Are people right to question the safety and effectiveness of the Covid-19 vaccines given how quickly they have been developed?

## Introduction

A new disease was first reported in Wuhan, China in December of 2019 [1] 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 [2]. Little was known about the virus that was set to reshape the world in the year to come.

In its original report on January 5th 2020, the World Health Organisation (WHO) – a subsection of the United Nations responsible for international public health - stated there was “no evidence of significant human-to-human transmission” [3]. However, by 11th March 2020 the situation had severely escalated and was declared a pandemic [4]. At the end of 2020, a total of 81,485,119 people had been infected and had claimed the lives of 1,784,125 globally [5]. The world was in desperate need of a vaccine, but with the previous fastest vaccine having taken 4 years to develop, it didn’t seem like one would be available for a number of years. Yet, by the end of the same year, the Sinovac, Pfizer-BioNTech and Oxford-AstraZeneca vaccines had all been approved and by January ~~of~~ 2021 all three were in being administered to the general public. It seemed the impossible had been made possible; in 13 months a vaccine had been developed and approved while, under normal circumstances it takes, on average, ten to fifteen years. However, the speed of their development led many to question the safety and validity of the results. But should people be questioning their safety?

To asses this, one must first understand the traditional process vaccine development follows, why these processes are followed and what rate limiting factors to the process exist. It is then possible to compare the processes followed for the new Covid-19 vaccines with the traditional approach and assess the impact the differences have had on both the development time and the safety of the vaccines.

Before reading this paper, one must be aware that safety is a relative term; it is a balance of risk and there is almost always a risk in some way.

## The History of Clinical Trials

Throughout human history, many medicines have come and gone but it is not until relatively recent history that something similar to a modern-day Clinical Trial had been developed. In 1747, James Lind carried out the first scurvy trial which contained most of the characteristics of a controlled trial [6], meaning it was a trial where multiple groups if patients were given different treatments and the results were compared. In 1943 there was the first “double blind” trial of patulin for the common cold [6]. A “double blind” trial is one where neither the doctor nor patient know who is receiving what treatment in order to make the analysis more accurate as the results aren’t influenced by what is expected to be seen. The early 1800s ushered in the arrival of the placebo though it was not used in clinical trials until 1963 [6]. 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 origin in the 1906 Pure Food and Drugs Act, though it was known by a different name [7], and, in the UK, The Medicines and Healthcare products Regulatory Agency (MHRA) was developed soon after the Thalidomide incident in the 1950s [8].

Currently, the clinical trials process is divided into four distinct phases in humans 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 evidence of testing in 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 [9]. 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 bodies were developed to help maintain the quality and safety of the drugs released, by setting up key expectations and standards, like the need to run trials in humans in four different phases in order to assess the efficacy and safety of a new drug.

### The Modern-Day Clinical Trial Process

It is important to note that all people involved in a trial must be volunteers – it is personal choice if someone desires to be included and they must and fully informed on the risks of the trail so they can consent

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 [10] the phases are as follows:

* Phase 1: the new treatment is given to a small group of healthy volunteers with the aim of determining if 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 phase and move onto Phase 2 [10].
* Phase 2: the drug is tested on a larger group of people – up to several hundred - with the target disease or condition. Here, the efficacy is tested and side effects are looked for. Around 67% of drugs fail at this trial [10].
* Phase 3: a much larger group of patients, a few thousand, are tested. Once again, this looks for the efficacy but now also looks at less common adverse reactions. Around 25% of treatments or vaccinations make it past his phase. [10]
* 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.

***INSERT TIMELINE HERE***

*With average timelines of 10-15 years it is necessary to examine what factors cause this to take so long.*

## Rate Limiting Factors in the Clinical Trial Process

This process is prolonged by several variables that remain constant outside of the conduction of the actual trials e.g. administrative dealings, financing and the Regulatory bodies.

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. Pre-clinical trials, and finding a compound of therapeutic value, can take upwards of two years.

The total cost of developing a new drug, on average, supersedes US $1 billion [12]. The company running the clinical trial must find some way of attaining this funding and most of the time it will be sourced through 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” [12]. This will inevitably increase time between phases, prolonging the process.

Additionally, actually recruiting enough volunteers can add years to the whole process. In an interview with Matt McCarthy – Product Line Executive of ERT - 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” [13]

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.

While Regulatory Bodies were introduced in order to maintain standards, they have played a major role in lengthening the time spent in the Clinical Trial Process 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 at the approval stage. This can add up to 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 most of which is spent waiting for the analysis to begin. However, being passed through one body does not guarantee a pass through another. In the UK, the MHRA must approve of the drug once again after Phase 3 if it is to be released into the UK. 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 the current process does allow to reduce this 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” [14]. By this, it means providing drugs for diseases which have no current 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. However, if there are existing treatments, certain criteria must be met in order to qualify for the trial; must show “superior effectiveness”, avoid “serious side effects”, improve diagnosis “where early diagnosis can result in an improved outcome”, “address emerging or anticipated public health need” and decrease of toxicity [14]. 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 are examined first when their data is collected. This results in a reduced review time as most of the time in this stage is caused by the waiting, but it also means that there are less questions the Bodies need to answer during their review resulting in a decreased time for Regulatory Review.

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

Having examined the current process and the challenges around it is now possible to look at how the process is different for Covid-19.

The Covid-19 vaccines have been developed on an expedited timeline, only possible due to certain differences within the rate limiting factors so as no not compromise safety by interfering with the actual Human Phases.

Firstly, general factors that apply equally to all vaccines will be assessed before considering the differences specific to each vaccine.

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 questioning their safety, it is sensible to look at the first vaccine released globally – Sinovac – and the first two released in Europe – Pfizer-BioNTech and Oxford-AstraZeneca. The three vaccines being examined here have all benefited from a number of common factors. But each also has a number of specific advantageous factors 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 and not another type of virus. 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 [15]. 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 there was a base knowledge available where there wouldn’t have been for a novel 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 trial these requirements do not exist. When talking to Matt McCarthy, he said, for a medicine trials “You’ve got to find a sick person, with the right disease, who’s 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 eligible” making it much faster to recruit volunteers.

The recruitment process was further expedited by the media coverage of the Covid-19 vaccines. 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 treatment. Thus the rate of recruitment was higher for this vaccine trial – as of August “over 100,000 people have volunteered to take part in Covid-19 vaccine trials” [16]. However, concerns have been raised over the amount of Black Asian and Minority Ethnicity community volunteers. They account for about 5% [17] of volunteers despite accounting for about 14% [18] of the UK population. There appears to be 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.

The expedited review process, previously discussed, was heavily influential to the decreased time period for the Clinical Trials. 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. In an interview with Dr Alison Messom – Chair of the Board of the Institute of Clinical Research – she said “Where things that would normally take between 30 and 60 days to get approval, there was a real commitment from regulators to turn that around in 5 to 10 days. So massive reductions in that” in regards to the approval process prior to the trials taking place.

A final thing to note is that as of January 2021 these three vaccines are actually still in Phase 3 trials [19] – they have not completed the full 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 2021 Oxford is not expected to have primary outcomes until March 2021 [20] and Pfizer is not expected to have primary outcomes until August 2021 [21]. In Brazil, Sinovac is not expected to have primary completion until September 2021 [22]. 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 data they submit to the regulatory bodies reach certain criteria, they can be approved for use.

## Sinovac vaccine

In addition to the differences all Trails benefited from, there were a number of unique differences for Sinovac. Within China, there is a distinctive 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” [23] 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” [23] 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” [23].

However, many institutes in China are working from published data on the virus and cannot access a direct sample as only a limited number of laboratories have the “necessary biosecurity.” [23] 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” [23] to one of the secure laboratories. An issue, which, naturally raises concerns internationally. Despite this, funding for immunology research on Covid-19 has dramatically increased. Li Wu said “There are always announcements for new grants.” [23]

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% [24] effective but in January revised that after reviewing more evidence. Now, it sits just above the minimum to “prevent disease or decrease its severity” [25] – which is 50% - at 50.4%. [24]

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, Brazil’s health regulator, said there an “adverse serious effect” [26] had occurred but 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 [27]. Other countries followed within a week, and the FDA in USA passed “emergency authorisation” on December 11th 2020 for the vaccine [28]. 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 [29]. However, this is the first time this type of vaccine has been approved of for use outside trials although many people have received them in Clinical Trials. Despite this, the Pfizer 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 [30]. This meant that the company already had a good understanding of mRNA vaccines and, upon realising this had potential to combat Covid-19, had research and information they could transfer. There is also history between BioNTech and Pfizer; in 2018, they teamed up to create an mRNA vaccine to combat the flu. By the time the coronavirus outbreak was reported they were already had big advantage over other companies. This meant there was applicable prior knowledge of a specialty that could be carried over. It isn’t brand new technology, but rather a previous method revamped.

In January 2020, BioNTech began “Project Lightspeed” – a ten month path to develop an effective vaccine in a short amount of time [31]. This is not to be confused with America’s “Operation Warp Speed” from which the company was not involved in. 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 [31]. The vaccine has been found to be 95% effective while the WHO has a minimum 50% efficiency policy [32]. 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 [33].

As explored above, finance is incredibly important in any Clinical Trial. However, for this vaccine, 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 [34] and further funding of €375 million from the German Government in September [35]. This meant that, not only were they not struggling for money, but they had the funding relatively quickly.

## Oxford-AstraZeneca Vaccine

After the 2014-16 Ebola outbreak, to which the world was slow to move and 11,000 people died [16], 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 an unknown disease dubbed “disease X” [15]. This was the beginning of the work that went into the Oxford-AstraZeneca vaccine. A method to reduce the time of development was in the works, giving pre-thought out methods that allowed for a shorter over all Clinical Trials Programmes.

As stated above, the coronavirus had already attempted to infect humans twice before. For the 2012 incident, the Oxford team developed a ChAdOx1 vaccine [15]. 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 [17].

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 could produce vaccines for smaller Trials. However, funding was needed to produce the number of doses needed for larger trials but, 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” [38]. This meant that the time lost waiting for funding was removed so the phases could take place quicker.

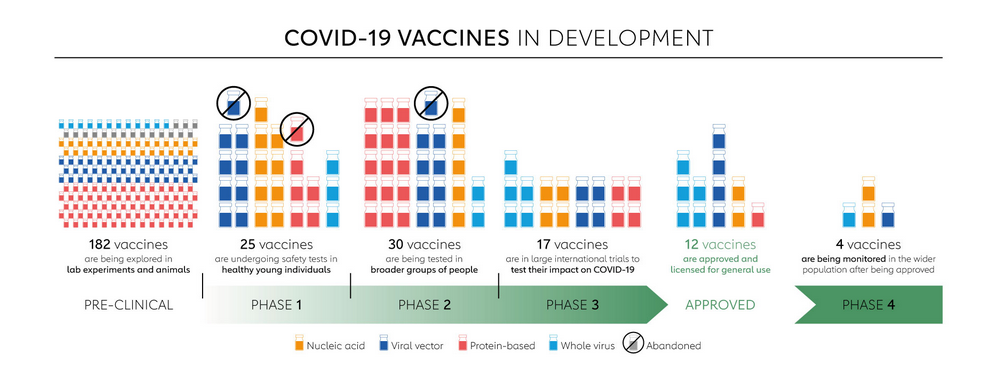
The Oxford vaccine was approved 30th December 2020 [15] and the first doses were released within the next week. The process was heavily expedited but it does not seem like any corners were cut within the process. The evidence gathered was ultimately approved by the regulatory bodies suggesting there was no discrepancy in its validity.

When talking with Dr Messom, she described the “unintended consequences” of the Pfizer role out on the Oxford Trials. “A lot of the subjects they had in that study were healthcare workers and so the Pfizer vaccine obviously got rolled out first and they were being offered the Pfizer vaccine” and it resulted in the patients wanting to “pull out and find out what they had” – the placebo or the vaccine.

On January 28th, it was announced that Germany was set to limit the vaccine to under 65s [39]. This is because, once Germany’s vaccine committee had checked the data they had decided there was “insufficient data” for the over 65s category. This issue arose it was realised that fewer 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.”

### The Current Status

Although this study has only examined three vaccines, they are not anomalies. Multiple vaccines have been approved and are currently undergoing more trials.



As of the 4th March 2021 this is an up-to-date log of the Covid-19 vaccines in development and those with EUAs [40]. There are multiple vaccines that have been approved, and despite less media coverage, even more that are in the Process.

## Summary

It can be seen, then, that there are a number of areas which combine to significantly lengthen the traditional medicine development process. These factors have also played a major role in the reduction of the time taken for the Covid-19 vaccines.

The work above shows that is not the testing that has been cut down, so much as the red tape around it. Where previously certain obstacles had to be maneuvered around in the administrative area, most of – if not all of – these were cut directly though as a result of the severity of the threat Covid-19 posed to society. It is necessary to remember that the vaccines that have been approved have been approved for EUAs and are still in Clinical Phases, their testing being incomplete. The refusal for over 65s in Europe for the Oxford-AstraZeneca vaccine – one the basis there was not enough data to prove efficacy – has lead the Oxford team to carry out more trials, specifically targeting over 65s.

Funding a Clinical Trial is a risk for pharmaceutical companies. If the trial gets shut down, or at the end, doesn’t pass though regulation, then the money they invested will have been lost. Due to this, companies are very selective with what they chose to fund. However, in the last year, both governments and companies have been more willing to loan money to companies who were working towards vaccines.

Volunteering for a Clinical Trial has always posed certain risks so it can take a long time to recruit the necessary amount of volunteers – especially for smaller, lesser known diseases. However, in this situation where the risk of no vaccination is so prominent and so well covered in the media, it seems volunteers flooded in. The data collected has covered all of the desired and the target number of volunteers were still exposed despite it being taken over a shorter time period. Where time could have been lost on studying the virus, it was not due to previous studies and understanding of the disease.

Finally, a major concern 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 trial that looks at the long term consequences is carried out after the release of the new medicine. Post-release, vaccines have already begun their Phase 4 Trials and these will not be finished for years in order to gauge an idea of long term effects and efficacy in the general public.

## Conclusion

When considering the safety of the vaccines, the public appears to fear corners in the Clinical Trial Process have been cut. What is not realised by the majority of the public is that multiple factors have played a role in reducing he time frame around the phases without interfering with the testing. The quality for standard regulation has been met in a much shorter time frame due to these factors.

Firstly, the aspect of “luck” that the disease was caused by a known virus that some organisations had already anticipated could pose a risk and had done previous work on. Then, there is the aspect of funding and the global shift of focus to combating Covid-19. The unknown virus that quickly over ran the world resulted in companies banding together and governments providing support to the Clinical Research teams previously unseen Where slow recruitment has previously been a massive issue, the general public’s response and readiness to volunteer easily resolved this issue. There has been a significant increase in cohesion between the regulators and the pharmaceutical companies, with both working for the goal of compressing review time. This mutual understanding has dramatically decreased waiting time during the regulatory release process.

When assessing safety, one must remember this is a relative term; a measurement of the risk of the danger balanced against the risk of the treatment – in this case the risk of death from catching Covid-19 against the risk of taking the vaccines. These vaccines may have little data about long term effects and about their interactions with more specific situations - such as the further studies on over 65s in Europe – but they have been produced with a well-established process and based on existing treatments where long term data is available.

Overall, it can be seen that, given the severity of the Covid-19 risk, the vaccines are a comparatively safe option and people should not be any more concerned taking these vaccines than any other vaccine.

In fact, as these vaccines should be considered as safe, the public is asking the wrong question. It shouldn’t be “how can we call these vaccines safe with so little time spent on them?” it should be “how can we carry forward what we have learned to speed up the development for treatments for other life threatening diseases?”

How can we carry forward what we have learned to tackle other life threatening diseases?

Why haven’t we been wopkring this effieicently before?

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