How have the Covid-19 vaccine been developed safely but also under a year?

## Introduction

A new disease was first reported in Wuhan, China in December of 2019 after a group of patients began showing pneumonia symptoms of an unknown cause. It was named “severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)” – Covid-19 for short - on 11th of February 2020 due to its genetic similarities to the coronavirus responsible for the SARS outbreak in 2003. In its original report on January 5th 2020, the WHO stated there was ‘no evidence of significant human-to-human transmission’. Little was known about the virus that was set to reshape the world in the year to come.

It was declared a pandemic on the 11th March 2020. By the end of the same year, the Sinovac, Pfizer-BioNTech and Oxford-AstraZeneca vaccines had been approved and by January of 2021 all three were in circulation. It seems the impossible had been made possible; in 13 months, decades of work had been done. The vaccines had been tested and approved while, under normal circumstances, it takes, on average, ten to fifteen years. However, this leaves many to question the safety and validity of the results. How could these vaccine have been developed so quickly while it took years to do so for others?

To understand this, one must first understand the process of clinical trials, why they have been developed and what slows the process only with that knowledge can the vaccine process for the Covid-19 vaccines’ be assessed.

## The Clinical Trails Process

Throughout human history, many medicines have come and gone but it is not until relatively recent history that something similar to modern day Clinical Trial had been developed. The 1747 scurvy trial, by James Lind, contained most of the characteristics of a controlled trial and in 1943 there was the first double blind controlled trial of patulin for the common cold. The early 1800s ushered in the arrival of the placebo though it was not used in clinical trials until 963. Governments began recognising the need to provide some form of regulation on these trails in the 20th century. In America, the Food and Drug Administration (FDA) found its foundation in the 1906 Pure Food and Drugs Act, though it was known by a different name, and, in the UK, The Medicines and Healthcare products Regulatory Agency (MHRA) was developed soon after the Thalidomide incident in the 1950s.

Currently, the clinical trials process is divided into four distinct phases however this process arose after several incidents such as the Thalidomide Scandal. It became apparent, after these events, that more regulations were needed in order to guarantee the safety of the drugs that were being used. Thalidomide is a drug that was developed in the 1950s, originally intended as a tranquiliser though was used for treating many other conditions such as the flu, nausea and morning sickness in pregnant females. While there is evidence of it passing safety tests on animals – in some cases, dosages of over 600 times the normal human dosage had no effects on rodents – there is little in the way of testing on humans. Upon being released to the wider public it became common treatment for relieving symptoms caused by pregnancy, despite never having been tested on pregnant ladies. It was not known, at the point of release, that the drug could pass through the placenta and cause harm to the foetus. For children whose mothers had consumed thalidomide whilst pregnant with them, the death rate at or shortly after birth was 40% and many children, if they survived, were born with life altering birth defects. This incident forced governments and medical authorities to review their licensing policies and as a result the way drugs were tested and inspected improved internationally. Regulatory developed to help maintain the quality and safety of the drugs released.

The four phase process currently in use is optimised to ensure the safety of the drug and it has become mandatory that all treatment is tested in humans, including the target bracket. According to the FDA the phases are as follows:

* Phase 1: the new treatment is given to a small group of health volunteers with the aim of ensuring the new medicine is safe and to determine dosage. It is also determined here if the drug it could offer therapeutic value. Approximately 70% of drugs are successful within this phases and move onto Phase 2
* Phase 2: the drug is tested on a larger group of people – up to several hundred - with the target disease or condition. Here, the efficiency is tested and side effects are looked for. Around 67% of drugs fail at this trial.
* Phase 3: a much larger group of patients, a few thousand, are tested. Once again, this look for the efficiency but now also looks at less common adverse reactions. Around 25% of treatments or vaccinations make it past his phase.
* Regulatory Review: At this point, regulators check the evidence collated over the years it took for this process to take place and it is determined which patients qualify for the treatment. After this the drug can be launched.
* Phase 4: Post-release, the drug goes through a fourth phase, with several thousand patients where the safety is once again tested and further data is collected – such as how the drug interacts with other medicines, or long term effects. It is significant that Phase 4 is not carried out until after release meaning that many – if not all – of the drugs that are approved are done so without knowledge of all the long term effects. The evidence available is examined to predict what, if any, long term effects there are to the drug and a judgement is made from this.

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This process is prolonged by several variables that remain constant throughout; administrative dealings, financing and the Regulatory bodies.

## Rate Limiting Factors in New Drug Development

Before the in human Clinical Phases explained above can take place, there must be pre-clinical trials. This includes examining the safety of the new medicine, looking at toxicity and if the drug has possibility to help often within animals. This process has raised a few controversial questions of its own. It has recently come under scrutiny for how ethical it is to be testing on animals, as there are other options such as computer run simulations. Pre-clinical trials, and finding a compound that with therapeutic value, can take upwards of two years.

The total cost of developing a new drug, on average, supersedes US $1 billion. The company running the clinical trial must find some way of attaining this funding and most of the time it will be sources by financers, who need to be assured the research ‘is important and addresses a clear need, well designed, feasible and scientifically valid, and offers value for money.’ This will inevitably increase time between phases, prolonging the process. Finally, actually recruiting enough volunteers can add years to the whole process. In an interview with Matt McCarthy he said ‘it can take years to recruit two, three hundred people into a […] study.’ Patient recruitment makes up about 30% of the trial process which consequently increase the time taken for a clinical trial programme. Internationally, more than 80% of trials ‘fail to enrol on time resulting into an extension of study’

If all these things can be more easily achieved, it would significantly decrease the time a clinical trials takes. However, the introduction of regulatory bodies has also increased time. As there are so many drugs in development – and each needs approval before they can be released – it leads to a very long waiting list. This can add up to nearly two years and all the time spent on this trial could be for naught if the approval is not achieved. Regulatory Bodies are often the last hurdle. The respective Body for the country will analyse the data presented and decide if it can be used which can take upwards of two years. However, being passed through one body does not guarantee a pass through another. Furthermore, in the UK, before a new trial can begin the Medicines and Health products Regulatory Agency (MHRA) must approve of it. This means that pre-clinical testing can be redundant if it does not pass this inspection. The MHRA also conducts randomised site checks to ensure the process is being carried out with ‘good clinical practice.’ The MHRA then approves the drug once again after Phase 3 if they believe it to be safe. The licensing process shows the treatment met certain criteria and is deemed safe and effective. It does not mean, however that the research into the drug stops.

One thing that can be done to speed up the review time is an Expedited Review or Fast Track. This in a process that has been developed to ‘facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need’. By this, it means providing drugs for diseases which have no previous treatment, prevention or cure or provide something that is drastically better than what is available for serious conditions such as cancer, Alzheimer’s, AIDS and depression. There are certain criteria that have to be met if there are available treatments in order to qualify for this process; must show superior effectiveness, avoid serious side effects, improve diagnosis where early diagnosis can result in an improved outcome, ability to address emerging or anticipated public health need and decrease of toxicity. Within this, frequent meetings with regulatory bodies are held in order to reduce the time spent examining the paperwork at the end of the trials. These drugs also skip the waiting list, meaning they ae examined first when their data is collected.

## How has the Clinical Trial process changed for Covid-19?

The vaccines developed for Covid-19 seem to have done the impossible and complete at least a decade worth of work within a few months. This is only possible due to certain changes. The medical community had to adapt quickly – patients still needed check-ups but the risk of coming into hospitals scared people meaning there has been new difficulties arising in the Clinical Trial community. To combat this, a new approach was needed.

Covid-19 has made many things unsafe. One, of course, is meeting in person. Despite this, the clinical trials process still needs to happen. When interviewing Matt McCarthy he talked about the changes he has witnessed within the medical community. A key idea he raised was ‘decentralised trials’ – trails conducted over digital calls. The FDA defines decentralised clinical trials as ‘those executed through telemedicine and mobile healthcare providers.’ This essentially means that patients remain at home and have calls unless they are in immediate need of care or have had an emergency. When questioned if this could run the risk of invalidating certain data collected, he replied ‘It depends what the test is – some tests we believe are actually more accurate in the home.’ He went on to explain that certain tests, like blood pressure, are more accurately tested in the home, going so far as to suggest that there might be a future in decentralising more trials and check-ups.

While talking about general changes to the clinical trials is certainly an effective method to understanding how they have been conducted so quickly, it is just as important – if not more so – to look at specific cases. To access how the fast tracked vaccines have developed and if there is any foundation in calling them safe, it is sensible to look at the first vaccine released globally – Sinovac – and the first two released in Europe – Pfizer-BioNTech and Oxofrod-AstraZeneca. The three vaccines being examined here have all benefited from a number of common factors. But each also has benefited from a number of factors specific to them. The process each vaccination took will be broken down and the most significant changes explained below.

## What each case had in common

Before delving into each individual case, it should be noted that the scientists weren’t working from scratch. In a rather peculiar turn of events, we are quite lucky that the virus to make the leap from animals to humans was in fact a coronavirus. This same strain of virus had tried to move to humans twice before in the last 20 years – once in 2002 and again in 2012. This meant that, not only were scientists aware there was a risk it would jump, but also aware of its biology and behaviour. This alone saved vital time as studies didn’t have to be conducted into the virus.

It should also be considered that a vaccine trial has different requirements to a medicine trial. For a medicine trial, volunteers must meet certain requirements whereas for a vaccine trail these requirements don’t exist. When talking to Matt McCarthy – Product Line Executive of ERT – he said, for a medicine trials ‘You’ve got to find a sick person, with the right disease, whose willing to take part in the study, that meets the criteria, that there is no other treatment that would be better for them’. This means it can, and often does, take much longer to recruit the necessary amount of volunteers. However, for a vaccine trail ‘almost anybody is legible’ making it much easier to recruit volunteers.

The media coverage expedited the recruitment process to Covid-19 vaccine trials. With the population so acutely aware of the threat and the virus effecting so many people personally, the general consensus was that people were willing to do whatever it took to get some form of medical combat out there. Thus the rate of recruitment was higher for this vaccine trial – ‘over 100,000 people have volunteered to take part in Covid-19 vaccine trials’. However, concerns have been raised over the amount of BAME community volunteers. They account for about 5% of volunteers despite accounting for about 14% of the UK population. There is little to no fear within the scientific community that race plays a role in the effectiveness of the vaccine, but due to lack of data, it cannot be proven either way.

Above, the Expedited review Process was explored. For the vaccines released in Europe, the Regulatory Bodies of the country have been working in tandem, hosting more frequent meetings with them and keeping up to date. Need quote from Dr Alison Messom

A final thing to note is that these three vaccines are actually still in phase three trials – they have not completed the process yet. With multiple branches of phase three trials taking place, it is difficult to say when they will be completed. However, as of January 2020, Oxford is not expected to have primary outcomes until March 2021 and Pfizer is not expected to have primary outcomes until August 2021. In Brazil, Sinovac is not expected to have primary completion until September 2021. This means these vaccines can only be approved of for emergency use – Emergency Use Authorisation (EUA). This means treatments – in this case vaccines – can be used during a public health emergency. A EUA is a separate request that can be made by the manufacturers. If the date they submit to the regulatory bodies reach certain criteria, they can be approved for use.

## Sinovac vaccine

Within China, there is a unique drive very few countries have to release a vaccine quickly. In an interview with Nature, an online science journal, Elanah Uretsky said after the ‘mishandling’ of the early stages of the pandemic, there is a sense that if they come up with a vaccine, then they’re saving the world and can exonerate themselves in the eyes of the public. This drive resulted in the first vaccine approval in a country. As of July 2020, it has been approved for use by the Chinese government ‘for emergency use in high-risk groups.’

However, many institutes in China are working from published data on the virus. Many cannot access a direct sample as only a limited number of laboratories have the ‘necessary biosecurity.’ In an interview with Nature, Li Wu, deputy director of the immunology institute at Tsinghua University of Beijing said ‘you have to book for a long time before you can get in’ which naturally raises concerns internationally. Despite this, funding for immunology research on Covid-19 have dramatically increased. Wu said ‘There are always announcements for new grants.’

Internationally however, there has been less success. As of 25th January 2021, the Sinovac vaccine is still in third phases clinical trials in Brazil, Indonesia and Turkey. Initially, Brazil released data showing the vaccine to be 78% effective but in January revised that after reviewing more evidence. Now, it sits just above the minimum to be approved by regulatory bodies at 50.4%.

Prior to this, in late October the Sinovac trials had been halted in Brazil after the death of a volunteer in the vaccine trial. Anvisa said there had an ‘adverse serious effect’ had occurred. It was later determined that the death had nothing to do with the vaccine and the trial resumed.

## ***Pfizer-BioNTech Vaccine***

On December 1st 2020, the UK became the first country to approve of the Pfizer vaccine for emergency use. Other countries followed within a week, and the FDA in USA passed ‘emergency authorisation’ for the vaccine. It took only ten months to complete steps that normally take ten years. It is a type of mRNA vaccine – a method that was first successful in animals 1990. However, this is the first time this type of vaccine has been approved of for use in trials although many have received them in clinical trials. This vaccine has been approved of in the most countries and has the highest efficacy rate of these three vaccines.

Prior to any work in Covid-19, BioNTech worked with mRNA treatments that could combat cancer by training the immune system to attack cancer cells. This meant that the company already had a good understanding of mRNA vaccines and, upon realising this had potential to combat covid-29, had research and information they could transfer. There is also history between these two companies; in 2018, they teamed up to create an mRNA vaccine to combat the flue. By the time the coronavirus outbreak was reported they were already had big advantage over other companies.

In January 2020, BioNTech began ‘Project Lightspeed’ – a ten month path to develop and effective vaccine in a short amount of time. Within this plan, its phase by phase study is set out with phase one beginning in Germany April 23rd 2020 and its second phase beginning July 27th 2020. The vaccine has been found to be 95% effective while the WHO has a minimum 50% efficiency policy. In accordance with the FDA specifications, Pfizer did not file for a EUA until half of their volunteers had been observed for any safety issues 2 months after their second dose.

The company also received incredibly large investments; the European Investment Bank (EIB) set up plans to provide up to €100 million in debt financing in June and further funding of €375 million from the German Government in September.

## Oxford-AstraZeneca Vaccine

The Oxford vaccine seems to have done 10 years of work within 10 months. This, naturally, leads to certain concerns about the validity of the results and its safety. However, few know or understand the process the vaccine went though.

After the Ebola outbreak to which the world was slow to move and 11,000 people died it became apparent to the medical world that a plan was needed to tackle the next outbreak. So, the Oxford research team began work on a plan to tackle and unknown disease dubbed ‘disease X’. This was the beginning of the work that went into the Oxford-AstraZeneca vaccine.

As stated above, the coronavirus had already attempted to infect humans twice before. For the 2012 incident, he Oxford team developed a ChAdOx1 vaccine. They used this as the base of the vaccine they developed against Covid-19 meaning they already had a working vaccine to combat this specific family of viruses. What they needed was the complete genetic code of the virus, which was provided by China on the 11th January 2020.

As stated previously, funding is a massive issue when creating a vaccine. Despite this, the Oxford-AstraZeneca vaccine had a key advantage that many other trials did not. Oxford has its own vaccine manufacturing plant which was a good start but funding was needed to produce the number of doses needed for larger trials. However, with the world on standstill and economies failing, money flooded in. In May 2020, the Government ‘announced £65.5 million of new funding for the vaccine being developed at the University of Oxford’.

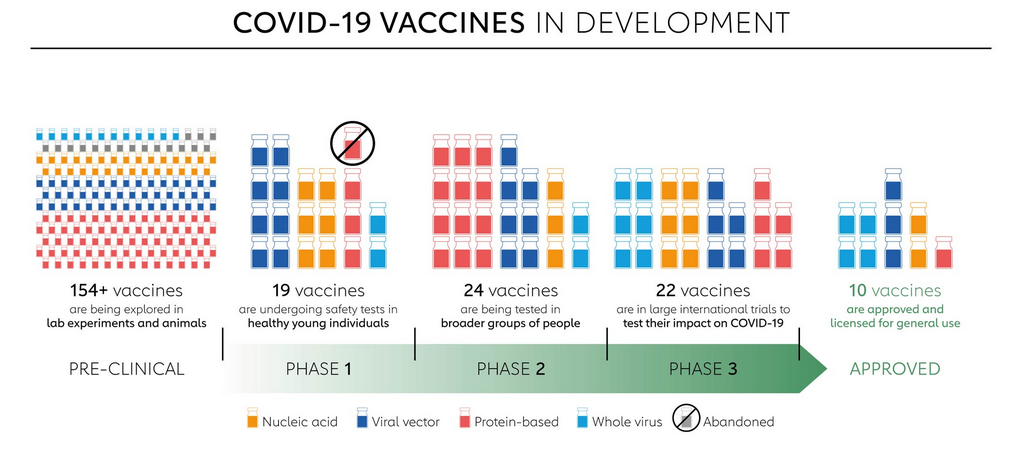
The Oxford vaccine was approved 30th December 2020 and the first doses were released within the next week. The process was heavily expedited but it does not seem like any corners were cut within the process. The evidence gathered was ultimately approved by the regulatory bodies suggesting there was no discrepancy in its validity.

One issue this vaccine found was, after the approval of the Pfizer vaccine, volunteers began wanting to pull out – they wanted to know if they had been given the placebo or the vaccine to see if they needed the Pfizer vaccine. This of course caused many issues within the trial. Need quote from Dr Alison

However, on January 28th, it was announced that Germany was set to limit the vaccine to under 65s. This is because, once Germany’s vaccine committee had checked the data they have decided there was ‘insufficient data’ for the over 65s category. This has come after it was realised that less elderly people were recruited than younger. Dispute this, the scientists who ran the study said there is other evidence suggesting effectiveness in adults. Paul Hunter, professor of Medicine at the University of East Angelia, said ‘We do know that it is safe in people over 65. They have much fewer side effects than younger people and it almost certainly provides substantial benefits in terms of preventing severe disease and reduce the chances of going into hospital.’

## Putting it all into context

While it seems incredible that these vaccines have been approved for use, it is important to put these vaccines into context.



As of the 20th February 2021 this is an up-to-date log of the Covid-19 vaccines in development and those with EUAs. Clearly there have been multiple vaccines have been approved despite still being in the development stage. Clearly, despite these vaccines getting what seems like the most media coverage, other companies have made similar break through – these aren’t one off occurrences.

One of the major concerns with the vaccines is that, due to the short period of time the vaccines have been studies, there may be unknown long term consequences. However when questioned, Matt McCarthy said that with ‘any new medicines you don’t know the long term effects until you have studied it for decades but there are many lives being saved by medicines that have been developed.’ The trail that looks at the long term consequences is carried out after the release of the new medicine. This has never been such a big issue before because these are vaccines people have waited with baited breath for.

## Conclusion

So can these vaccines be considered safe? Yes, of course they can. The safety precautions within the Clinical Trials process have not been removed, or side stepped. The data collected still meets the necessary requirements for the Regulatory Bodies satisfaction. Time has been saved through the public being more willing to volunteer and the financing having been given far easier.

There is a common misconception that these vaccines have completed the clinical trials – they have not. Meaning the timeline shown above is not complete for them. The longer Phase 3 have not been concluded but it has been decided that the evidence available suggest the safety of them. This means they have only been approved for a EUA – not a full licence.

So it seems that the question shouldn’t be “can these vaccines be considered safe?” or “how have they been produced so quickly?” The real question is what can we learn from this? What can we take forward to speed up future Clinical Trials?