COVID-19 Pandemic: The Road to a Vaccine

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Introduction

In April 2020 we shared a conversation with Professor Gerry Graham, Chair of Immunology at Glasgow University. This provided an insight into the scientific nature of the COVID-19 coronavirus in the context of pandemics, how the spread might evolve, and the potential government and scientific responses. With regards to treatment options, Professor Graham suggested three broad options which were being explored: anti-virals, cytokine blockers, and vaccines. Both anti-virals and cytokine blockers are now being used on a regular basis to reduce the severity of disease in hospitalised patients and are seen as important resources to reduce mortality and healthcare costs. A vaccine for COVID-19 has yet to be approved, and despite the media assuming success is a sure bet, a difficult journey to approval remains ahead. However, rapid progress has been made.

Despite the now widespread usage of anti-virals, cytokine blockers, and a host of other strategies (such as dexamethasone and interferon β) the effects of the COVID-19 coronavirus pandemic on both general health and the global economy are meaningful and potentially sustained. Just to give an indication of scale: 188 countries have now been affected with more than 16m cases and over 600,000 deaths confirmed worldwide though there have been persistent misconceptions in several important areas of reporting on the pandemic such as how to measure mortality rates. Healthcare services and economies around the world continue to feel the effects of the virus and the abrupt changes it has wrought on everyday life. A credible, effective vaccine is a vital and significant step forward in the fight to quell the global pandemic caused by COVID-19. Large-scale immunization is a prerequisite to minimising the mortality rate and the evolving economic damage. It can be difficult from the, sometimes breathless, commentary on potential vaccines to gauge vaccine progress. The purpose of this paper is to provide an update on the development of a vaccine for COVID-19 and a potential timeline for its approval and roll-out balanced against the likely pitfalls that may occur along the way.

Misconceptions – Progress of the Pandemic and Mortality Rates

One of the issues with science is that terms tend to have a fairly precise meaning which can easily be misinterpreted when they reach public and political domains. To give an extreme example, in some jurisdictions, if someone with COVID was knocked down by a bus they would be classified as a COVID-related death. This simply emphasises the need to take great care with statistics and inferences drawn from data by non-specialists. Also, as noted above, there are a number of misconceptions circulating in the public domain which may well affect government policy and which are worthwhile clearing up before we proceed to a discussion on a potential vaccine.

The first of these is the notion that the US is experiencing a second wave of the virus. The reality is that parts of the US – namely, the southern and western states – are experiencing a rise in infections which can be traced to the rapid lifting of lockdown restrictions by state governors. However, as is shown in Figure 1, whilst there has indeed been a recent surge in cases in states such as Florida, Texas, and Arizona, it is not because these states are experiencing a second wave of the pandemic. Rather, these states are in their first wave of infections. A single chart mapping cases for the entire US is, then, the aggregate of two different experiences which combined makes it look like a second wave is underway.

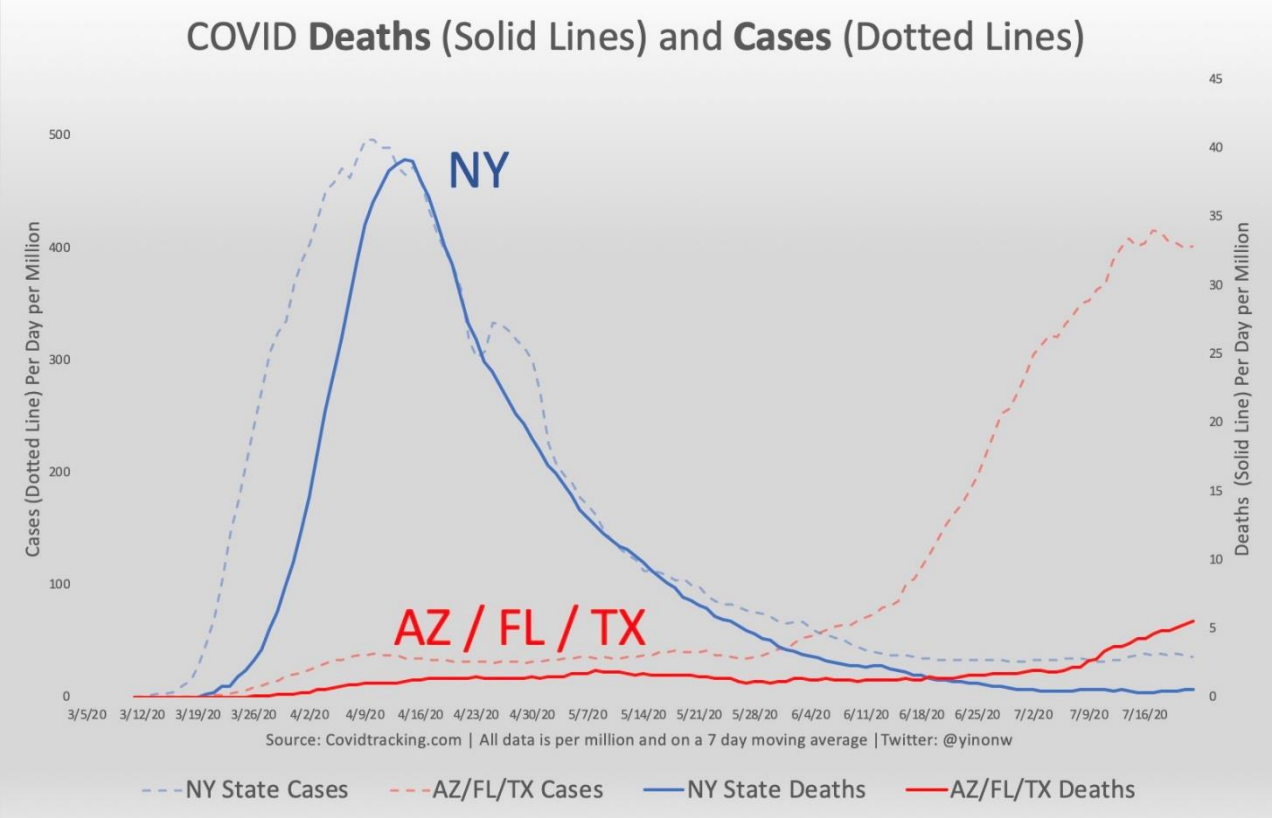

Figure 1: Comparative COVID infections (covidtracking.com and www.twitter.com/yinonw)

A second area that merits some consideration is mortality. For some, lower mortality rates in the US provided some comfort against the rise in infections. A significant part of this was simply the time lag between infection and the virus taking hold. However, mortality rates have certainly declined. There are several explanations for this. The disease is particularly dangerous for those with pre-existing conditions and much of the early deaths can be explained in this way. The corollary is that the age cohort of those now infected is significantly younger and more resilient. Secondly, the medical profession has quickly learned from the experience of treating patients and this will have impacted treatment regimes which have also benefitted from the availability of anti-viral drugs.

Notwithstanding the decline in mortality rates, the virus remains highly efficient in its ability to transmit meaning that the need for a vaccine has not diminished.

The Current Vaccine Situation

Globally, there are over 100 discrete vaccines in development for COVID-19 at companies, universities, and state-funded laboratories. Most of these candidates are in the very earliest stages of development and testing but a handful of frontrunners have now moved into Phase II or Phase III trials with their candidates. This group includes large, public companies such as Sanofi, AstraZeneca (in concert with Oxford University), and Pfizer as well as smaller companies such as BioNTech, Novavax, CanSino, and Moderna.

The companies in this frontrunner group have utilised a variety of different technologies in the development of their vaccine candidates; most of which involve imparting immunity by injecting either the whole COVID-19 virus (in a dead or attenuated form) or a portion of the virus such as genetic information or a part of one of the viral proteins. The other main technology currently under investigation is called a viral vector. This method uses a live version of another virus (such as a flu or cold virus) which has been weakened to carry DNA fragments of the COVID-19 virus into a subject's cells and induce an immune response.

What Does the Data Suggest?

A vaccine is used to generate an immune response in the inoculated individual such that, should this individual come into contact with the virus, the body will react to either prevent infection or reduce the severity / longevity of infection. When we speak of an immune response, we mean the body's creation of proteins called antibodies and white blood cells called T-cells which circulate in the blood, prepared for an attempt by a specific virus to infect the body. Antibodies neutralise virus particles by binding to them so they cannot enter and infect cells. In general, the higher the number of antibodies – and the longer they remain in an individual's bloodstream – the more robust the immune response. T-cells, on the other hand, kill cells already infected with the virus. A vaccine which can show it precipitates a good number of neutralising antibodies and attacking T-cells stands a reasonable chance of providing some form of protection from COVID-19.

The clinical data we have seen so far from the likes of AstraZeneca / Oxford University, Moderna, and Pfizer / BioNTech, though very early stage, is encouraging. Phase I / II trials are used to establish dosing and safety, not to establish efficacy – this comes in Phase III. That said, we do have some clues as to the potential benefits. So far, the candidates farthest along in development have been shown to be safe for human use and dosage has been established to be reasonable and not onerous. Encouragingly, the data are also showing that these vaccine candidates are all stimulating at least some sort of immune response in inoculated individuals. None of them is, so far, proving to be a sure bet but it is a positive sign that antibodies and T-cells are at least being generated. Large scale trials which establish efficacy, or lack thereof, in thousands of individuals are now needed to see if any of the candidates provide enough immune protection to gain approval as an effective vaccine. The best scientific advice we are getting suggests a vaccine which offers some form of efficacy, such as reducing the severity of the disease, is likely to be widely available in the first half of 2021.

It is important to note that a lot of media attention has recently been given to stories of governments underwriting promising vaccine candidates by signing agreements to purchase millions of doses. Several drug companies have even already started to manufacture doses of their candidate vaccines. This has incorrectly led some to assume that these vaccine candidates have the necessary efficacy and are effectively approved with Phase III trials simply a regulatory hoop to be jumped through. This is definitively not the case – a vaccine will need to show efficacy to be approved. This cannot be achieved in the test tube and requires full-scale trials in thousands of people. Governments are underwriting plausible candidates to allow companies to begin manufacture, so that if the vaccines work they will be immediately available. The governmental underwriting of financial risk is necessary to shorten the critical path to market.

Timeline for Approval and Roll-Out

Under normal circumstances, vaccine development typically takes five to ten years from the discovery of a potential candidate through to approval. Most companies involved in developing COVID-19 vaccine candidates are trying to gain approval in a matter of months. For example, AstraZeneca and Oxford University are suggesting Phase III data will be available in late summer and, if approved, the vaccine itself could be available in Q4 2020. Below is an illustration of the best-case timeline from the announcement that a viral cluster was identified in Wuhan to the potential shipping of approved vaccine doses by Oxford and AstraZeneca:

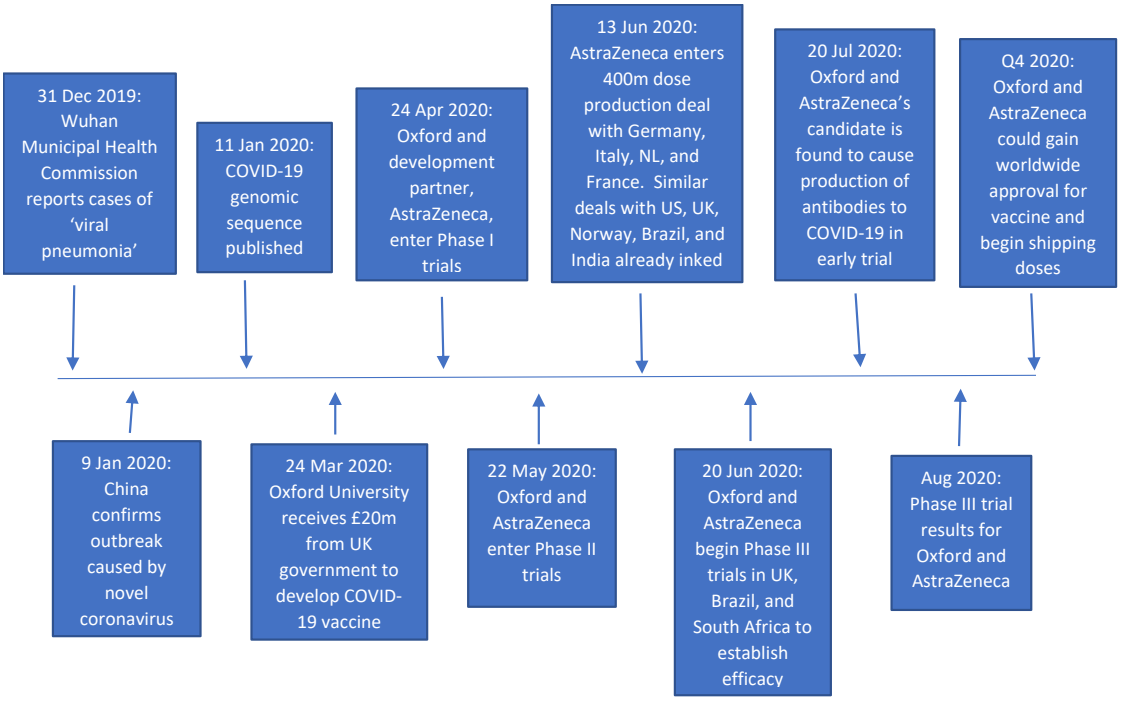

Figure 2: COVID-19 vaccine approval timeline – best case (Edinburgh Partners research)

If such a timeline were to come to pass, it will be a remarkable achievement – one that would not have been possible just 10 years ago. Even if a credible vaccine took several more months to reach the market, such a feat would be revolutionary. Advances in genetics, genomics, proteomics, etc. are allowing us to understand the nature of viruses and the diseases they cause in a way not possible before and more efficiently develop treatments to address them.

However quickly an approval might come, it will likely take some time to ramp-up the scale of manufacturing and the first doses are likely to go to frontline healthcare workers and certain vulnerable groups. If everything goes smoothly, large-scale inoculation of the global population is likely to take place throughout 2021 into 2022. Perhaps not surprisingly, most of the countries that have signed agreements with drug companies to buy vaccines doses are the rich Western countries like the US, UK, and much of Europe. A portion of doses will be set aside for humanitarian usage, but it is likely a great deal of the world's poorest people will face what could potentially be a significant wait for any approved vaccine. This may well exacerbate existing economic disparities.

Where Could Things Go Wrong?

Whilst a sense of hope is building in the wake of potentially promising early trial data, it is important to remember that there is a long road between where we are today and having a viable, effective vaccine approved and manufactured on a global scale.

The biggest risk is that a truly effective vaccine remains elusive for some time. This could be because none of the frontrunning candidates ends up producing a potent enough immune response and we are forced to wait to see if any of the earlier-stage candidates prove to be any more effective. Whilst a less-than-optimal vaccine could still help by reducing the severity of the disease, thereby lessening the strain on healthcare services and economies, it may be that the virus is still able to spread in the community and, therefore, some form of social distancing or spot lockdowns are still required for the foreseeable future.

There is also the risk that the virus remains a long-term threat even if an effective vaccine is found. There are a few reasons why this could occur. The first is that the COVID-19 virus could mutate such that the vaccine is no longer effective against it. However, it should be noted that, whilst there was some mutation early in the pandemic, the COVID-19 virus appears to be a 'slow mutator' and has not yet undergone any

significant changes in form or function. The second reason is that the immune response generated by the vaccine may not prove to be very durable. Some data is suggesting that antibodies in individuals who have gotten and then recovered from COVID-19 only remain in the body for a few months. If the immune response is not durable, there is the potential of having to vaccinate repeatedly. This introduces issues over the short-to-medium term when trying to get billions of people inoculated once, let alone multiple times.

The final risk worth considering is that manufacturing a vaccine on a global scale could prove to be an immensely challenging undertaking. Vaccines are complex, biologic products which require equally complex manufacturing, quality control, safety, and fill / finish processes. There is a very real risk that a company with an approved vaccine may run into issues when attempting the manufacture and distribution of hundreds of millions of doses, given stringent safety protocols and strict requirements for everything from the temperature at which the vaccine is shipped to the way the vaccine is put into glass vials. Such challenges should prove surmountable but may take a significant amount of time to work out and are important to consider when attempting to estimate when a vaccine may be available on a large scale.

Conclusion

The world needs a vaccine to begin to put the COVID-19 pandemic behind us and focus on repairing the societal damages it has wrought thus far. Whilst early data from the most advanced vaccine candidates is encouraging, it is nonetheless important to remember that nothing is certain in drug development and a vaccine could still be a long time coming.

However, if we remain optimistic and imagine a world in which a credible vaccine is available in the first half of 2021, then there is a decent chance that life may begin to look slightly more 'normal' again. That said, the reckoning with the impact of the COVID-19 virus will only just be beginning. Healthcare costs are likely to rise as we begin to diagnose and treat those whose care was delayed due to the virus and as we begin to better understand and deal with the long term mental and physical effects the virus has on many of its victims.

A public reckoning as to how governments are to pay for these rising costs as well as all the fiscal stimulus needed over the past several months will have to occur. Austerity and / or tax rises at some point will have to be considered even if the current prevailing mood seems to be that the current fiscal and monetary responses are cost-free. The global economy is unlikely to bounce back in a so-called v-shaped recovery due to the lingering impact of the virus on employment and consumption in many markets. All this may mean a prolonged recession with a potential rebasing of equity markets due to lower profits. So, whilst a vaccine would be excellent news and would, in most cases, make a real difference in our fight against COVID-19, the economic fallout is likely to be with us for some time to come.

Lauran Halpin August 2020

About the Author

Lauran Halpin MSc, BA: Lauran Joined EP in November 2013 from Baillie Gifford with 7 years of investment experience. Lauran Joined Baillie Gifford in September 2007 as a graduate trainee, where she undertook a three year rotational programme spent analysing European and North American Equities as well as Corporate Bonds. In June 2010, she was made Baillie Gifford's global Healthcare analyst. Whilst at Baillie Gifford, she managed the Glenfinlas Global Healthcare fund. The fund was an unconstrained, global best ideas in Healthcare fund.
Lauran has an MSc. in Ecological Economics from University of Edinburgh 2005 and BS. in Biology from Davidson College (North Carolina, USA) 2003.

Lauran is responsible for researching the global Healthcare and Automotive sectors and assisting in the management of client portfolios.

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