NEUBERGER BERMAN

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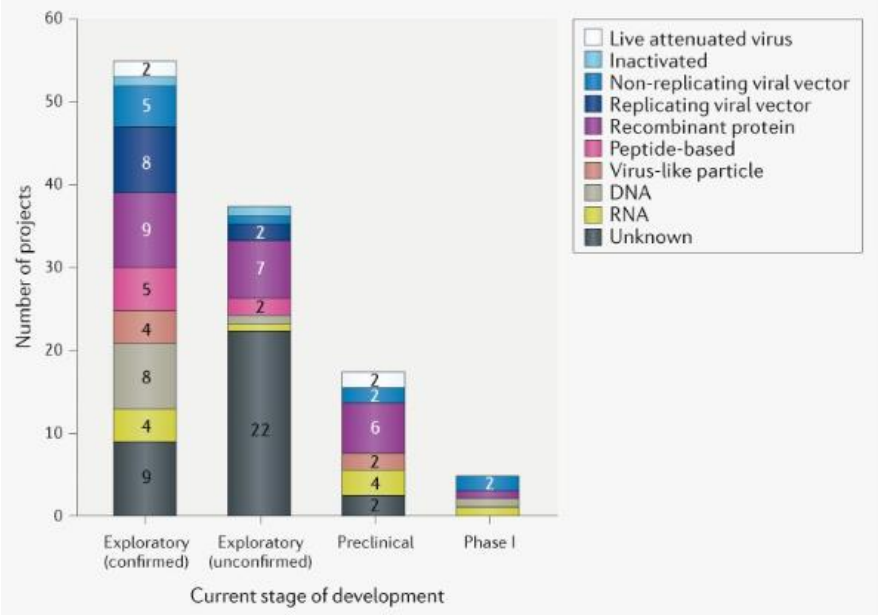
Update: COVID-19 Vaccines in Development

With over 70 vaccine candidates now in development (according to the World Health Organization) targeting SARS-CoV2, we thought we would highlight the programs that appear furthest along, discuss their positive attributes and risks, and offer potential timelines for data. Note that the ultimate goal for the US population is to have hundreds of millions of doses available for the general public by the second half of 2021, though we admit these are aggressive timelines.

While the rush to develop a vaccine to end this horrific pandemic is laudable, we remind readers that the historical timeline for vaccine development has averaged six to eight years more recently, not the 18–24 months we are currently projecting. Advances in technology and novel modalities address some of the speed at which we are operating, but we believe the safety of vaccines is key and should not be overlooked, even in a pandemic with a fatality rate in the U.S. of ~ 4%. Below we walk through what we believe are the most advanced vaccine programs, and offer our views on their odds of success.

No Shortage of Organizations Exploring SARS-CoV2 Vaccine Development

The chart below depicts the number and types of vaccines currently in development by public and private groups, ranging in stages from preclinical studies to clinical trials.



Source: nature.com, "The COVID-19 Vaccine Development Landscape," April 9, 2020

While different modalities are in development, most if not all vaccines we highlight target the Spike protein of SARS-CoV2.

- The SARS-CoV2 virus makes structural proteins and non-structural proteins, the latter of which allow the virus to replicate (i.e., the RNA polymerase, protease). The former structural proteins consist of a membrane (M), envelope (E), nucleo-capsid (N) and the Spike (S) proteins.
- The Spike protein is what the virus uses to engage a receptor on the host cell, called ACE-2 (angiotensin converting enzyme two), which allows it to bind to the surface and gain entry into the cell, begin replicating, packaging itself and then extruding from the infected cell to begin the "multiplicity of infection" into many other cells, resulting in viremia (high titers of virus) in the affected individual.

- Hence, in our view, it is quite logical to develop an antibody against the Spike protein, have it bind tightly to the appropriate configuration, and thereby prevent the virus from getting into the cell so as to prevent viremia.

Passive Immunity as a bridge to vaccine development

- Recall that we have highlighted recombinant antibody programs from the likes of Regeneron and Vir Biotech, which aim to generate antibodies to the Spike protein and passively infuse them into severe COVID-19 patients in an attempt to halt infection. These studies, which are likely to begin enrolling in the next two months from now, expect to report initial data by mid-Fall and represent the lowest risk studies in our view. Also, one could envision these recombinant antibodies, provided they demonstrate safety & efficacy could be used to passively immunize healthcare workers, first responders etc. as early as late 2020, somewhat as a bridge to vaccinations which will likely take longer to develop.
- Additionally, we have spoken about "convalescent plasma exchange," whereby recovered COVID-19 patients who have mounted an immune response to the virus and have since generated antibodies (presumably to the spike protein and presumably neutralizing) donate blood (plasma) to severe patients so as to transfer their protective antibodies directly to the COVID-19 patients. This approach is currently being deployed on an ad-hoc basis, with US studies underway after positive reports out of a study in China as well as other parts of the world. These too could be used to temporarily protect those at the front lines, but may not be scalable and hence the aforementioned recombinant program holds broader appeal.

Only a successful vaccination could achieve immunity on a large scale and protect the population from SARS-CoV2 infection.

The chart below highlights the most advanced vaccine programs in development across multiple modalities, with most if not all targeting the Spike protein. It outlines the positives and negatives and offers timelines for data, the earliest being results from the Phase I healthy volunteer study in late May/early June out of the Moderna mRNA technology program. For our part, we would order the odds of success with traditional protein vaccinations first, although from a timing perspective they will likely take the longest to execute. Regarding newer modalities, we favor mRNA-based approaches over the adenoviral vector systems, but not by much. We are least optimistic about DNA vaccines, given limited if any safety data to date, the risk of genome integration, a lack of humoral immune response and questions around supply.

SARS-CoV2 Vaccines							
	Viral Vectors		mRNA technology		Live Attenuated	Traditional Protein subunit	DNA vaccine
Company	JNJ	CanSino Biologics	Moderna	BioNTech/PFE	BCG vaccine	Sanofi, Vir, Novavax, etc.	Inovio
Positives	Employs rare adenoviral vector so low risk of resistance to vaccine Spike protein target	Employs AAV5 adenoviral vector so safety established Spike protein target	Targets the Spike protein of SARS-CoV2 Rapid turnaround time & cell free synthesis Easily adaptable to mutations		Vaccine commercially available with broad vaccinations of children's in Asia, LATAM etc. Antibodies generated are durable	Traditional vaccine program with BARDA, using tried & true influenza technology	Does not induce humoral immunity, lower risk of ADE?
Negatives	Manufacturing hurdle, host genome integration risk is real but low	Many may be excluded from receiving the vaccine due to baseline antibodies to AAV5	Limited data on efficacy given new technology Immune enhancement a risk Duration of protection is unknown		No direct evidence it works against SARS-CoV2	Longer manufacturing process, awaiting animal toxicity data	May integrate into the host genome
Clinical trials	Studies begin in early summer, JNJ committed to scale up at risk	Phase I began in March , moving to a 500 patient phase II in May	Both mRNA vaccines in healthy volunteer testing, Moderna's data in late May /early June First available for high risk individuals in late 2020		4,000 patient trial underway in Australia, planned in the UK Theory gaining traction globally	Phase I studies to begin this autumn with scale up at risk and capacity in the "multi-millions	INO-4800 currently in Phase I healthy volunteers
NB opinion	Cautiously optimistic given novel adenoviral vector and need to get into the nucleus	No data has been released from the Phase I study to date	Confidence in Moderna's technology based on evidence of immunogenicity and safety in > 1,000 patients to date across 6 different viruses		Data from regions where BCG vaccinations are mandated suggests fewer COVID-19 cases	Safe bet ….Sanofi also partnered with Translate Bio on an mRNA vaccines	Our least favorite as an unproven modality

Source: Neuberger Berman, clinicaltrials.gov, biomedtracker, RBC reports as of April 13, 2020

We are cautiously optimistic on the mRNA vaccines in terms of efficacy, but long-term safety remains an open question.

Moderna's mRNA technology has been used to address six different viruses to date (RSV, H7, H10, CMV, Zika and HMPV-PIV3), with solid safety and tolerability demonstrated, impressive immunogenicity data in healthy volunteers and now in phase II/III studies. Regarding mRNA1273, the vaccine against SARSCoV2, we like the fact that this vaccine targets the full-length Spike protein, including the pre-fusion form which we believe will be important in mounting not only a robust antibody response, but production of neutralizing antibodies as opposed to marker antibodies. Regarding PFE/BNTech BNT-162, we are less familiar with the delivery vehicle used at BioNTech, and are not aware of any other preclinical published data on the technology, but are looking and will report back findings. Finally, regarding Johnson & Johnson's adenoviral approach, we think the careful identification of the antigen is a plus, and have been told by experts that the specific AAV vector subtype used has shown limited if any baseline antibodies in humans, which could reduce risk in development.

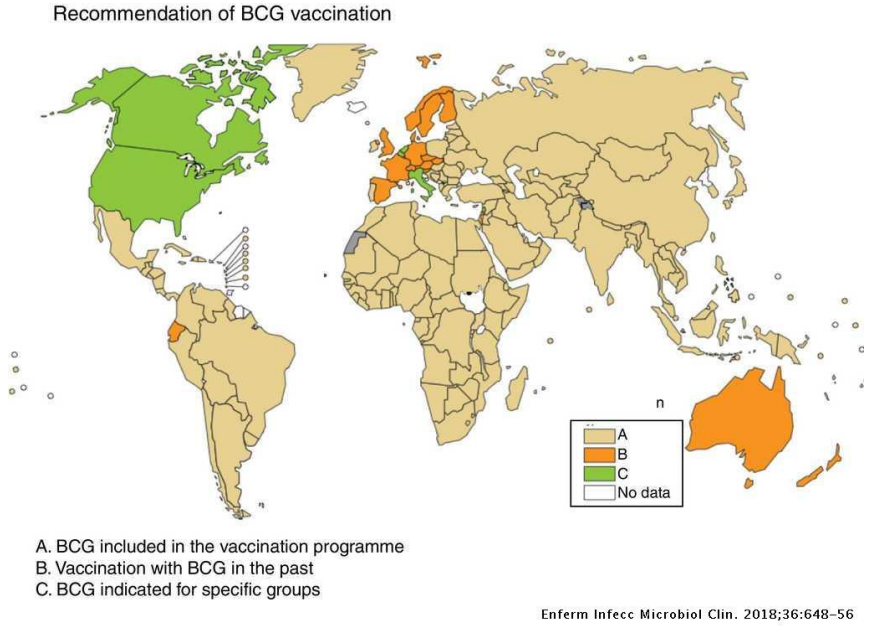
Most importantly, any successful vaccine should produce immunity in at least 85% of subjects tested as the lower bound for success and moreover should produce neutralizing antibodies to SARS-CoV2. While total antibody titer is step one in measuring an immune response, simple marker antibodies may not do much to protect an individual from infection. The key is to have neutralizing antibodies that inactivate the virus upon entry, thereby preventing infection and stopping the transmission of this challenging coronavirus known as SARS-CoV2.

We will leave you with one last thought:

Could the BCG vaccine against tuberculosis afford broad protection against respiratory infections and SARS-CoV2?

While limited if any hard evidence exists, our curiosity has been piqued by emerging links to the BCG vaccine (against tuberculosis) and geographic incidence rates/severity of COVID-19. Perhaps happenstance, perhaps not, we note from the below figure lower rates of infections and fatalities in countries/regions with universal vaccinations of BCG such as Asia, Southeast Asia, Latin America, Iran and Japan (preliminary study published by medRXiv). Notably, the western world has largely moved away from mandatory TB vaccinations with BCG, with examples including the U.S., and Western Europe, where the infection rates and severity of disease is notable. Intriguing dynamic occurring in Germany, where eastern Germany (part of the USSR until 1990, with mandated BCG vaccination of children) has been reported to have lower COVID-19 cases versus western Germany, which may explain the low fatality rate in Germany overall of 2.4%, but we have yet to confirm. Several clinical trials are now underway to answer this question, including a 4,000 hospital-worker study in Australia and five other countries focusing on individuals at the front lines.

Vaccine Regimes May Affect Outcomes



Source: WHO Global Tuberculosis Report 2017. Recommendation of BCG vaccination. The countries where BCG is included in the vaccination program are in beige (A), the countries where BCG vaccination used to be but is no longer done are in orange (B) and the countries where BCG is indicated only in specific population groups are in green (C).

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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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