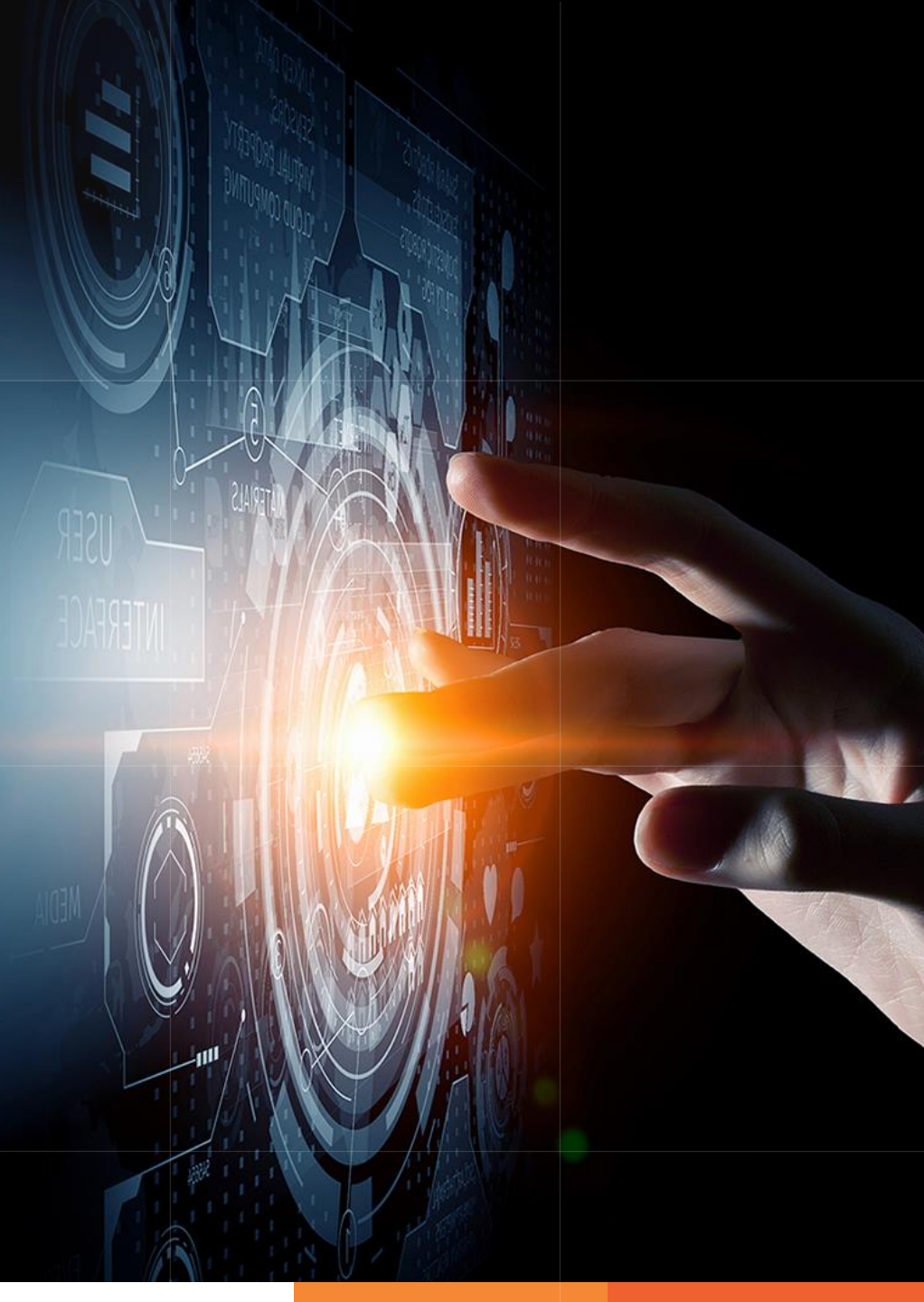
COVID-19 vaccines

November 2020



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Pfizer BioNTech COVID-19 vaccine

Light at the end of the tunnel?

What we know about the Pfizer solution.

- Pfizer has made two press releases relating to its vaccine in the past two weeks
- It's an mRNA vaccine candidate, named BNT162b2.
- The vaccine encodes the SARS-CoV-2 spike (S) protein, modified slightly to lock it into a "prefusion conformation". This is delivered in lipid nanoparticles.
  - The vaccine immune response will target the encoded protein.
- The vaccine demonstrated 95% efficacy on the "final efficiency analysis" in its Phase 3 trial, based on 170 cases of infection.
- Ten severe cases of COVID-19 were observed with only one of these in the vaccinated group.
- The trial has involved 43,661 participants and is ongoing.
- The trial has included participants with ethnically diverse backgrounds across 150 sites globally. 41% of the global participants are of 56 to 85 years of age.
- No serious safety concerns identified.
- It requires two doses.
- Pfizer expects to apply for Emergency Use Authorisation any day now.
- Pfizer is claiming they can produce up to 50 million doses in 2020 and 1.3 billion in 2021.
- The vaccine requires long term storage at around -70 C, but Pfizer believes transport is manageable utilising its cold-chain infrastructure.

Moderna COVID-19 vaccine

A second light at the end of the tunnel?

What we know about the Moderna solution.

- Barely a week after Pfizer's first announcement, Moderna announced early data on the Phase 3 trial of its vaccine.
- It's an mRNA vaccine candidate, named mRNA-1273.
- The vaccine encodes the full length prefusion stabilised S-protein and is delivered in lipid nanoparticles (though likely a different formulation to Pfizer's).
- The vaccine demonstrated 94.5% efficacy on the "first interim analysis" in its Phase 3 trial, based on 95 cases of infection.
- Eleven severe cases of COVID-19 were observed, all in the non-vaccinated group.
- The trial has involved greater than 30,000 participants and is ongoing.
- The trial has included ethnically diverse backgrounds, and a significant percentage of medically high-risk groups (42%).
- No serious safety concerns were identified with most side effects considered mild or moderate.
- It requires two doses.
- Moderna expects to apply for Emergency Use Authorisation within the next few weeks.
- Moderna is claiming it can manufacture 20 million doses by the end of 2020 and 500 million to 1 billion by the end of 2021.
- The vaccine remains stable at 2 C to 8 C for up to 30 days (normal refrigerator temperature).

AstraZeneca/University of Oxford COVID-19 vaccine

The third light?

What we know about the AstraZeneca/University of Oxford solution.

- In the past 24 hours AstraZeneca made an announcement on its candidate.
- It's an Adenovirus based vaccine candidate, named AZD1222.
- The vaccine is a replication deficient simian adenovirus vector that contains the full-length S-protein.
- The modified adenovirus infects the recipient's cells, eliciting an immune response. The virus is incapable of reproducing.
- The vaccine demonstrated 90% efficacy with a half dose followed by a full dose at least a month apart (based on 2,741 observations) and 62%efficacy with two full doses at least a month apart (based on 8,895 observations).
- This interim analysis was based on 131 COVID-19 cases, with no severe cases in recipients of the vaccine.
- Currently the trial has over 23,000 participants across the UK and Brazil and it intends to expand this to up to 60,000 participants globally. It intends to enrol a diverse group of participants by ethnicity and underlying medical conditions.
- No serious safety concerns were identified.
- AstraZeneca is preparing regulatory submissions for countries with conditional or early approval frameworks, plus an Emergency Use Listing from the World Health Organisation for an accelerated pathway to vaccine availability in low-income countries.
- AstraZeneca claims it can manufacture up to 3 billion doses of the vaccine in 2021.
- The vaccine remains stable at 2 C to 8 C for up to six months.

Comments

- High efficacy shown in the trials is highly promising. It shows vaccination against SARS-CoV-2 is possible and that it can be highly efficacious. It is also positive that this has been confirmed in multiple independent trials:
  - But the results haven't been peer reviewed and trials are ongoing – numbers could change.
  - We also don't know how long lasting the protective immune response is – it could be short. All studies to date suggest this is possible.
- The Moderna and Pfizer vaccines are similar in terms of efficacy. The AstraZeneca vaccine has similar efficacy with one of the two dosing regimes, but this is based on a much smaller population of recipients.
- The AstraZeneca vaccine is much more stable than the other two at higher temperatures. This will make transport and use in the developing world much simpler with this candidate. This is expected given the instability of RNA. The Moderna vaccine remains stable at refrigerator temperatures for a reasonable period of time (one month) whereas the Pfizer vaccine requires very low temperature storage, which will make distribution more difficult.
- No safety issues is promising, though there are suggestions some side effects could be higher than normal.
- As the response to a vaccine and viral infections can vary across different groups, it is positive that the trials have addressed this by inclusion of a number of different medical risk, age and ethnic groups.
- mRNA vaccines have not been used in humans previously, which means facilities to manufacture the vaccine won't be as widespread as for traditional vaccines. While adenovirus-based vaccines have not been widely used previously, it appears they can be manufactured in many existing facilities. The cost to manufacture is also expected to be considerably lower than for the mRNA-based vaccines.
- mRNA based vaccines work by introducing the mRNA into the recipient's cells where it is translated into protein. This provides the target for the immune response. As it mimics in some ways an actual viral infection, this can (in theory) generate a more effective immune response than some other more traditional technologies.
- As adenovirus-based vaccines infect the recipient's cells, this should elicit a similar type of immune response to the mRNA vaccines. However, it has been suggested that immunity to the adenovirus itself could also occur, which may prevent future revaccination. This may explain why the half dose followed by full dose regime was more effective. Pre-existing immunity to the adenovirus is also possible, which could reduce the efficacy of the vaccine in some people.
- We don't know how the viral population will adapt to the vaccines – it depends on the specific target of the vaccine and how well conserved this is.
  - Using the full S-protein means potentially more antibody targets are available (called epitopes), which could reduce this risk compared to a more targeted vaccine, but still unknown.

Summary

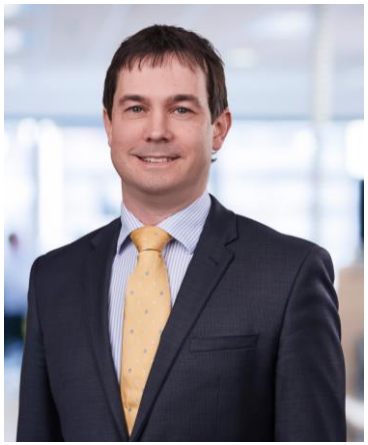
- High efficacy shown in the trials is highly promising. It shows vaccination against SARS-CoV-2 is possible and that it can be highly efficacious. It is also positive that it has been confirmed in multiple independent trials.
- The broad range of groups being included in the trials is beneficial as efficacy and safety can vary across different population groups.
- Each vaccine has pros and cons:
  - The AstraZeneca vaccine is cheaper to manufacture and can be transported at higher temperatures. This will make it a more viable candidate in less developed countries. It also appears that it can be manufactured in existing facilities (CSL has already commenced producing the vaccine in Australia for example). Many more doses are expected to be manufactured in 2021 for this vaccine than the other two. However, there is a question around recipients developing immunity to the vaccine vector itself which could prevent later revaccinations.
  - The Moderna vaccine is reasonably stable at higher temperatures, but for a much shorter period than the AstraZeneca vaccine. The Pfizer vaccine requires storage at dry ice temperatures (-70 C) which makes transport and storage more difficult. Both have a higher efficacy than the AstraZeneca vaccine.
- The duration of the protective immune response generated by the vaccine candidates is still unknown. A short lived protective immune response will reduce the effectiveness of a vaccine as a tool for controlling the pandemic.

Author:

Dr Martin Thompson is a Senior Consultant at Frontier, having joined the firm as an Associate in 2009.

Previously Martin has worked in technology commercialisation at the University of Melbourne and the Bio21 Institute, and virology research at Murdoch University. Immediately prior to joining Frontier, Martin worked at Starfish Ventures, an Australian venture capital fund manager focused on high growth life sciences, information technology, and clean technology companies.

Martin has a Master of Applied Finance through Macquarie University, a PhD in Molecular Cell Biology, and a Bachelor of Science with first class honours in Microbiology.



Level 16, 222 Exhibition Street
Melbourne, Victoria 3000
Tel: +61 3 8648 4300

frontieradvisors.com.au
@frontier_adv

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