Office of the Prime Minister's Chief Science Advisor
Kaitohutohu Mātanga Pūtaiao Matua ki te Pirimia

COVID-19 vaccines: Summary of current state-of-play

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The COVID-19 pandemic has spurred a global effort to find a vaccine to protect people from SARS-CoV-2 infection.

This summary highlights selected candidates, explains the different types of vaccines being investigated and outlines some of the potential issues and risks that may arise during the clinical testing process and beyond.

Key points

- There are at least **22 vaccine candidates registered in clinical (human) trials**, out of a total of at least 194 in various stages of active development.
- It is too early to choose a particular frontrunner as we lack safety and efficacy information for these candidates.
- It is difficult to predict when a vaccine will be widely available. The fastest turnaround from exploratory research to vaccine approval was previously 4–5 years (ebolavirus vaccine), although it is likely that current efforts will break this record.
- There are a number of challenges associated with accelerated vaccine development, including ensuring safety, proving efficacy in a rapidly changing pandemic landscape, and scaling up manufacture.
- The vaccine that is licensed first will not necessarily confer full or long-lasting protection.

Contents

1. Types of vaccines

Vaccines introduce the human immune system to certain protein molecules from the pathogen of interest. This controlled exposure provokes an immune response that ultimately leads to some period of immunity from the pathogen. The immune response elicited would ideally consist of both neutralising antibodies (that block the virus particle from entering cells) and T cells, which identify infected cells and eliminate them.

In the case of SARS-CoV-2, the 'spike' protein is an ideal target for vaccines.[1] This is because the spike protein is essential for the virus to latch onto human cells (via the ACE2 receptor) and infect them. It is therefore conserved across different strains. Most current vaccine efforts target the spike protein. Some might target the whole protein (also known as an antigen) while others may only target specific bits of the spike. However, limited information publicly available means that any differences between targets, or the prevalence of other targets aside from the spike, remains unclear.[2] Other antigens aside from the spike protein are able to induce a T cell response.[3]

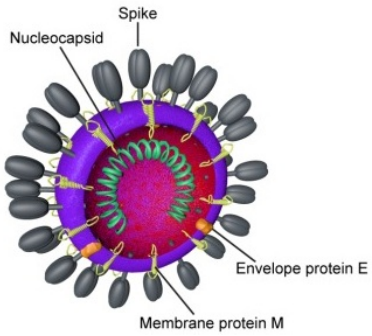


Figure 1: Diagram of a coronavirus virion with the spike protein labelled. CC BY 3.0.[4]

In addition to the spike protein, some vaccines contain an adjuvant: a molecule that signals to the immune system that it's time to jump into action. In particular, subunit vaccines often require an adjuvant to induce a sufficient immune response.

There are different ways of introducing the 'spike' protein (or other target) to the body. Some of these methods are experimental while others have a proven track record.

Table 1: Types of vaccine platforms

Virus	Live, attenuated virus	A live organism with its virulent properties disabled – usually by being repeatedly passed through animal or human cells until a strain is generated with mutations that make the virus less potent. Typically invoke longer-lasting immune responses and responses to a number of antigens but may not be suitable for immunocompromised individuals.	**Example**: influenza vaccine administered by nasal spray; poliovirus vaccine.
	Inactivated virus	A vaccine containing whole viruses that have been killed through heat or chemical treatment. Production requires large quantities of infectious virus and can take longer to culture than other vaccine types. Protection usually weaker than live virus vaccines, so booster shots may be needed.	**Example**: intramuscular influenza vaccine
Protein	Subunit	Rather than introducing a whole organism, this type of vaccine only includes a fragment or individual protein molecule. These protein molecules maybe covered with different sugars to	**Example**: hepatits B vaccine

		those on the natural virus antigens, depending on method of manufacture, which may pose challenges for efficacy. Will probably require an adjuvant and multiple doses.	
	Virus-like particle (VLP)	Essentially a subset of subunit vaccines, VLPs consist of an antigen repackagaed in a particle that resembles a virus (usually with lots of viral surface proteins) but does not contain any genetic material and therefore cannot replicate. Considered safer than live, attenuated virus vaccines but can be difficult to manufacture.	**Examples**: HPV vaccine, hepatitis B vaccine
Viral vector	Non-replicating viral vector	A harmless virus unrelated to SARS-CoV-2 that contains instructions to create the spike protein e.g. an adenovirus that has been modified so it cannot replicate. Pros: long-term stability, high level protein expression. Cons: many people already have some level of immunity to certain vectors such as some adenoviruses.	No licenced vaccines using this method
	Replicating viral vector	The same concept as a non-replicating viral vector, however the virus retains the ability to replicate. This can enhance the immune response as more cells are exposed to the spike protein. Pros: long-term stability, induce strong immune response, high level protein expression	**Example**: ebola virus vaccine.
Nucleic acid	RNA	A vaccine made of viral RNA molecules that direct human cells to express the spike protein. Pros: speed of production, flexibility, cell makes protein with correct sugars attached Limitations: RNA is inherently unstable and requires cold storage plus careful distribution methods	No licenced vaccines use this method
	DNA	Similar to RNA vaccines. A vaccine comprising DNA that is incorporated into human cells and instructs them to express the viral protein, triggering an immune response. Pros: speed of production, flexibility, cell makes protein with correct sugars attached	No licenced vaccines use this method

As of 16 July 2020, there are at least 194 candidate vaccines in various stages of active development.[5] Although this may seem like a huge number of options, the attrition rate for vaccines is very high. The market entry probability for the average vaccine candidate is just 6%.[6] Another study found that the 'probability of success' for infectious diseases clinical trials is around 25%.[7]

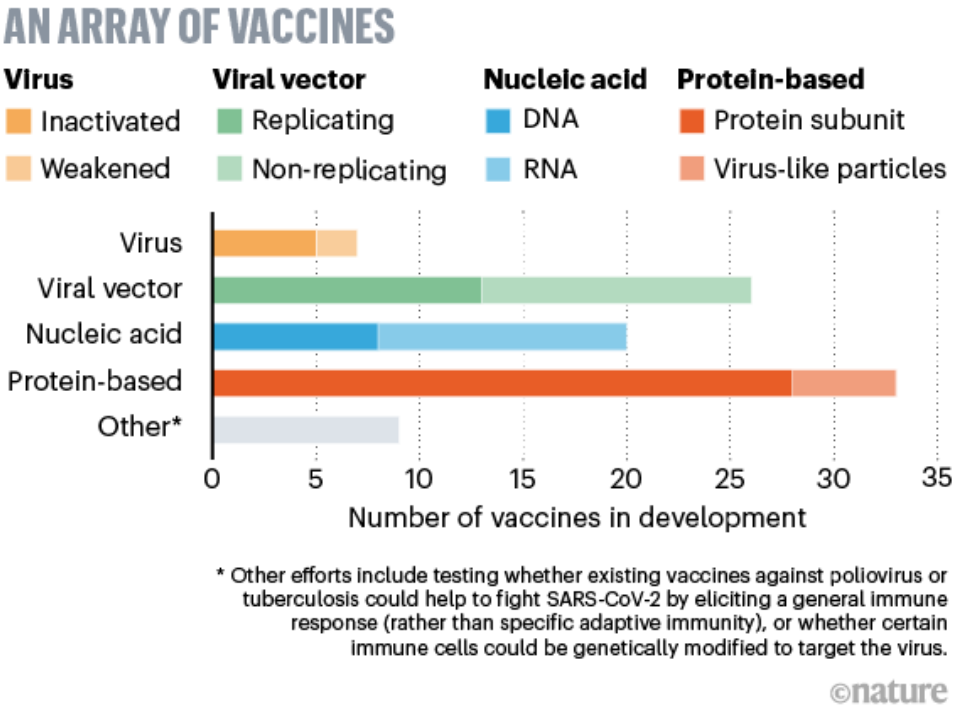


Figure 2: chart breaking down the different platforms being investigated for potential COVID-19 vaccines. Reproduced from *Nature*[8]

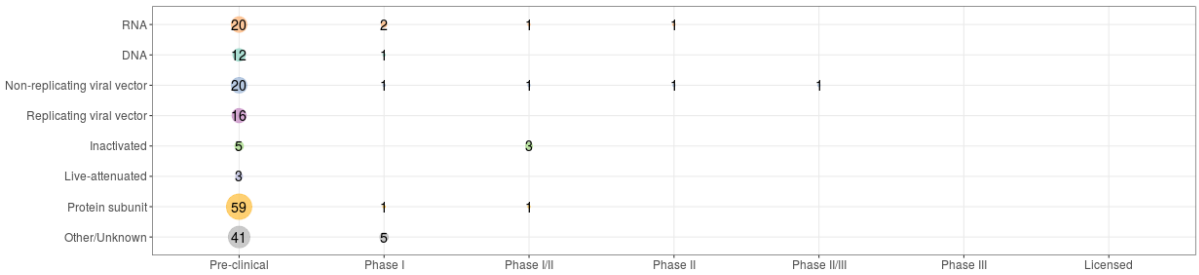


Figure 3: Different vaccine types and their progression along the development timeline. Reproduced from the 'COVID-19 vaccine development pipeline' tracker published by the Vaccine Centre at the London School of Hygiene and Tropical Medicine.[9]

1.1. Vaccine trackers

The COVID-19 vaccine landscape is rapidly evolving. The following resources are tracking the number of vaccine candidates in development and their progression through the clinical trial pipeline.

- World Health Organization – Draft landscape of COVID-19 vaccine candidates
- Milken Institute – COVID-19 vaccine and treatment tracker
- Vaccine Centre, London School of Hygiene and Tropical Medicine – COVID-19 vaccine development pipeline
- BioRender – COVID-19 vaccine and therapeutics tracker
- *Stat News* – COVID-19 drugs and vaccines tracker
- *The New York Times* – Coronavirus vaccine tracker
- *The Guardian* – Coronavirus vaccine tracker: How close are we to a vaccine?
- *The Scientist* – COVID-19 vaccine frontrunners

2. Timeline: When will we have a vaccine?

While some pharmaceutical companies are aiming for emergency use dispensation of their vaccines within months,[10, 11] the World Health Organization (WHO) cautions that the full process will likely take at least 12-18 months, if not longer.[12] The average vaccine takes more than ten years to progress from preclinical development to market,[6] although the recent example of an ebolavirus vaccine turnaround of five years signals that the process can be accelerated.[13]

Typically, once a vaccine candidate is identified, it will proceed through the following steps:

1. **Pre-clinical trials** – studies in animal models (genetically modified mice, but also ferrets and non-human primates[14]) to provide a preliminary assessment of safety and generation of an immune response/antibodies.
2. **Phase I clinical trials** – first trials in humans with usually a few dozen healthy participants; primarily to assess safety and side effects, and figure out the optimal dose.
3. **Phase II clinical trials** – several hundred participants; assesses efficacy and continues to monitor safety and side effects.
4. **Phase III clinical trials** – ideally thousands to tens of thousands of participants with the disease of interest; assesses effectiveness and value in clinical practice.
5. **Regulatory approval** – bodies such as the Food and Drug Administration (FDA) and European Medicines Agency (EMA) review the trial results and other information about the vaccine to determine whether the vaccine can go to market
6. **Scaled-up manufacture** – doses of the vaccine must be produced at scale and distributed. Different vaccine types require different manufacturing infrastructure.

The Coalition for Epidemic Preparedness Innovations (CEPI) has proposed a "pandemic paradigm" that allows for accelerated vaccine development.[15]

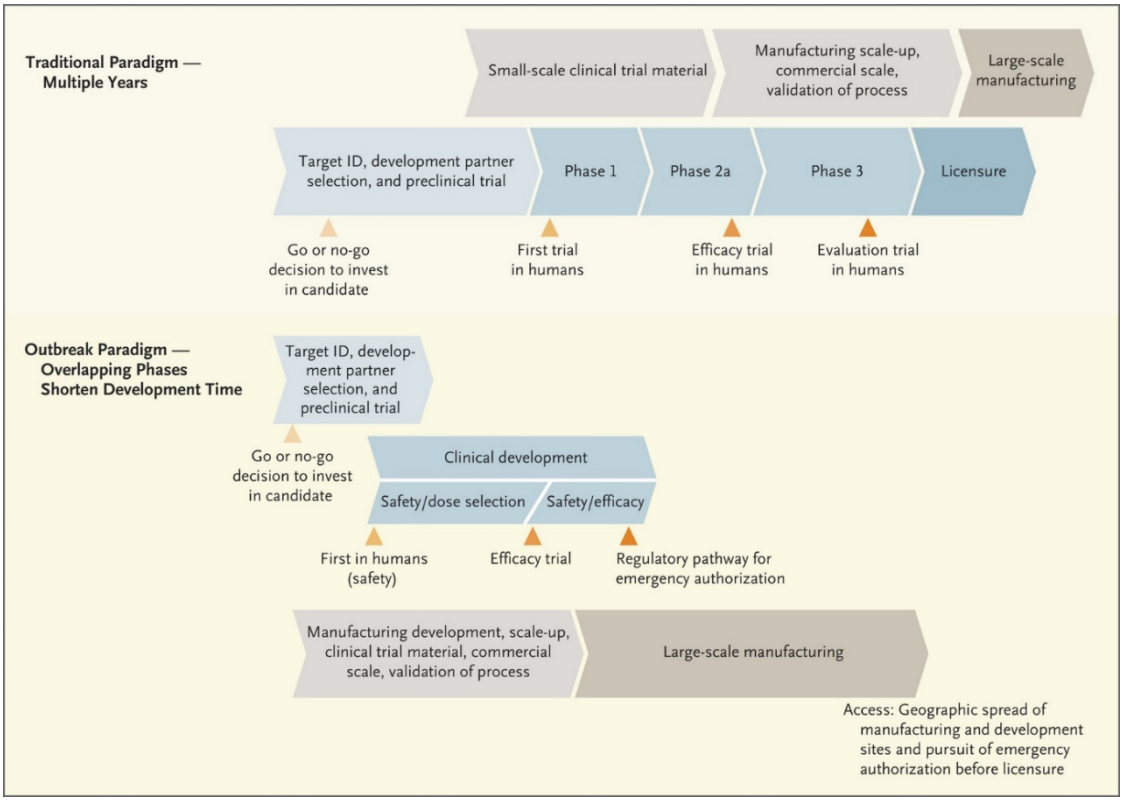


Figure 4: Difference between the traditional vaccine development paradigm and an accelerated "pandemic paradigm" as proposed by CEPI.[15]

The US National Institutes of Health (NIH) is spearheading a collaborative program called Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV).[16] This brings together public and private stakeholders to advance the vaccine development timeline in a coordinated manner (Figure 2).

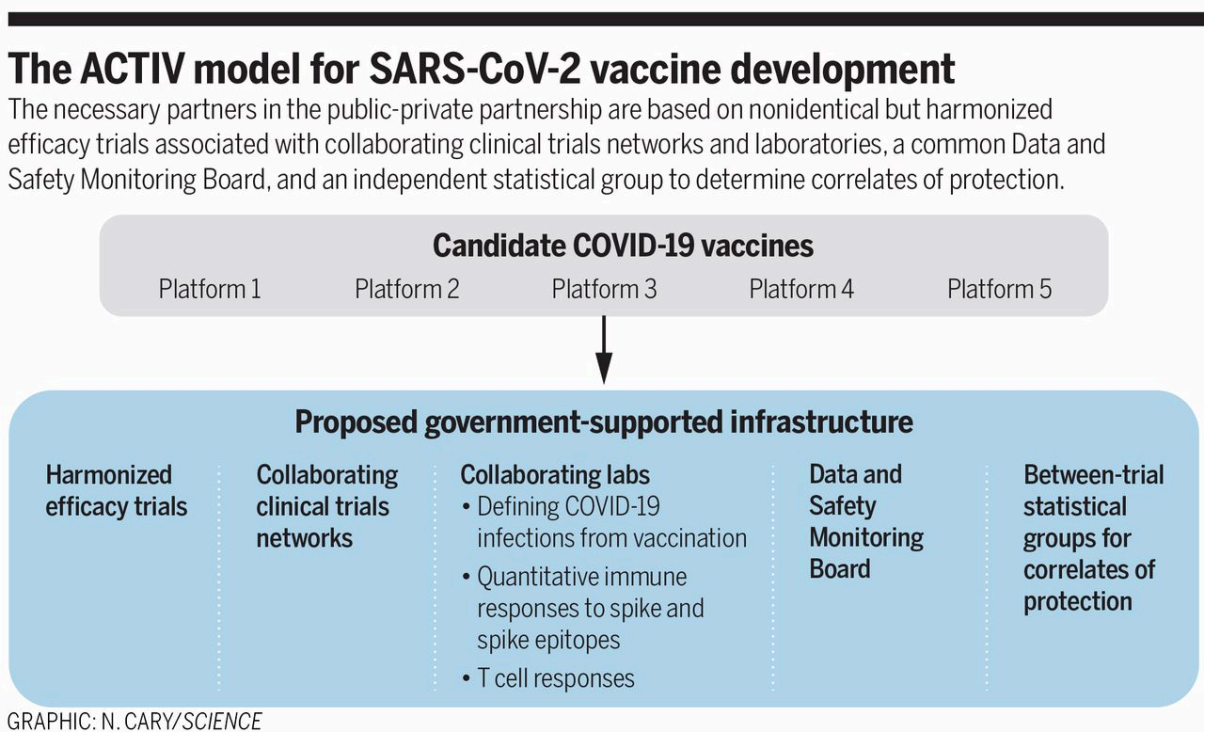


Figure 5: the ACTIV model for SARS-CoV-2 vaccine development.[16]

Beyond models, this useful interactive from *The New York Times* explores specific ways we could potentially accelerate the timeline.[17] These include:

- Assuming we already understand the coronavirus by relying on work from studying the related SARS and MERS coronaviruses.
- Undertaking different phases in parallel.
- Using emergency provisions to vaccinate at-risk populations (e.g. healthcare workers) earlier.
- Anticipating which candidates are likely to be successful and begin manufacturing early to speed up production process.
- Fast-tracking regulatory approvals.

These 'shortcuts' are associated with varying levels of risk, further explored in section 3 'Potential issues'.

3. Organisations and projects of interest

3.1. Coalition for Epidemic Preparedness Innovations (CEPI)

CEPI is a global organisation that finances and coordinates the development of vaccines against infectious diseases. CEPI is supporting the development of ten vaccine candidates for COVID-19 which cover a variety of platforms (see table 2 below, and section five, 'Selected vaccine candidates'). CEPI estimate that it will take US$2 billion to bring a vaccine to widespread use.[18] In addition to the vaccine candidates listed, CEPI is partnering with pharmaceutical companies GlaxoSmithKline and Dynavax to make their proprietary adjuvants available to vaccine developers.

Table 2: COVID-19 vaccines in development supported by CEPI.

Vaccine name	Developer(s)	Vaccine platform	Current stage	
AZD1222	University of Oxford, AstraZeneca	non-replicating viral vector	phase I/II/III clinical trials	Phase III
mRNA-1273	Moderna, NIAID	nucleic acid, RNA	phase I/II clinical trials	Phase II
COVAC1	Imperial College London	nucleic acid, self-amplifying RNA (saRNA)	phase I/II clinical trials	
INO-4800	Inovio Pharmaceuticals	nucleic acid (DNA plasmid)	phase I/II clinical trials	
CVnCoV	CureVac	nucleic acid, RNA	phase I clinical trials	Phase I
NZX-CoV2373	Novavax	protein subunit	phase I clinical trials	
SCB-2019	Clover Biopharmaceuticals	protein subunit	phase I clinical trials	
Molecular clamp	University of Queensland, CSL	protein subunit	pre-clinical testing	pre-clinical
unnamed	University of Hong Kong	live, attenuated virus	pre-clinical testing	
MV-SARS-CoV-2	Institut Pasteur, Merck, University of Pittsburgh	replicating viral (measles) vector	pre-clinical testing	

3.2. Gavi, the Vaccine Alliance

Gavi is an international organisation that brings together the public and private sectors to enhance equitable access to vaccines worldwide.[19] In particular, they boost access to new and under-used vaccines for vulnerable children in low-income countries.

3.3. The Access to COVID-19 Tools (ACT) Accelerator

The ACT Accelerator is a collaborative initiative led by WHO, aiming to speed up the global pandemic response by supporting research, development and equitable access to tests, treatments and vaccines.[20]

The ACT Accelerator has four pillars: diagnostics, treatments, vaccines and health systems. The vaccines pillar is spearheaded by WHO, Gavi and CEPI. They recently announced an $18.1 billion plan called COVAX to purchase two billion doses of vaccine to distribute to high-risk populations worldwide.[21] Countries will be able to buy shares in the COVAX Facility, allowing them to access the nine CEPI vaccine candidates (or any other vaccines the consortium chooses to purchase). This

approach was chosen because we do not yet know which vaccine candidates will be successful in clinical trials; it is a way of not putting all of a country's funds into a single vaccine that might fail.

3.4. Operation Warp Speed (OWS)

A US-based operation, Operation Warp Speed aims to secure 300 million doses of a safe, effective COVID-19 vaccine for Americans by January 2021.[22] It is a partnership between government and industry led by the US Department of Health and Human Services.

OWS has been identifying promising vaccine candidates and supporting them with significant funding for clinical trials in animals and humans, as well as investing in manufacturing and distribution capabilities. However, many OWS activities and decisions remain opaque.[23] From an initial pool of 125 candidates, an NIH expert group undertook a scientific review of 50 vaccine candidates for OWS, which has not been made public.[23] This list was narrowed down to 14 frontrunners, and the taskforce planned a further winnowing to around seven candidates for adavancement to clinical trials.[22]

Table 3: COVID-19 vaccines in development supported by OWS.

Vaccine name	Developer(s)	Vaccine platform	Current stage	Amount of OWS funding (US$)	
AZD1222	University of Oxford, AstraZeneca	non-replicating viral vector	phase I/II/III clinical trials	$1.2 billion[24]	Phase III
Ad26.COV2-S	Janssen (Johnson & Johnson)	non-replicating viral vector	phase I/II clinical trials	$456 million[25]	Phase II
mRNA-1273	Moderna, NIAID	nucleic acid, RNA	phase I/II clinical trials	$483 million[26]	
INO-4800	Inovio	nucleic acid (DNA plasmid)	phase I/II clinical trials	unknown – funded for non-human primate challenge study[27]	
BNT-162	Pfizer, BioNTech	nucleic acid, RNA	phase I/II clinical trials	Declined to accept OWS funding[28]	
NVX-CoV2373	Novavax	protein subunit	phase I clinical trials	$1.6 billion[29]	Phase I
VAAST	Vaxart	non-replicating viral vector	preclinical testing	unknown – funded for non-human primate challenge study[28]	pre-clinical
unnamed	Merck, Sharpe & Dohme	replicating viral vector	preclinical testing	$38 million[30]	

3.5. Vaccine development in Aotearoa New Zealand

The New Zealand Government has allocated $37 million to a COVID-19 vaccine strategy.[31] This comes after some New Zealand scientists called for the Government to invest in an onshore vaccine programme due to potential accessibility issues[32] and a letter in the New Zealand Medical Journal co-signed by 120 scientists supporting this approach.[33]

The strategy aims to secure a safe and effective COVID-19 vaccine in sufficient quantities for Aotearoa New Zealand. It includes $10 million for onshore vaccine research and $5 million for onshore vaccine production capability. Up to $15 million will go towards international research collaborations managed by CEPI, and a further $7 million in "official development assistance" is earmarked for Gavi, the Vaccine Alliance, to support vaccine distribution in developing countries.

A task force comprising MBIE, the Ministry of Health, Medsafe, Pharmac, and the Ministry of Foreign Affairs and Trade is overseeing implementation of the strategy.

Proposals for the programme include evaluation of vaccines developed internationally and a plan for vaccine roll-out. Suggestions also include establishing vaccine development programmes in-country alongside vaccine production capability. However, a proactively-released Cabinet paper notes that "It is unlikely that a wholly indigenous New Zealand vaccine will provide our quickest and most reliable route to a supply of vaccine."[34]

Consideration is also being given to working on a trans-Tasman initiative which would harness expertise across Australia and Aotearoa New Zealand and possibly mitigate the risks of being lowest priority for future supply. Further information on Australian vaccine development efforts can be found in the Rapid Research Information Forum's paper, 'The most promising vaccines for COVID-19'.[35] Meaningful participation in international vaccine development efforts will be important for securing access to vaccines when they become available.

In addition to the COVID-19 vaccine strategy, MBIE has established a COVID-19 Innovation Acceleration Fund.[36]

There are ongoing research projects at the University of Auckland and the University of Otago to understand immunity and embark on the first steps towards a vaccine (in a traditional development paradigm).[37]

4. Potential issues

4.1. Proving vaccine efficacy on an accelerated timeline

As discussed in section two ('Timeline'), proving that a vaccine works is usually achieved through a series of comprehensive clinical trials. These typically involve thousands to tens of thousands of participants who receive either the vaccine or a placebo, and are then monitored to see who becomes infected. This is a time-consuming process.

Furthermore, acquiring the numbers necessary for proving efficacy will be difficult – especially at a time of social distancing and falling case numbers. Even if the pandemic is still in full-swing, we don't know where the epicentre will be in several months when the first vaccine candidates are ready to move into these large-scale phase III trials.

These difficulties could be addressed by a different approach: some have proposed a 'human challenge' study as a quicker – but potentially riskier – alternative.[38] This would involve deliberately exposing vaccinated participants to the virus which may reduce the development timeline by several months. However, participants would risk suffering severe disease or perhaps even death in such a study. While this method is not being actively pursued at this time, a grassroots movement called '1Day Sooner' has attracted 1500 willing volunteers.[39] Further, support is building for the approach among US lawmakers, who have written to the US Department of Health and Human Services and Food and Drug Administration (FDA) supporting the idea.[40]

4.2. Immune enhancement

Coronaviruses typically infect the upper respiratory tract, a part of the body that is difficult for the immune system to access.[41] If a virus isn't activating a strong immune response, an effective vaccine is hard to develop. In some cases, a vaccine can generate an immune response that goes awry, targeting the wrong cells.

This has been observed in previous vaccine candidates for related coronaviruses (e.g. SARS, MERS): an adverse reaction known as immune enhancement. In these cases, humans or animals who have been vaccinated developed more severe disease than those who had not been vaccinated.[42] This immune enhancement can occur via two known mechanisms:

- Antibody-dependent enhancement (ADE), where the virus co-opts antibodies to enhance infection and virus entry into cells.[43]
- Cell-based enhancement, which is when a faulty T-cell response triggers allergic inflammation.

Experts continue to debate whether either of these pathways could be an issue for SARS-CoV-2 vaccines. There is also speculation that ADE and other immune reactions gone awry may play a role in the severity of COVID-19 cases.[44] Although most people who catch COVID-19 suffer only a mild-moderate illness, in some individuals the illness will progress in severity. In these instances, it is possible that ADE may be responsible for the worsened condition.[42]

Both ADE and the rogue T-cell response played a part in the failure of a vaccine for respiratory syncytial virus (RSV) in the 1960s.[45] During clinical trials, several vaccinated children fell seriously ill with RSV and two toddlers died. To avoid any similar 'immune enhancement' disasters, it is essential that rigorous safety evaluations are not bypassed in the rush to develop a vaccine.

In previous efforts to develop a SARS vaccine, researchers found that immune enhancement occurred when the whole spike protein was used as a target. But when they switched tack and based their vaccine on just a small part of the spike – the bit that attaches to human cells – the immune

enhancement did not occur.[42] In other studies, the live virus resulted in complications including lung damage in mice[46] and liver damage in ferrets[47], while an inactivated virus vaccine led to immune enhancement in non-human primates.[48]

4.3. Vaccine-derived outbreaks

Vaccines that use live, attenuated virus cannot be given to immunocompromised individuals due to the risk of causing illness. Further, this type of vaccine has the potential to seed outbreaks in the community – a rare occurrence, but one that has been documented. For example, the polio vaccine inoculates a recipient with live, attenuated virus that replicates for a time in the intestine, generating antibodies.[49] Infective virus can be excreted, and in areas with poor sanitation, this can be passed on to other individuals. This can be helpful as a form of "passive immunisation". However, the longer these vaccine-derived viruses circulate in a (usually underimmunised) community, the more mutations they accumulate, sometimes leading to outbreaks of paralysing poliovirus. Vaccine-derived poliovirus is responsible for more than 50 recent polio outbreaks in West Africa.[50]

Only three current COVID-19 vaccine candidates are using a live, attenuated virus. All three are in pre-clinical development, according to the Vaccine Centre at the London School of Hygiene and Tropical Medicine.[9] Therefore, the likelihood of a live, attenuated virus vaccine reaching market is low, and thus the risk of vaccine-derived outbreaks is also low.

4.4. Mutation of the virus

As the SARS-CoV-2 virus spreads, it naturally accumulates mutations leading to an increasing diversity of genetic sequences. One analysis suggests that there are at least three distinct genomic variants of the virus found worldwide, distinguished by particular amino acid changes.[51] It is possible, although currently considered unlikely, that the virus may mutate to such an extent that any vaccine developed is rendered ineffective. Such mutation, known as antigenic drift, is one reason why a new influenza vaccine is needed every year.[52] Antigenic drift comprises a minor change in the genetic sequence of the virus. Sometimes, these changes result in differences on the influenza surface proteins (antigens) which are recognised by the body's immune system. If enough changes accumulate over time, a new strain emerges that is not recognised by the immune system, and a new vaccine is required.[53]

The antigenic drift rate of SARS-CoV-2 is slow and mutations that have occurred so far have not made the virus more deadly.[54] These are perhaps good signs for vaccine development.

In contrast, antigenic shift is a much more abrupt and substantial change resulting from reassortment of gene segments between two separate strains of the same virus. Antigenic shift is thought to be responsible for the 2009 H1N1 swine flu epidemic.[55] However, SARS-CoV-2 cannot undergo antigenic shift as coronaviruses do not have a segmented genome.[56]

Two preliminary studies, not yet peer-reviewed, have identified mutations in the critical spike protein that mediates virus entry into cells and is the target of many vaccine candidates.[57, 58] The authors of one study claim the observed D614G mutation enhances the transmissibility of the virus,[57] but this interpretation is hotly contested.[59] Continued monitoring of mutations is essential to ensure any potential vaccine remains effective. One reason the spike protein has been targeted in vaccine development is that a mutation major enough to prevent antibodies raised by a vaccine binding to it is likely to prevent it binding to cell receptors and therefore no longer being infective.

4.5. Duration of immunity

It is possible that the first vaccine to reach market may only provide immunity for a limited duration, or immunity in only a low percentage of vaccine recipients.[60] In this case, it could be used as an interim solution until a longer-lasting vaccine is developed and passes clinical trials. As stated by Professor Danuel Altmann, an immunology researcher at Imperial College London, "We need to bear in mind that we're hunting here for 'good enough' protection, not complete 'sterilising immunity' which might be hard to achieve."[61]

Immunity is a somewhat murky issue. For SARS-CoV-2, there are some reports of recovered patients being reinfected.[62] It is possible, however, that these patients simply returned a false negative test in the midst of ongoing infection. Rather than catching the virus again, the viral load may have dropped below the sensitivity of the test as it fluctuates towards the tail-end of the infection. One study found that patients continued to shed viral RNA, but not infectious whole virus particles, between seven and 20 days from the onset of symptoms.[63]

In a recent study, rhesus macaque monkeys were infected with the SARS-CoV-2 virus and developed symptoms similar to those observed in humans.[64] Once the initial infection had cleared, the monkeys were re-infected. They displayed an immune response and a significant reduction in viral load, indicating that they had developed protective immunity against re-infection. However, durability of immunity remains unclear, with previous observations that antibody responses induced by coronavirus infection in humans may wane over time in some cases.[65] Indeed, a recent study (not yet peer-reviewed) tested samples from 23,000 healthworkers in Wuhan who were exposed to infected patients.[66] Four percent had the typically long-lasting IgG antibodies as of April, but it is estimated that up to 25% of this cohort may have contracted COVID-19. The authors suggest that those with mild or asymptomatic cases may not develop protective antibodies. Even among those who do, the protection may not last long.

It is possible that no long lasting vaccine will be developed and regular booster shots will be required.

4.6. Immune senescence

Most severe cases of COVID-19 occur in individuals aged 50 years or more.[65] Protecting this segment of the population with immunisation is therefore of particular interest. However, older people typically don't respond as well to vaccines due to ageing of the immune system, known as immune senescence. This phenomenon is seen with the influenza vaccine, where older individuals may require a formulation with different antigens or adjuvants to elicit protection.[67]

Even if vaccination in older people is ineffective, they will still benefit indirectly from uptake of the vaccine among younger people that prevents widespread transmission.

4.7. Scalability and accessibility

The ability to scale up production of a vaccine is a key issue, with different vaccine platforms more scalable than others. For example, it is theoretically possible to produce large amounts of vaccine based on the mRNA platform, but established platforms, such as live attenuated vaccines, already have existing infrastructure that can easily be used to manufacture vast quantities.

Johnson & Johnson (J & J) believe they can produce 300 million doses of their Ad26 vaccine in a 2000-litre vessel on an annual basis. They currently have one vessel with another coming online by the end of the year. However, they estimate they will need at least one billion doses available to avoid a "vaccine war".[10] Similarly, German company CureVac currently estimates it would be able to manufacture 400 million doses of its RNA vaccine candidate per year.[68] BioNTech and Pfizer say

they can produce millions of doses of their RNA vaccine this year, with scale-up to hundreds of millions possible from 2021.[69]

These numbers are still too small to meet expected worldwide demand. With a fixed number of vaccine doses available, the issue then becomes one of accessibility: who gets the vaccine first? WHO is working to address this issue through their Covax facility. Current best-case estimates suggest Covax could provide a few hundred million doses of vaccine by December 2020, scaling up to two billion by the end of 2021.[70] At-risk populations may be prioritised, including healthcare workers and countries or territories suffering high casualties at the time a vaccine is available.

However, hoarding by individual wealthy countries may eventuate, as was seen during the 2009 H1N1 influenza epidemic when Australia was among the first to manufacture a vaccine, but delayed exporting to provide the vaccine to its own citizens first.[68] Similar practices have already been observed in the current pandemic – for example, the US buying the entire global supply of remdesivir.[71] A Cabinet paper proactively released on the COVID-19 vaccine strategy says that this history suggests "that there will be strong incentives on manufacturing countries to restrict the export of vaccines until they have ensured sufficient supply for their own needs".[34]

In Aotearoa New Zealand, care must be taken to ensure any vaccine is available equitably. This may involve prioritising at-risk people, such as those aged over 65, pregnant women, and people with certain chronic illnesses – as has been done with the influenza vaccine this year.[72] Access will also mean ensuring geographical spread of vaccine stocks across the country and may involve more proactive targeting of at-risk populations including Māori, Pasifika, and rural communities. Cost should also be considered as this may be a barrier to vaccination for some.

4.8. Vaccine uptake

Even if a vaccine is available, a sufficient proportion of the population must be vaccinated in order to substantially reduce transmission. A recent poll conducted by Stickybeak on behalf of *The Spinoff* asked 605 respondents: "If and when a COVID-19 vaccine becomes available, will you aim to get vaccinated?"[73] Sixty-five percent of respondents said "yes", while 20% said "unsure" and 16% said "no". These results conform with expectations, according to Professor Peter McIntyre, a member of the WHO Strategic Advisory Group of Experts (SAGE) and researcher at the University of Otago. Both McIntyre and Dr Caroline McElnay, the Ministry of Health's director of public health, estimate that around 60–70% uptake will be required to achieve herd immunity and dampen the spread.

5. Selected vaccine candidates

It is too early to say which of the vaccines in development will be successful. The RRIF paper 'The most promising vaccines for COVID-19' says that, "… we do not yet know enough regarding the safety or efficacy of each candidate, or global capability to manufacture them at large scale under Good Manufacturing Practice conditions".[35]

5.1. Vaccines in clinical evaluation

As of 16 July, there are at least 22 vaccines registered in clinical (human) trials.

5.1.1. University of Oxford and AstraZeneca

Name:	Type:	Current stage:
AZD122	**Non-replicating viral vector**	**Phase I/II/III**

The University of Oxford, with the support of CEPI and AstraZeneca, have developed an adenovirus-based vaccine named **AZD1222** (formerly ChAdOx1). The vaccine uses an attenuated chimpanzee adenovirus as a vector which displays the SARS-CoV-2 spike protein on its surface.

Current stage: two phase I/II clinical trials concurrent with two phase II/III trials.

- The earliest phase I/II trial began on 23 April 2020 with 1090 participants in the UK. It aims to determine the efficacy, safety and immunogenicity of AZD1222 in healthy adults aged 18 to 55. The single-blinded, randomised study has different groups receiving different sequences of doses plus booster doses over six months.[74]
- Another phase I/II study has commenced in South Africa as of 24 June 2020. The double-blinded, randomised and placebo-controlled study is investigating safety, efficacy and immunogenicity in two cohorts: adults without HIV, and adults living with HIV.[75]
- A phase II/III study in the UK began on 28 May 2020 involving up to 10,260 healthy volunteers across six study groups.[76]
- A phase III trial in Brazil began on 20 June 2020 and will enrol 5000 volunteers.[77]
- There is an ongoing phase I clinical trial in Saudi Arabia using the same adenovirus vector to target the related coronavirus that causes Middle East Respiratory Syndrome (MERS).[78]

Results:

- A preprint (not yet peer-reviewed) describing results from testing in rhesus macaque monkeys revealed no evidence of immune-enhanced disease following challenge in vaccinated animals.[79] Vaccination induced an immune response and reduced viral load but did not completely protect the animals from infection and symptoms. These results prompted Professor Eleanor Riley, an immunology researcher at the University of Edinburgh, to state, "If similar results were obtained in humans, the vaccine would likely provide partial protection against disease in the vaccine recipient but would be unlikely to reduce transmission in the wider community."[80]
- Another preprint describes results of testing in pigs, with two doses of the vaccine generating a greater neutralising antibody response than a single dose.[81]

Future: Preliminary results from the clinical trials are expected in August/September 2020.[82]

The AstraZeneca CEO has stated that the vaccine is expected to provide protection for about one year.[82] It is unclear whether recipients would then receive a booster dose, switch to a different vaccine, or simply rely on treatments if subsequent infection were to occur.

AstraZeneca has at least ten deals with countries to supply its vaccine, considered by WHO to be a frontrunner.[83] More than one billion doses of AZD1222 have been ordered by Europe, Britain, the US and Gavi, the Vaccine Alliance.[84] Thirty million of these will be made available in Britain by September 2020.[84] The Serum Institute of India is producing one billion doses, with 400 million expected to be available by the end of 2020, mostly for low- and middle-income countries. One dose of the AZD1222 vaccine costs about the same as a cup of coffee.[84]

5.1.2. CanSino Biologics and Beijing Institute of Biotechnology

Name:	Type:	Current stage:	
Ad5-NCoV	**Non-replicating viral vector**	**Phase I/II**	**Approved for military use**

Supported by China's Academy of Military Medical Sciences, CanSino Biologics (CanSinoBIO) have fast-tracked development of a vaccine known as **Ad5-nCoV**. This vaccine uses a non-replicating adenovirus vector – a platform that has been used to produce an ebolavirus vaccine, Ad5-EBOV, which is approved for clinical use in China.[85]

Current stage: temporary, year-long approval for use among Chinese military personnel.

Recruitment for phase II clinical trials underway, as CanSinoBIO forges ahead based on preliminary safety data from phase I trials which began mid-March.[86] The phase II study will enrol 500 participants to receive low or medium vaccine doses or a placebo. They will be monitored for six months to assess reactions and antibody production.

Results:

- Results of a phase I trial, reported in *The Lancet*, were mixed.[87] One hundred and eight articipants received injections at low, middle or high doses. Although no "serious" side effects were observed, nearly half of the participants experiencing fever, fatigue or muscle pain. The immunogenicity stats were also "lukewarm"[88] with around half of the recipients in the low- and middle-dose groups developing neutralising antibodies. This rose to around 75% in the high-dose group, but was accompanied by an increase in adverse side effects.
- Results from a phase II trial of 508 people were reportedly "much better" than phase I but have not been released publicly.
- Preclinical animal studies showed a "good safety profile".[89]

Future: Results of phase I/II expected approximately six months from now. Phase III trials with 40,000 participants are expected to begin soon as CanSinoBIO is in talks with Russia, Brazil, Chile and Saudi Arabia.[90] A collaboration with Canada to test the vaccine there was previously announced in May.[91]

5.1.3. Moderna and NIAID

Name:	Type:	Current stage:
mRNA-1273	**Nucleic acid (RNA)**	**Phase I/II**

Another candidate to enter human trials at record pace, Moderna's **mRNA-1273** candidate is also supported by the National Institute of Allergy and Infectious Diseases (NIAID) and CEPI. The vaccine, injected into the arm, consists of a small piece of messenger RNA (mRNA) wrapped up in lipids so it can enter a cell.

Current stage: phase I clinical trials to assess safety and immunogenicity began 16 March 2020 in Seattle, US. Trial run in conjunction with the NIAID and involves 45 healthy adults receiving two doses of the vaccine 28 days apart.[92] This trial is ongoing.

A phase II trial has completed recruitment for 600 participants in two cohorts: healthy adults aged 18-55, and adults aged over 55.[93]

Results:

- Moderna has released a preliminary report detailing results from its phase I trial. The vaccine induced anti-SARS-CoV-2 immune responses in all participants, and despite some adverse events being recorded, there were no trial-limiting safety concerns identified.[94]
- Four people in the study of 45 experienced "Grade 3" adverse events. One of these was a low-dose recipient who developed rash at the injection site; the other three received the highest dose and had reactions "that involved their whole bodies."[95]
- The vaccine was not tested in animals prior to phase I beginning.

Future: phase III study involving 30,000 participants has been delayed as changes are made to the trial protocol, but the trial is still expected to commence on 27 July.[96] The vaccine could be available in the US under emergency use authorisation in late 2020 depending on results and regulations.[97]

5.1.4. Inovio Pharmaceuticals

Name:	Type:	Current stage:
INO-4800	**Nucleic acid (DNA plasmid)**	**Phase I/II**

With the support of CEPI, Inovio has developed a DNA-based vaccine candidate called **INO-4800**.

Current stage: pre-clinical trials in Australia/elsewhere concurrent with phase I/IIa trials in the US.

- The Australian pre-clinical trials involve a challenge study using ferrets while Inovio told *Nature* that challenge studies are also underway in monkeys.[98]
- The phase I trial involves 40 adults in Philadelphia, Pennsylvania and Kansas City, Missouri receiving two doses of vaccine four weeks apart.[99] The first dose was administered on 6 April 2020.[100]
- The phase I/IIa study, to be undertaken in South Korea, is not yet recruiting.[101] INO-4800 will be administered via injection followed by electroporation. The study aims to evaluate the safety and immunogenicity of INO-4800.

Results:

- Inovio issued a press released claiming "positive" interim results from the phase I trial.[102] However, they did not include information on how many patients produced neutralising antibodies – key to understanding whether the vaccine actually works.

- Results from mice and guinea pigs were recently reported, with the vaccine eliciting both antibodies and a T-cell response.[103]
- An Inovio-developed MERS DNA vaccine candidate underwent Phase I testing, yielding high levels of antibodies.[104]

Future: Inovio expects to have one million doses available by the end of 2020 for ongoing trials and possible emergency use.[100] They plan to proceed with larger trials later this year.

5.1.5. Sinovac Biotech

Name:	Type:	Current stage:
CoronaVac	**Inactivated virus**	**Phase I/II/III**

Beijing-based company Sinovac have rapidly progressed their vaccine candidate '**CoronaVac'** (previously PiCoVacc) through clinical trials. While the inactivated virus platform is considered "old school", it is a vaccine type that many low-middle income countries will have the ability to manufacture.[105]

Current stage: Phase I/II trials ongoing; phase III due to start imminently. The phase I/II clinical trials (randomised, double-blinded, placebo-controlled) involve 744 healthy adults (144 phase I, 600 phase II) in Jiangsu, China.[106] The trials began in mid-April and aim to evaluate the safety and immunogenicity of the vaccine.

Results:

- Preliminary results from the phase II study indicated that CoronaVac is safe and induces neutralising antibodies in more than 90% of recipients 14 days post-vaccination.[107] Detailed results will be published in academic peer-reviewed literature.
- Studies in mice, rats and non-human primates found that the vaccine induced neutralising antibodies.[108] Different doses were tested, with the highest dose providing complete protection against SARS-CoV-2 in macaque monkeys.

Future: The phase III trial is due to start in July. The double-blind, placebo-controlled study will assess the safety and efficacy of the vaccine across more than 8800 healthcare professionals in Brazil.[109]

5.1.6. BioNTech and Pfizer

Name:	Type:	Current stage:
BNT162	**Nucleic acid (RNA)**	**Phase I/II**

This collaboration between US-based Pfizer and Germany-based BioNTech involves simultaneous testing of four RNA vaccine candidates, each with a different mRNA format and target antigen. They are referred to as **BNT162 a1, b1, b2 and c2**.

Current stage: four candidate vaccines in randomised, placebo-controlled phase I/II trials.[110] The parallel trials began on 29 April 2020 and consist of three stages. In the first stage, the aim is to identify the best vaccine candidate, appropriate dose and schedule of administration if multiple

doses are warranted. Stages two and three will comprise expanded participant cohorts (giving a projected total of 7,600) to assess safety, immunogenicity and potential efficacy. The study will be split into different age cohorts including one 18–55 years, 18–85 years, and 65–85 years across multiple locations in the US and Germany.

Results: interim results for the BNT162 b1 variant were released on preprint server medRXiv.[111] Twnety-four participants received two injections three weeks apart, either 10µg or 30µg (a third, higher dose of 100µg was only administered once after causing pain at the injection site). After 28 days, participants had developed higher levels of SARS-CoV-2 antibodies than those observed in infected patients. Seventy-five percent of the 24 participants developed a short fever following the second dose.

Future:

- Both companies are anticipating positive results and are investing in scaling up manufacturing infrastructure in the US, Belgium and Germany.[69] They aim to produce millions of vaccine doses by the end of 2020, increasing to hundreds of millions in 2021.
- On the back of an FDA fast-track label, the companies are now planning for a July start date for a phase IIb/III trial that could enrol up to 30,000 subjects.[112]

5.1.7. Shenzhen Geno-Immune Medical Institute (GIMI)

Name:	Type:	Current stage:
LV-SMENP-DC	**Replicating viral vector**	**Phase I/II**

Name:	Type:	Current stage:
COVID-19/aAPC	**Virus-like particle (VLP)**	**Phase I**

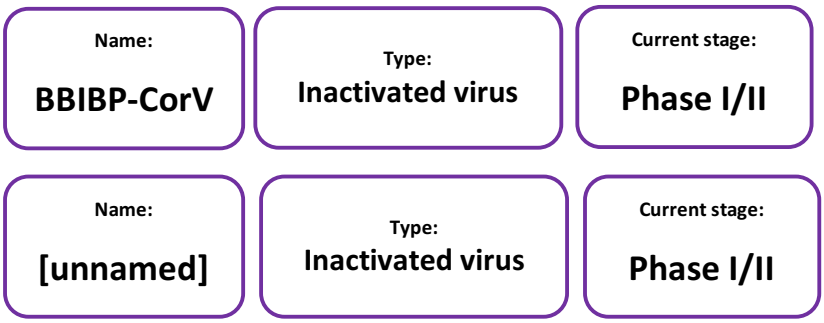
An institute founded by the Shenzhen government in China, the GIMI currently has two vaccine candidates in clinical trials.

LV-SMENP-DC is a vaccine using a lentiviral vector. Lentiviruses are a subset of retroviruses, with the most well-known example being the human immunodeficiency virus (HIV). They have long been investigated as vectors for gene therapy, and more recently vaccines, due to their ability to efficiently deliver genetic material into cells, which is then incorporated into the host genome.[113] However, they have not crossed into widespread clinical use. Use of lentiviruses or other retroviral vectors can lead to random insertion of genetic sequences in host cells, potentially leading to cancer development, as documented in some studies.[113] The LV-SMENP-DC vaccine uses a lentiviral vector to deliver “minigenes” encoding the SARS-CoV-2 spike protein, as well as immune modulatory genes that activate T-cells and modify dendritic (antigen-presenting) cells. One hundred COVID-19 patients will receive injections and IV infusions of the vaccine plus cytotoxic T-cells (CTLs) in the phase I/II trial that aims to assess the vaccine’s safety and efficacy. The trial began on 24 March 2020.[114]

COVID-19/aAPC is a vaccine platform using artificial antigen-presenting cells (aAPCs). The aAPCs are made specific to SARS-CoV-2 by applying a lentiviral vector (see above) containing viral minigenes and immune modulatory genes. The aAPCs are inactivated before being administered to participants

via arm injection in this phase I trial. The trial, which began on 1gm5 February, is enrolling 100 healthy or COVID-19-positive individuals to assess the efficacy and safety of the vaccine.[115]

5.1.8. Sinopharm



The state-backed Chinese company Sinopharm is developing two vaccine candidates based on 'old school' methodology of whole, inactivated virus particles. Both are currently in phase I/II clinical trials. **BBIBP-CorV** is being developed out of the Beijing Institute of Biological Products, while an unnamed candidate is being developed at the Wuhan Institue of Biological Products.

Current stage:

- According to the Chinese Clinical Trial Registry, phase I/II trials are ongoing for BBIBP-CorV, with 480 participants in phase I and 1648 in phase II.[116]
- The unnamed vaccine has reporterdly entered phase III trials in the United Arab Emirates.[117]
- There are reports that employees at some large state-run companies in China have been offered either of the two vaccines prior to overseas travel.[118]

Results:

- Some preliminary results released by Sinopharm for the unnamed vaccine indicate it triggers a 'high' neutralising antibody response, although specific data has not been shared publicly.[119] No serious adverse reactions were observed. All volunteers in the phase I/II trial have received two injections of the vaccine. The participants were split into placebo, low, middle and high dosage groups and received the injections either 14, 21 or 28 days apart. The middle-strength dose 28 days apart appeared most promising, according to Sinoparm.
- In early June, Sinopharm published positive results for BBIBP-CorV in *Cell* from animal studies in mice, rats, rabbits, guinea pigs and two different monkey species.[120] The vaccine induced neutralising SARS-CoV-2 antibodies and did not spur any serious adverse reactions. The vaccine also protected rhesus macaque monkeys who were 'challenged' with the virus and did not trigger antibody-dependent enhancement.

Future: A new manufacturing facility has been constructed in Beijing alongside a sister facility under construction in Wuhan. Together, the two facilities will have capacity to produce 200 million doses.

5.1.9. Imperial College London (ICL) Department of Infectious Diseases

Name:	Type:	Current stage:
COVAC1	**Nucleic acid (RNA)**	**Phase I/II**

An RNA-based vaccine candidate called **COVAC1** with funding support from CEPI. The vaccine consists of self-amplifying RNA (saRNA) which is injected intramuscularly. The ICL team received funding from CEPI in December 2018 to develop their saRNA platform for general use against infectious diseases.[121]

Current stage: phase I/II clinical trials. More than 300 participants have been screened for the UK-based trials, and ICL is continuing to recruit for the study.[122] The first phase of the trial is expected to last two months.[123]

Results:

- The ICL team conducted preclinical safety testing in animal models prior to starting the trials in humans, with "promising" results.[124]
- Within 14 days of receiving the genetic sequence of the virus in January 2020, the team had developed a vaccine candidate.[125]

Future: plans to proceed with phase II/III trials to assess efficacy with 6000 participants beginning in October.[122]

5.1.10. Novavax

Name:	Type:	Current stage:
NVX-CoV2373	**Protein subunit**	**Phase I**

Named **NVX-CoV2373** and supported by both CEPI and Operation Warp Speed, this candidate was identified from a range of constructs. The vaccine consists of nanoparticles carrying modified spike protein antigens, as well as a saponin-based adjuvant called Matrix M. Novavax has never brought a product to market before.

Current stage: phase I clinical trials ongoing.[126] The trial is randomised, observer-blinded and placebo-controlled in 131 participants. It aims to assess the safety and immunogenicity of the NVX-CoV2373 vaccine both with and without the Matrix M adjuvant.

Results: Pre-clinical trials have yielded neutralising antibodies in animal models.[127]

Future:

- Preliminary results are expected in July 2020. The study will proceed to phase II if phase I results are promising. Phase III efficacy trials are planned for later in 2020 and interim results are expected by the end of 2020 also.[128]
- Novavax has a $60 million contract with the US Department of Defense to deliver 10 million doses to American troops.[128]
- Through Operation Warp Speed, Novavax has a deal to deliver 100 million doses to the US by the beginning of 2021.[128]

5.1.11. University of Queensland

Name:	Type:	Current stage:
Molecular clamp	**Protein subunit**	**Phase I**

The University of Queensland (UQ) has received support from CEPI and the Queensland Government to develop a "molecular clamp" protein subunit vaccine – an experimental platform that could be repurposed for other pathogen targets. The "molecular clamp" holds the viral antigen in the correct conformation. UQ is partnering with CSL Ltd to use their adjuvant technology and as a trusted manufacturer should clinical trials be successful.[129]

Current stage: phase I clinical trials in Brisbane, Australia with 120 participants aged 18 to 55. The study was placebo-controlled and first doses were administered on 13 July 2020.[130]

Results: preclinical testing showed induction of neutralising antibodies and demonstrated baseline safety.[130]

Future:

- Preliminary data from the phase I trial is expected in about three months' time.[131]
- If results are positive, UQ will proceed to larger trials.
- The molecular clamp technology is a general-purpose technique that may be applied to other pathogens.

5.1.12. Symvivo Corporation, University of British Columbia and Dalhousie University

Name:	Type:	Current stage:
bacTRL-Spike	**DNA, bacterial medium**	**Phase I**

Symvivo is adapting its **bacTRL** platform for SARS-CoV-2.[132] This consists of a bacterial cell containing plasmid DNA that encodes antigens and neutralising nanobodies. The vaccine is ingested (like taking probiotic capsules) and the bacteria bind to gut epithelial cells. This delivers the plasmid DNA in a manner similar to a natural infection. The vaccine currently being tested is called **bacTRL-Spike**, with the virus' spike protein serving as the antigen target. There are two further bacTRL formulations for SARS-CoV-2 undergoing investigation.

Current stage: 84 participants aged 18–45 in a randomised, placebo-controlled and double-blind phase I trial.[133] The Canada-based study aims to evaluate safety and immunogenicity.

Future: study is expected to start in July.

5.1.13. CureVac

Name:	Type:	Current stage:
CVnCoV	**Nucleic acid (RNA)**	**Phase I**

This RNA vaccine candidate, dubbed CVnCoV, is being developed by CureVac with funding support from CEPI. It uses messenger RNA (mRNA), which has already been used by CureVac to develop a rabies vaccine that generates immunity.[134]

Current stage: a placebo-controlled phase I clinical trial in 168 participants in Germany and Belgium.[135] The study will evaluate safety, appropriate dose, adverse reactions and immune responses generated.

Results: preclinical testing found that a low dose of CVnCoV generated nautralising antibodies.[136]

Future: Depending on the outcomes of the phase I trial, larger phase II trials will begin in the later half of 2020.[136]

5.1.14. Other vaccine candidates in clinical trials

Table 4: Other vaccine candidates in clinical trials as of 15 July

Vaccine name	Vaccine type	Developed by	Current stage	Reference
AG0301-COVID19	Nucleic acid (DNA)	AnGes Inc.	Phase I/II	[137]
V-SARS	Inactivated virus	Immunitor	Phase I/II	[138]
AV-COVID-19	Virus-like particle (VLP) / modified APC	Aivita Biomedical Ltd	Phase I/II	[139]
[unnamed]	Inactivated virus	Chinese Academy of Medical Sciences	Phase I/II	[140]
Gam-COVID-Vac	Non-replicating viral vector	Gamaleya Research Institute	Phase I/II	[141, 142]
AlloStim	Living cell	Immunvative Therapies Ltd	Phase I/II	[143]
GX-19	Nucleic acid (DNA)	Genexine Inc	Phase I/II	[144]
[unnamed]	Virus-like particle (VLP)	Medicago Inc	Phase I	[145]
SCB-2019	Protein subunit	Clover Biopharmaceuticals	Phase I	[146]
COVAX-19	Protein subunit	GeneCure Biotechnologies	Phase I	[147, 148]

5.2. Selected examples of vaccines in preclinical stages

5.2.1. Janssen/Johnson & Johnson

Name:	Type:
Ad26.COV2-S	**Non-replicating viral vector**

Janssen, a research division of corporation Johnson & Johnson (J&J), is collaborating with the US Government's Biomedical Advanced Research and Development Authority (BARDA) via Operation Warp Speed. Each organisation is committing nearly US$500 million in funding to the effort, for a total of nearly US$1 billion.[10] The vaccine candidate being funded, named **Ad26.COV2-S**, uses a non-replicating viral vector platform, specifically an adenovirus.

Current stage: Currently in pre-clinical trials. The Ad26 vector has been used as platform for other vaccine candidates and is currently in various phases of clinical trials. An ebola virus vaccine using the Ad26 vector was rolled out in the Democratic Republic of the Congo in November 2019.[149]

Future: Janssen has accelerated phase I/IIa trials to evaluate the safety and immunogenicity, and now plans to commence these in mid-late July 2020.[150] The trial will enrol 1045 healthy adult volunteers in the US and Belgium. Janssen is also in discussions with the NIAID to accelerate phase III efficacy trials (pending phase I results).[151]

5.2.2. Arcturus Therapeutics and Duke-NUS

Name:	Type:
LUNAR-COV19	**Nucleic acid (RNA)**

This collaboration between an RNA medicines company and medical school is working on a messenger RNA (mRNA)-based vaccine for Singapore.[152] The vaccine uses Arcturus' proprietary STARR™ technology (self-transcribing and replicating RNA) with a lipid-mediated nanoparticle delivery system called LUNAR® to deliver RNA encoding the SARS-CoV-2 spike protein.[153] This technology means that the vaccine can likely be administered in a single shot at very low dose.[154]

Current stage: preclinical development.

Results:

- Preclinical data from studies in rodent models released thus far shows that LUNAR-COV19 triggers multiple elements of the adaptive immune response, including neutralising antibodies and T cells.[155, 156]
- The STARR™ mRNA elicited higher levels of IgG antibodies than conventional mRNA at equivalent doses.[156]

Future:

- Arcturus expects to begin phase I clinical trials in Singapore "this [northern hemisphere] summer".[157] Current plans involve enrolment of up to 76 healthy adult volunteers (including elderly individuals) who will be followed for several months to evaluate immunogenicity.[154]

- Arcturus have announced a deal with Catalent Inc, based in Wisconsin, US, to support human clinical trials and potential manufacture and commercialisation of LUNAR-COV19.[158]

5.2.3. University of Pittsburgh School of Medicine and UPMC

Name:	Type:
PittCoVacc	**Protein subunit**

In addition to their role in a consortium developing a measles vector vaccine (see below), the University of Pittsburgh is working on another approach. This candidate is called **PittCoVacc** and consists of a protein subunit (a section of the spike protein) delivered via a microneedle patch (essentially a bandaid with tiny vaccine 'needles' made of protein and sugar that dissolve in the skin).

Current stage: Pre-clinical trials.

Results: A recent study reports that vaccinated mice produced antibodies specific to SARS-CoV-2.[159] This represents the first peer-reviewed research into a COVID-19 vaccine candidate.[160]

Future: Awaiting approval to begin phase I clinical trials to assess safety.[161]

5.2.4. The University of Hong Kong

Name:	Type:
SARS-CoV2-RBD LAIV	**Live, attenuated viral vector**

A vaccine candidate in development at the University of Hong Kong (HKU) with support from CEPI, **DelNS1-SARS-CoV2-RBD LAIV** is based on an established live attenuated influenza virus (LAIV) platform.[162] The influenza vector has a key virulent element deleted from its genome and is modified to express a SARS-CoV-2-specific antigen.

Current stage: pre-clinical trials and proof-of-concept studies in animal models.

Future: Expected to enter phase I clinical trials in July.[163]

5.2.5. Instiut Pasteur, Thémis and the University of Pittsburgh

Name:	Type:
MV-SARS-CoV-2	**Replicating viral vector**

This consortium is collaborating with the support of CEPI to repurpose their measles virus vector. The candidate is called **MV-SARS-CoV-2** and uses a replicating viral vector: the measles vaccine virus (MV). This platform has previously been used by the consortium above to develop and investigate

vaccines for SARS, MERS and Chikungunya.[164] Note that Thémis has now been acquired by MSD/Merck & Co.[165]

Current stage: pre-clinical development.

Future: Although technically further behind on the development timeline, this candidate uses a licensed platform (measles vaccine virus) with an established safety and efficacy record.[166] This means it will potentially clear hurdles faster. In addition, this type of vaccine is easy to produce in large quantities.

6. Repurposed vaccines: an interim solution for future pandemics?

Several clinical trials are aiming to assess whether vaccines for other diseases could induce non-specific immune-enhancing effects[167], thereby reducing morbidity from COVID-19. These include:

- The Bacille Calmette- Guérin (BCG) vaccine to prevent tuberculosis[168]
- The oral polio vaccine[169]
- The measles, mumps and rubella (MMR) vaccine[170]

6.1. The BCG vaccine

Trials in Australia and the Netherlands are underway to assess whether the bacilli Calmette-Guérin (BCG) vaccine can reduce the severity of COVID-19 symptoms.[168] The BCG vaccine has been used as a tuberculosis vaccine for nearly one hundred years.[171] Around two billion doses have been administered during this time, and 130 million children worldwide continue to receive the vaccine every year in countries where TB is still prevalent. It has an excellent safety profile and side effects are rare.

Beneficial off-target effects of the BCG vaccine have recently been recognised, including an immune-boosting effect which trains the innate immune system (the frontline response) to respond to infections. Previous research has found that individuals who receive the BCG vaccine suffer from fewer respiratory viral infections,[172] and experimental infection studies show that the vaccine reduces the level of virus present in the body. A number of preprints yet to be peer-reviewed claim to have found that countries with active BCG vaccination regimes also have lower instances of COVID-19,[173, 174] but others caution against over-interpreting such ecological studies with many confounding factors.[175] A recent analysis from Israel did not find a link between BCG vaccination status and prevalence of COVID-19.[176] Meanwhile, an epidemiological study published in *PNAS* that controlled for multiple confounding factors found “several significant associations between BCG vaccination and reduce COVID-19 deaths”.[177]

Although the ongoing trials are endorsed by WHO, the organisation has also released a scientific brief stating that they do not currently recommend BCG vaccination for the prevention of COVID-19.[178] In addition to WHO, the trial has also received support from the Bill and Melinda Gates Foundation with a donation of AU$10 million.[179]

Researchers in Australia are investigating whether the BCG vaccine can be ‘rejigged’ with antigens from SARS-CoV-2 to make it more specific.[180] They are calling this vaccine BCG:CoVac and say “initial results are promising”.

7. Further reading

The most promising vaccines for COVID-19 *Rapid Research Information Forum*

The COVID-19 vaccine development landscape *Nature Reviews Drug Discovery*

The virus and the vaccine *ABC Australia*

COVID-19 vaccine frontrunners *The Scientist*

COVID-19 vaccine development pipeline *London School of Hygiene & Tropical Medicine*

Coronavirus disease (COVID-2019) R&D *WHO*

Could BCG, a 100-year-old vaccine for tuberculosis, protect against coronavirus? *The Conversation*

SARS-CoV-2 vaccines: Status report *Immunity*

Cochrane COVID-19 Study Register *Cochrane*

8. Acknowledgements

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