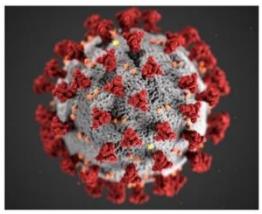
Insight

THE RACE FOR COVID-19 VACCINES

Scientists across the world are working around the clock to develop vaccines against SARS-CoV-2, the virus which is responsible for the COVID-19 global pandemic. Although therapies such as Gilead's newly approved antiviral drug Remdesivir and repurposed decades-old steroid dexamethasone have shown to have some positive impacts against the severity of the disease, a safe and efficacious vaccine is still the best hope for ending the pandemic and returning society to normal.

There are a number of promising vaccine candidates, some of which could lead to vaccines being available as early as the end of this year in our opinion. The implications for our societies, economies and investments could not be greater. That is why we would like to offer an overview of the current efforts and their likelihood of success based on our background and experience in healthcare analysis and immunology. Few of us are epidemiologists or immunologists so we would like to start with basic definitions before discussing the different vaccine candidates in detail.

How does a vaccine work?



Structure of SARS-CoV-2

Source: Centre for Disease Control and Prevention

To understand how vaccines work, let us first look at how our immune system works. When a harmful bacteria/virus enters our body, our immune system quickly recognises it as an invader. It triggers a complex chain of reaction involving many white blood cells (Macrophages, B-lymphocytes and T-lymphocytes) working together to fight off infection. One type of white cell (B-lymphocytes) can make antibodies whose shape has the exact fit to the surface of bacteria/virus like a key (antibody) to a lock (antigen). It takes several days for our body to produce the 'key' (antibody) giving the bacteria/virus time to replicate within our body and possibly make us ill. Once our antibody production factory is fully online and antibodies start to kill bacteria/virus, most of us get better. Our immune system remembers what it learnt about how to protect our body after the recovery and some white cells (T-lymphocytes) have memory and can go into action quickly if we encounter the same bacteria/virus again. B-lymphocytes, which produce antibodies, attack the invaders and protect us from getting ill the next time round.

Vaccines work the same way. They contain weakened or dead bacteria/virus, fragment or a genetic coding of it. They help to develop immunity by imitating an infection but without causing the disease. Our immune system responds as if the real invader has got in and produces T-lymphocytes and antibodies. Sometimes, the imitation infection can cause minor symptoms which is normal as our body builds up its immunity. Once the imitation infection has gone away, our body is left with memory T-lymphocytes as well as B-Lymphocytes that remember how to fight the disease in future.

Overview of Vaccine Platforms

According to the World Health Organisation (WHO), as July 15, there are about 163 vaccine candidates in development and 23 in clinical evaluation around the world. These programs use several different vaccine platforms. Some, such as live attenuated vaccines, inactivated vaccines and recombinant protein vaccines, are well known and are tried and tested, with

J. Stern & Co
4 Carlton Gardens
London SW1Y 5AA
United Kingdom

Tel: +44 20 3478 1800
Fax: +44 20 3478 1799
info@jsternco.com
www.jsternco.com

existing vaccines already on the market and manufacturing facilities in place. Live attenuated vaccines in particular offer a longer and durable immunity and may last for a lifetime. Inactivated and recombinant protein vaccines often require an adjuvant to boost immune response. In theory, the choice of adjuvant is infinite which can provide a great deal of flexibility to enhance a vaccine. The use of an adjuvant is particularly helpful in people whose immune systems do not respond well to vaccination, for example older people. However, these 'traditional' vaccines tend to take a longer time to develop. Other platforms in vaccine development are viral vectors vaccines and nucleic acid vaccines. The viral vector vaccines use weakened viruses as a carrier to bring encoded DNA of antigen (in this case SARS-CoV-2) into human cells. They are popular in veterinarian vaccinations and more recently are used in gene therapies and the prevention of Ebola. The drawback of this type of vaccine is some people have pre-existing immunity to the viral vector itself and hence do not respond to vaccinations.

The newest approach in vaccine development is nucleic acid vaccines, in particular mRNA vaccines, which are currently at the forefront of the race for vaccine development for COVID-19. An mRNA vaccine consists of an mRNA strand that is encoded with SARS-CoV-2 antigen. Once the mRNA strand in the vaccine is inside the body's cells, the cells use the genetic information to produce the antigen which then displays on the surface of the cell. This induces a production of antibodies by our immune system. This technology allows a more rapid generation of vaccine candidates and is particularly advantageous if the virus mutates as the technology can quickly generate new vaccine candidates to target the mutated virus. Manufacturing scale-up is also relatively easy and offers a potential for cost effective manufacturing. One drawback of some mRNA vaccines in their current form is the need to store them at minus 80 degrees Celsius. The industry is working on reformulation of mRNA vaccines that are stable at around 0ºC in refrigerators. In addition, there are no mRNA vaccines on the market currently and therefore their long-term safety profile is unknown.

The table below summarizes different vaccine platforms and examples of companies working on each platform.

	Live Attenuated Vaccines (LAV)	Inactivated Vaccines (IV)	Recombinant Protein Vaccines (RPV)	Replicating Vector/ Nonreplicating Vector Vaccines (RVV/NVV)	Nucleic Acid Vaccines (DNA/mRNA)
Immune Response	Durable, potential lifetime protection with 1 or 2 doses	Shorter Immunity than LAV, generally need booster or adjuvants to sustain protection	Require adjuvants to induce T-cell immune response Generally safer than LAV and IV	Induce immune response without adjuvants with robust T-cell response Pre-existing immunity to the viral vector is a concern but could be overcome	Trials showed presence of binding antibody and neutralising antibody titre at and above convalescent sera
Development Timeline	Slow due to complex handling and safety testing	Shorter to clinic than LAV	Slighter shorter than LAV/IV	Shorter than LAV/IV	Shortest timeline, more adaptable if virus mutates
Scale Manufacturing	Existing manufacturing infrastructure can be leveraged	Existing manufacturing infrastructure can be leveraged	Cell line manufacturing – requiring time to scale	Existing manufacturing infrastructure can be leveraged	Manufacturing process can be scaled-up quickly
Stage of Development	Pre-clinical	Clinical	Clinical	Clinical	Clinical

	Live Attenuated Vaccines (LAV)	Inactivated Vaccines (IV)	Recombinant Protein Vaccines (RPV)	Replicating Vector/ Nonreplicating Vector Vaccines (RVV/NVV)	Nucleic Acid Vaccines (DNA/mRNA)
Examples of companies/ organisations involved	CODAGENIX INC. / SERUM INSTITUTE OF INDIA PVT. LTD.	SINOPHARM, sinovac, valneva	SANOFI / gsk, CSL / Seqirus, NOVAVAX	AstraZeneca / OXFORD, CanSinoBIO, Johnson&Johnson, MERCK / iavi	moderna, Pfizer / BIONTECH, SANOFI / Translate Bio
Examples of existing Vaccines	MMR (combined vaccine) Smallpox, Chickenpox Yellow fever Rotavirus	Hepatitis A Flu Polio Rabies	Hepatitis B HPV Varicella Zoster Influenza	Vector vaccines are used in animal vaccination such as Rabies and Distemper. Gene therapy and Ebola vaccine also use viral vectors	None

Who are the Front Runners?

Three vaccines are currently front runners. These are three mRNA vaccine candidates (the best one will be selected for phase III trial) from Pfizer/BioNTech, one mRNA vaccine candidate from Moderna and a non-replicating viral vector vaccine candidate from AstraZeneca/University of Oxford.

It is generally accepted that people who have recovered from a viral disease will have immunity preventing them from being re-infected, at least for a certain period of time. By comparing the levels of binding antibody and of neutralising antibody titre from those who had vaccines with those who had the disease (i.e. convalescent sera), we get the first indication if new vaccines are effective. Interim phase I data in healthy volunteers aged 18-55 from Moderna and Pfizer/BioNTech are very encouraging. Here are the summaries of the results.

Moderna (mRNA-1273 – Full length SARS-CoV-2 Spike Protein)– Two injections (prime and boost) at 28 days apart using 25 ug, 100 ug and 250 ug dosage in an open label study. The binding antibodies were observed in all participants after the first vaccination at day 15. After two vaccinations, at day 57, the binding antibody level exceeded that seen in convalescence sera. The neutralising antibody titre levels are shown to be at 2.1 (25 ug) and 4.1 (100 ug) times, respectively, of those seen in convalescent sera two weeks after the second dose (day 43) using the live virus assay (plaque-reduction neutralisation test, PRNT80). A similar finding of neutralising antibody titre was observed using the pseudo typed lentivirus assay. Th1-biased CD4 T-cell response (i.e. intracellular response to fight virus) was also observed for 25 ug and 100 ug dose levels following the second vaccination.

Pfizer/BioNTech (BNT162b1 – SARS-CoV-2 Receptor Binding Domain (RBD))– Two injections (prime and boost) at 21 days apart using 10 ug and 30 ug dosage and at 100 ug using a single dosage in a randomised triple blind placebo-controlled trial. The binding antibody levels are at 8 (10 ug) and 46.3 (25 ug) times, respectively, seen in convalescent sera one week after the second dose (day 28). The neutralising antibody titre levels are shown to be at 1.8 (10 ug) and 2.8 (30 ug) times, respectively, of those seen in convalescent sera one week after the second dose (day 28).

Based on the data provided so far, both Moderna and Pfizer/BioNTech vaccines are shown to be safe and well tolerated. Side effects are mild or moderate and transient.

AstraZeneca/Oxford University (AZD1222) – In a blinded randomised controlled phase I/II trial involving over 1,000 healthy volunteers, 95% of participants had a four-fold increase of antibody levels after one month of injection and 100% after the second dose. In all participants, a T-cell response was induced, peaking by day 14 and maintained two months after injection. The neutralising antibody titre were seen in 91% of participants one month after vaccination and in 100% after the second dose. The level of neutralising antibody titre is similar to those seen in convalescence sera. The vaccine is safe and well tolerated. Side effects are temporary. Our recent discussion with the company suggests that the vaccine can provide protection for around 12-24 months. Phase II/III UK trial in 10,000 adult volunteers has been started in May 2020 and more recently also in Brazil and South Africa.

It is important to point out that it is difficult to compare trial data. The important message here is that three vaccine candidates have shown that neutralising antibody titre are at or above the level of the FDA guidance for treatment of COVID-19 using donor plasma (i.e. plasma obtained from people who had COVID-19).

Vaccines Could be Available as Early as the End of 2020

Large phase III clinical trials involving 30,000 healthy volunteers for each lead vaccine candidate are planned in the US. The volunteers will be randomised into two cohorts with 15,000 receiving the vaccine and 15,000 on placebo. The US trials are expected to start in July for all three vaccine candidates.

The FDA recently published a COVID-19 vaccine development guideline that requires the primary efficacy endpoint to be at least 50% above the placebo and the lower bound of the confidence interval should be greater than 30%.

Based on the FDA's guideline, Moderna announced its phase III trial design. The company has chosen 100 ug dose level for this trial. The primary end point will be the prevention of symptomatic COVID-19 disease. The efficacy analysis will be event driven based on the number of participants with symptomatic COVID-19 disease. Two interim analyses are planned when number of symptomatic cases reaches 53 and 108. The final analysis will be conducted when number of symptomatic cases is at 151. The target efficacy is set at 60%.

If these trials demonstrate the regulators' required efficacy and are safe to take for patients, we should have COVID-19 vaccines available before the end of this year.

Other vaccine candidates are also moving fast through the pre-clinical and clinical development. One from Johnson & Johnson is worth noting. It is a non-replicating viral vector vaccine candidate (Ad26.COV2-S) using the same and proven technology platform as its Ebola vaccine which was recently approved by the European Commission. The Ebola vaccine has been tested in 80,000 people already over the past few years and hence its safety profile is better understood. The company plans to accelerate the development timeline for COVID-19 and phase I clinical trial is expected to start in July with phase III potentially start in September. The management believes this vaccine could provide protection at a 70-80% rate (exceeding the FDA requirement of 50%) and durability with a booster dose 1-2 years following the initial vaccination. If

the accelerated clinical timeline can be achieved, the vaccine could be potentially approved by the end of 2020 or early 2021. Johnson & Johnson is committed to provide 1bn doses of vaccine by the end of 2021.

Table below outlines the timeline of the three most advanced vaccines in development.

	Pfizer / BIONTECH	moderna	AstraZeneca / OXFORD
Estimated start time for the US phase III trial	July/2020	27 July/2020	July/2020
Likely dosing	Two Doses, Prime and booster 21 days apart	Two Doses, Prime and booster 28 days apart	Single dose. Potentially a booster within 12-24 months
Estimated time for completion of enrolment	Late August/ Early September/2020	Late August/Early September/2020	Not disclosed
Estimated time for observing efficacy	September/2020	Event driven with two interim analyses at 53 events and 106 events, final analysis at 151 events Potentially September/October 2020	Not disclosed
Estimated earliest time for filing	October/2020	November/2020	Not disclosed but expect before the end of 2020
Doses Available in 2020	100m doses	Not disclosed, but potentially 100-200m doses	700-800m doses (including 400m doses delivered by Serum Institute of India to low income countries)
Doses available in 2021 and beyond	At least 1.3bn doses	Committed to 500m doses and potentially up to 1bn doses	2bn doses (including 1bn doses delivered by Serum Institute of India for low income countries)

Do We Have Enough Doses for Everyone?

Finding a safe and efficacious vaccine is only the first step. COVID-19 is a global pandemic and requires a global vaccination of two thirds of 7.8 billion people to achieve herd immunity. It is a massive and demanding task for manufacturing and distribution. In normal vaccine development timelines, companies would wait until a successful clinical trial is concluded before starting to manufacture at scale and to build vaccine inventory. That would take too long to get vaccines onto the market.

This time is different. Manufacturing of the vaccine at an industrial scale is being created simultaneously with the clinical trials that are expected to demonstrate efficacy and safety. Some companies are doing this at their own risk and others are receiving financial support from governments and charitable foundations. Although this fast-track approach has increased the financial risk, it does not increase the product risk.

Source: Becton Dickinson

In the US, the government has set up the most ambitious program called Operation Warp Speed (OWS) with a budget of over $10bn. The aim is to deliver 300 million doses of safe and effective vaccines for COVID-19 by January 2021 for Americans. The program identifies

the most advanced and promising vaccine candidates and provides co-ordinated government support. Protocols for clinical trials for demonstrating safety and efficacy are overseen and set by the federal government. This allows trials to proceed more quickly. The US government has already provided significant funding for clinical development and for manufacturing, also providing financial support for capacity expansion in fill & finish (i.e. putting vaccines in vials or pre-filled syringes) and in production of needles & syringes in preparation for mass vaccination. It is setting up plans and infrastructure necessary for a speedy distribution of vaccines by deploying the US Army once the vaccine is ready.

A supply agreement has been reached between the US government and AstraZeneca to supply 100m doses in 2020 and 300m doses in total by the first half of 2021.

Examples of Companies Receiving Funding from the US Operation Warp Speed

Vaccines Companies	Funding Received	Stage of Development	Platform
Johnson & Johnson	$465m	Phase 1 in July	Non-replicating viral vector (Ad26)
AstraZeneca / University of Oxford	$1.2bn	Phase 2/3	Non-replicating viral vector (ChAdOx1-S)
moderna / NIH National Institute of Allergy and Infectious Diseases	$483m	Phase 2 Phase 3 in July	RNA (LNP-encapsulated mRNA)
MERCK / iavi	$38m	Pre-clinical	Replicating viral vector rVSV
NOVAVAX	$1.6bn	Phase ½	Protein subunit – full length recombinant SARS Cov-2 glycoprotein nanoparticle vaccines adjuvanted with Matrix M
VAXART	Funding for non-human primate (NHP) challenge study	Pre-clinical	Non-replicating viral vector – oral vaccine

Manufacturing Companies	Funding Received	Purpose of Funding
emergent biosolutions	$628m	Manufacturing of vaccines and therapies for COVID-19
apiject	$138m	Supply 100m pre-filled syringes by end of 2020 to the US government Capacity expansion and supply 500m pre-filled syringes in 2021 to the US government.
CORNING	$204m	Capacity expansion to produce additional 164m Valor glass vials
SiO2 Materials Science	$143m	Capacity expansion for glass-coated plastic containers
BD	$42m	Capacity expansion in injection devices and supply 50m vaccine injection devices in 2020 to the US government

Elsewhere, the UK government has provided £65.5m funding to AstraZeneca/University of Oxford to supply 30m doses of its vaccines from September 2020 and 100m doses in total by the first half of 2021 for the UK population. It has also announced supply agreements with BioNTech to purchase 30m doses of mRNA vaccines and with Valneva to purchase 60m doses of inactivated viral vaccines. The UK government is betting on vaccines from

three different technology platforms in case some phase III trials are unsuccessful. In addition, it has provided £18.5m funding to Imperial College for development of its mRNA vaccines.

In June, the European Commission published an EU vaccines strategy which has two pillars: (a) securing the production of vaccines in the EU and sufficient supplies for its member states and (b) adopting the EU's regulatory framework to the current urgency and making use of existing regulatory flexibility. Significant funding will come from €2.7bn Emergency Support Instrument and loans from the European Investment Bank. AstraZeneca has signed an agreement with Europe's Inclusive Vaccines Alliance (IVA), spearheaded by Germany, France, Italy and the Netherlands, to supply up to 400 million doses of vaccine with deliveries starting from the end of 2020.

China is also forging ahead with its vaccine development. Combining the effort from academic research institutes, military research and private companies, China is behind seven out of 24 vaccines currently in clinics. The most advanced development is from Sinovac currently in phase III. The main focus of the Chinese effort has been on proven technology such as inactivated viral platform and viral vector platform. As these technologies are better characterised especially from the safety standpoint of view, they have a good chance of success.

Rich countries will not be safe until the entire world has the vaccine. As such the developed world has the responsibility and an interest to make a vaccine universally available and to ensure equitable access and fair allocation. Companies like AstraZeneca have already signed an agreement with international organisations like the Coalition for Epidemic Preparedness Innovations (CEPI) and Gavi, the Vaccine Alliance to supply 300m doses of its vaccine. AstraZeneca also signed an agreement with the Serum Institute of India to produce up to 1bn doses of vaccine for low-to-middle income countries with a commitment to provide 400m doses before the end of this year.

Challenging Path Ahead but Optimism will Prevail

Whilst the accelerated development programs have so far yielded promising short term efficacy and safety data, question marks remain on the durability of immunity, as well as the long-term safety of these vaccines. It may well turn out that the first generation of vaccines are not optimised and are only partially effective. But they will at least offer some immunity or make the disease less severe so society can get back to a certain level of normality. This also buys us time to work on a more efficacious second and third generation of vaccines that will provide well characterised long-term safety profiles, and potentially a more durable response. Some experts believe Sars-Cov-2 will be living with us for a long time and annual vaccination (like flu) may be required. Nobody really knows the exact path we need to follow to bring the pandemic to a stop. It may require combination therapies involving existing and new therapeutics as well as the use of both flexible and traditional vaccines in order to keep up with potential recurrences of the virus, as well as different strains and mutations.

However, with unprecedented global cooperation, thousands of scientists working around the clock and significant financial and regulatory support from various governments, we have good reason to hope that safe and effective vaccines will be with us sooner rather than later.

Zhixin Shu, PhD, CFA
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