate safety and immunogenicity.
- Healthy volunteer phase I data is expected to report in late May/early June with plans to begin the ~5,000 person study immediately following phase I data. Oxford and Astra Zeneca expect results by year-end as well as a filing for EUA in the U.S. with the goal of >1bn doses for broad dissemination sometime in 2021.

Company	Vaccine Class	Partners Manufacturing	Timing/Data
Moderna	mRNA, mRNA1273	BARDA, Lonza	Phase I end of May
University of Oxford	Non-replicating viral vector (Chimp AAV)	AstraZeneca & Vaccitech	Phase I/II, data end of May/early June
Johnson & Johnson	Non-replicating viral vector (AAV26)	BARDA, Emergent Biosolutions	Phase I to begin in September
Vaxart	Non-replicating AAV5		Phase I imminent
Can Sino Pharma	AA5 viral vector	AMMSIB	Phase II imminent
Sanofi/Glaxo	Protein subunit-S protein baculovirus	BARDA	Phase I imminent
Novavax	Full length glycoP NVX-coV2373	Emergent Biosolutions	Phase I begins mid-May
BioNtech/Pfizer	mRNA, BNT-162	Fosun China	Phase I initiated May
Translate Bio	mRNA	AMRI	Clinic by end of 2020
Vir Biotech/Alnylam	Inhibitory RNAs		Clinic by end of 2020
Inovio	DNA, INO4800	Richter-Helm, CEPI	
Merck & others	Live attenuated BCG	SNY, Powderject	Marketed/Phase III

Source: Neuberger Berman & Biomedtracker as of May 15, 2020.

Traditional recombinant protein subunit vaccine development is viewed as a safety net of sorts near-term should mRNA and viral vector approaches stumble, but could play a role longer-term in most scenarios. Those involved include Novavax and Glaxo SmithKline in partnership with Sanofi, to name a few, and have limited risk on the efficacy side, in our view, but require long lead times for manufacturing and require adjuvants to boost the response, the latter of which could be in limited supply.

With so many vaccine candidates, a coordinated path for development must be established; introducing the Administration's own Manhattan Project, "Operation Warp Speed." In order to establish a coordinated effort across vaccine development, accelerate timelines and harmonize manufacturing and supply chain needs, the Trump administration has launched this program with the goal of having 100mm doses of vaccine supply by year's end, ramping to 300mm doses in early 2021, all in collaboration with the private industry, government agencies and the U.S. military.

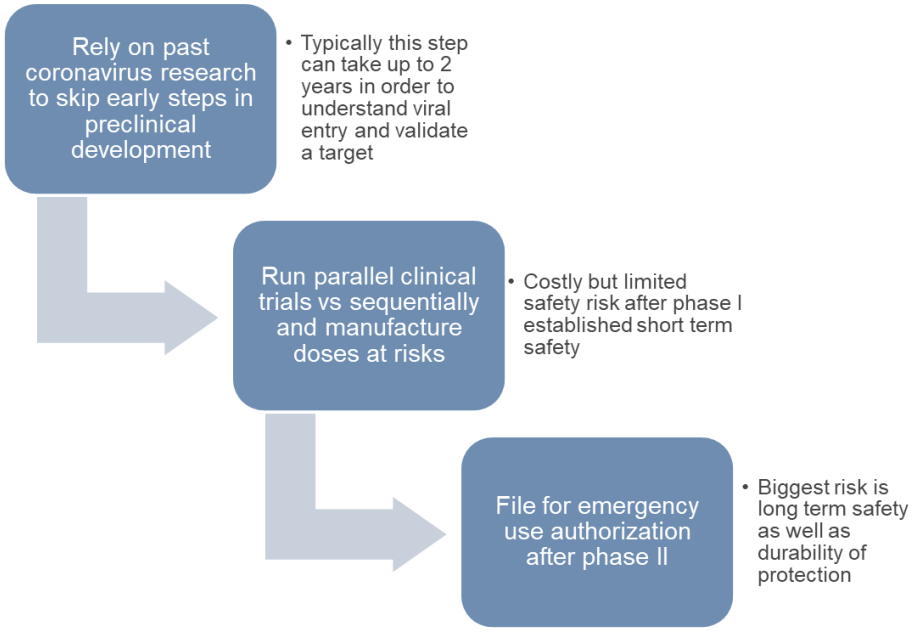
- The former head of GSK's vaccine division, Dr. Moncef Slaoui, has been tapped to head this initiative, with four-star Army General Gustave Perna overseeing logistical operations.
- The project will focus on making animal research resources available for preclinical work as well as establish a master protocol for phase II/III clinical trials where all sponsors and manufacturers would submit their plans/data.
- To date, 14 vaccine candidates have been initially identified with the aim of moving forward with three to four vaccines for final testing.
- Operation Warp Speed would also lend logistical support on the back end, including stocking of vials, syringes, stoppers, etc., as well as organize distribution of vaccines should studies prove successful.

Accelerated timelines are also supported by FDA guidance document: The FDA has allowed animal model data on efficacy, together with safety data from humans, in order to obtain accelerated approval in emergency situations, a la the anthrax scare of 2001. Additionally, the FDA has allowed immunogenicity (mounting an antibody response against the virus) as measured by antibody titers, as a surrogate for efficacy in phase III in place of large pivotal studies that take several years to gain real world experience/protection.

Risks to moving at warp speed: Since vaccine development typically takes years (five to seven in more recent times) to make it to market, what are we risking by advancing a SARS-CoV2 vaccine in less than 12-18 months from virus identification and sequencing to use in humans?

The flow chart below describes how up to two years could be saved based on relying on past coronavirus research (MERS, SARS-CoV2) to skip cumbersome early development steps. Also, running trials in parallel and manufacturing copious doses at risk may also save years, but could be costly.

Reducing the Vaccine Timeline



For illustrative purpose only.

Risks on the safety and durability side of the vaccine development equation:

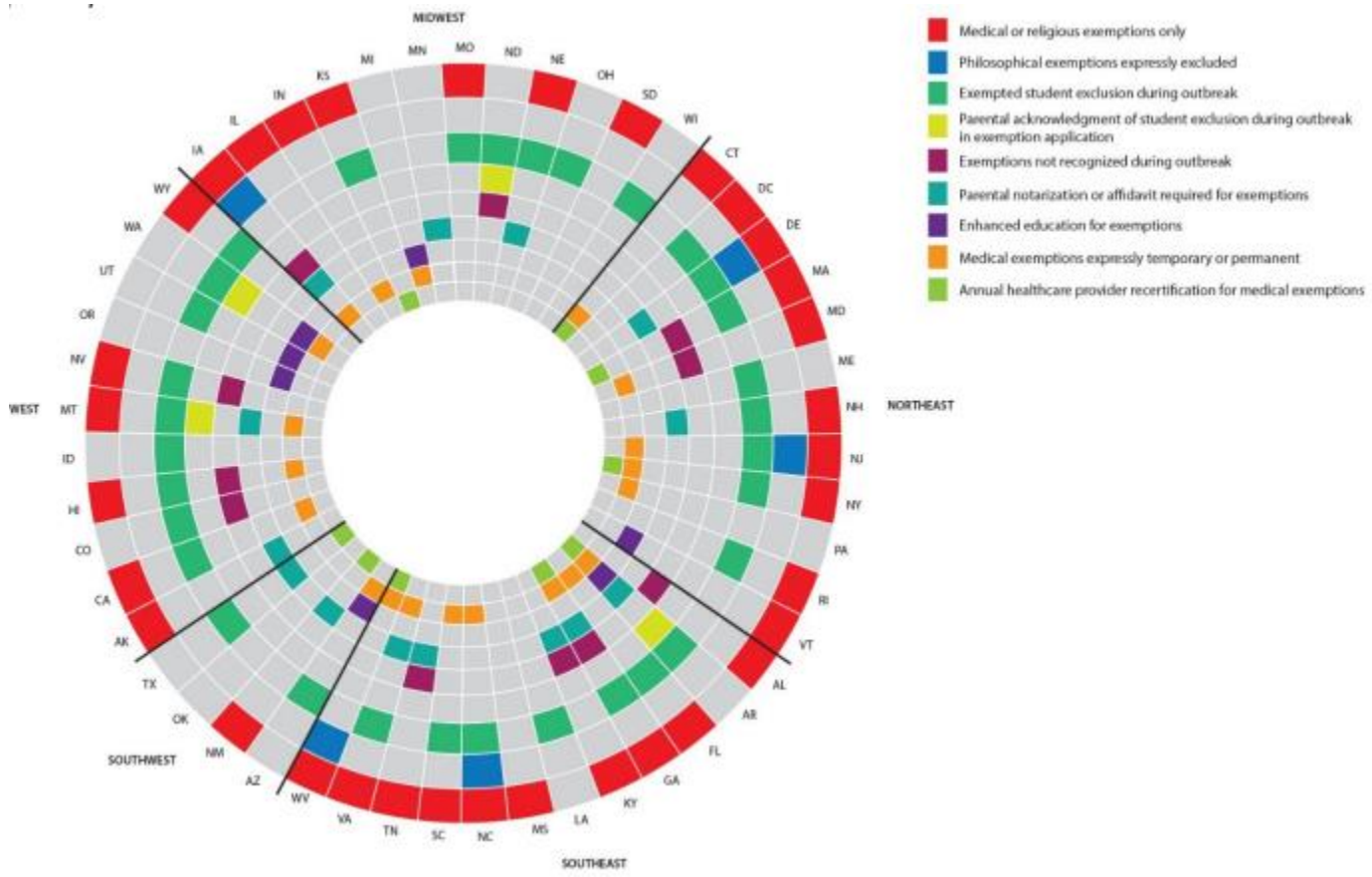
- From a safety perspective, we question the ability to capture rare events resulting from vaccination that may require tens of thousands of administered doses to identify.
- Risk of a rare but debilitating, and often fatal, side effect known as antibody dependent enhancement could result in increasing the infectivity of the virus, potentially leading to a more severe course of disease.
- Incomplete protection from infection across various patient subgroups such as the elderly and immunocompromised whose ability to mount an immune response in general is not as strong as healthier individuals is also a risk of moving too fast.
- Given that~ 80% of cases of COVID-19 resolve without hospitalization, who is best suited to take on vaccination risk, albeit low, needs to be better understood in an emergency-use authorization environment.

However, with a pandemic of such proportions, drastic measures must be taken and hence we err on the side of rationale, accelerated development. Notably, we highlight a coronavirus vaccine human challenge working group that has formed regarding ethical considerations for such a study post WHO ethical guidelines released last week. While the kneejerk reaction to such a study (vaccinate healthy volunteers and then deliberately expose them to SARS-CoV2 to test the effectiveness of the vaccine) would be decidedly negative and raises ethical concerns, we think hurdles would be surmountable provided passive antibody strategies in development prove efficacious and could be used somewhat as a "rescue" therapy. The most recent update from the human challenge SARS-CoV2 vaccine study group included >16,000 volunteers from 100 countries registering as willful participants in such a study. Should a human challenge study initiate, it would diminish the vaccine development risks resulting from moving at "warp speed" as highlighted above.

Will vaccines be mandated, provided ample supply exists?

A key question to how the COVID-19 pandemic will ultimately play out obviously hinges on the success of treatments and, ultimately, vaccines. But unlike treatments, vaccines are directed towards healthy individuals who may or may not opt in based on a variety of factors such as religious or philosophical objections, medical exemptions etc. The chart below illustrates the various levels of exemptions to vaccination programs by state in the U.S., with each color representing a specific reasons for exemption, which are fairly numerous in scope. Each year ~43% of Americans forgo influenza vaccinations, so this begs the question, will SARS-CoV2 vaccinations follow similar lines if voluntary? While we do not have an answer to this question, and understand apprehension, we do think the pandemic may lead to mandated vaccination in order to travel freely, interstate and globally, if not as a means to attend schools and universities, and possibly mandated by employers across the public and private sectors. Mandated vaccination could imply affordability and may necessitate free programs for children and the poor, as well as low or no copays for those with private insurance.

Vaccine Exemptions by State



Source: cdc.gov and West's Ann. Cal. Health & Safety Code § 120335; N.H. Code Admin. R. He-P 301.13; McKinney's Public Health Law § 2164. As of March 27, 2015. Updated February 2017.

To conclude, we are optimistic regarding an eventual vaccine against SARS-CoV2 within the next year or so, though we note that getting vaccinated will not be without risk. The next few months will yield a plethora of data across ~3-4 vaccine programs including other DNA-based vaccine programs we did not have time to discuss. For our part, we firmly believe that, between coordinated efforts across the public and private sectors as well as through philanthropic organizations such as the Gates Foundation, CEPI and others, the strength of global efforts will likely result in multiple vaccines against SARS-CoV2 in the coming months, not years. Regarding supply, we applaud the efforts of the Gates Foundation in particular on the manufacturing side as a means to address what we think will be substantial demand from the global community.

In the end, science will win, and lessons learned will hopefully drive future advances in time for the next contagion, stopping it at an epidemic rather than evolving into a pandemic.

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For more information on COVID-19, please refer to the Center for Disease Control and Prevention at cdc.gov.

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