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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 **39 vaccine candidates registered in clinical (human) trials**, out of a total of at least 210 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. Both viral vector and RNA platforms seem promising at this early stage.
- It is difficult to predict when a vaccine will be widely available but the earliest we could possibly have some vaccine doses available in Aotearoa New Zealand is mid-late 2021. 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 or sugar molecules (also known as antigens) 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, along with long-term immune memory.

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 while others may only target specific bits of the spike. Some target an antigen called the N protein, while others target multiple antigens.[2] Other antigens aside from the spike protein are able to induce a T cell response.[3]

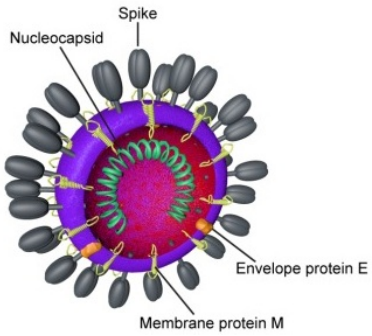

Figure 1: Diagram of a coronavirus virion with the spike protein labelled. CC BY 3.0.[4]

In addition to the antigen, some vaccines contain an adjuvant: a compound 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. At least 12 candidates in clinical evaluation use an adjuvant.[2]

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**: Measles, mumps and rubella vaccines, chickenpox vaccines, and rotavirus vaccines
	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, polio vaccine
Protein	Subunit	Rather than introducing a whole organism, this type of vaccine only includes a fragment or individual protein or sugar (polysaccharide)	**Example**: hepatits B vaccine, tetanus,

		molecule. Will probably require an adjuvant and multiple doses.	diphtheria, pertussis
	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 protein correctly folded. Immunogenic. Quickly degraded and likely very safe. 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 in correct conformation Limitations: more complex to administer requiring special equipment (electrical pulse to get cells to take up). Hypothetical possibility of integration into host genome.	No licenced vaccines use this method

As of 7 September 2020, there are at least 210 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]

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

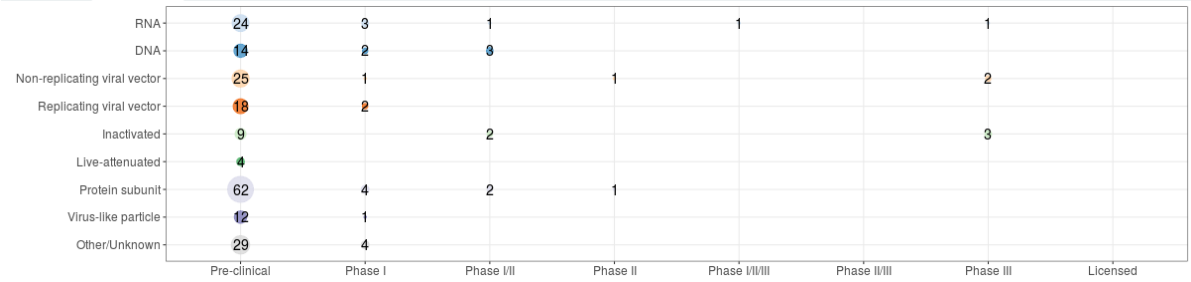

Figure 2: Different vaccine types and their progression along the development timeline. Reproduced from the 'COVID-19 vaccine development pipeline' tracker published by the Vaccine Centre at the London School of Hygiene and Tropical Medicine.[8]

2. Timeline: When will we have a vaccine?

While some pharmaceutical companies are aiming for emergency use dispensation of their vaccines within months,[9, 10] the World Health Organization (WHO) cautions that the full process will likely take at least 12-18 months, if not longer.[11] 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.[12]

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[13]) 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 in locations with the disease of interest circualting; assesses effectiveness, safety, 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.
7. **Phase IV safety and efficacy monitoring** – once the vaccine is available to the public, scientists and clinicians continue to carefully monitor its safety and effectiveness.

The Coalition for Epidemic Preparedness Innovations (CEPI) has proposed a “pandemic paradigm” that allows for accelerated vaccine development.[14]

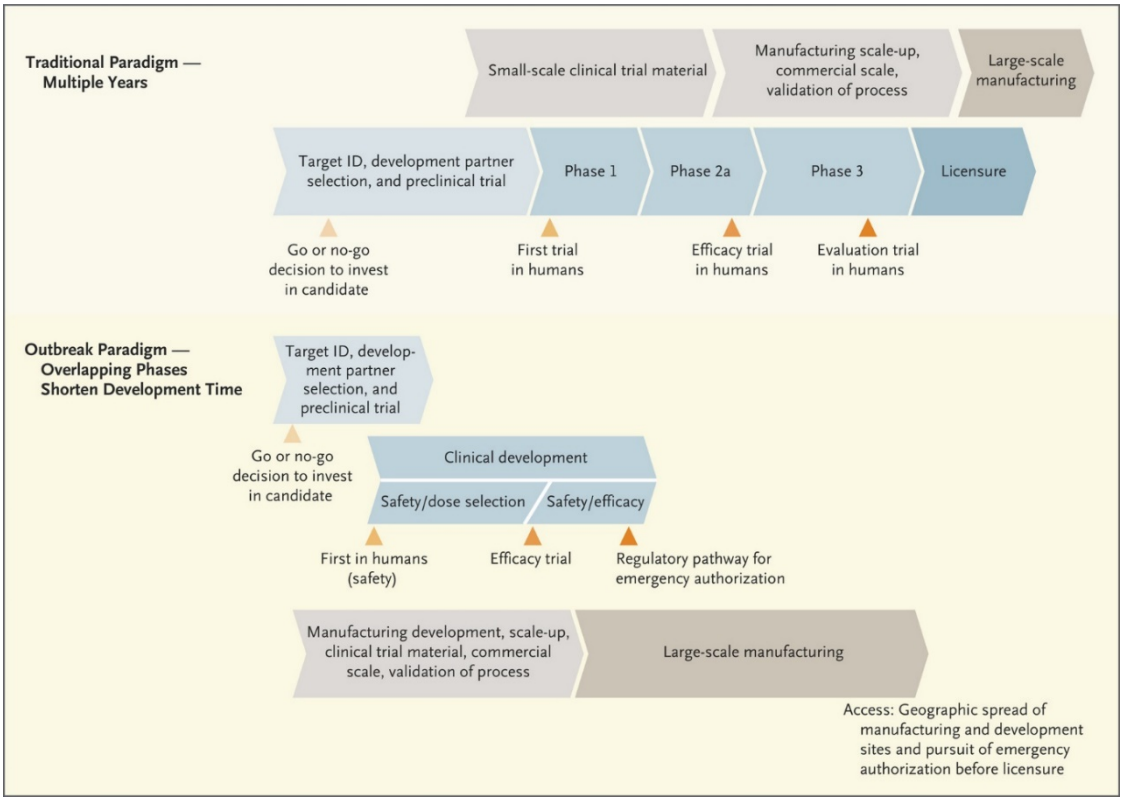

Figure 4: Difference between the traditional vaccine development paradigm and an accelerated “pandemic paradigm” as proposed by CEPI.[14]

The US National Institutes of Health (NIH) is spearheading a collaborative program called Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV).[15] This brings together public and private stakeholders to advance the vaccine development timeline in a coordinated manner (Figure 2).

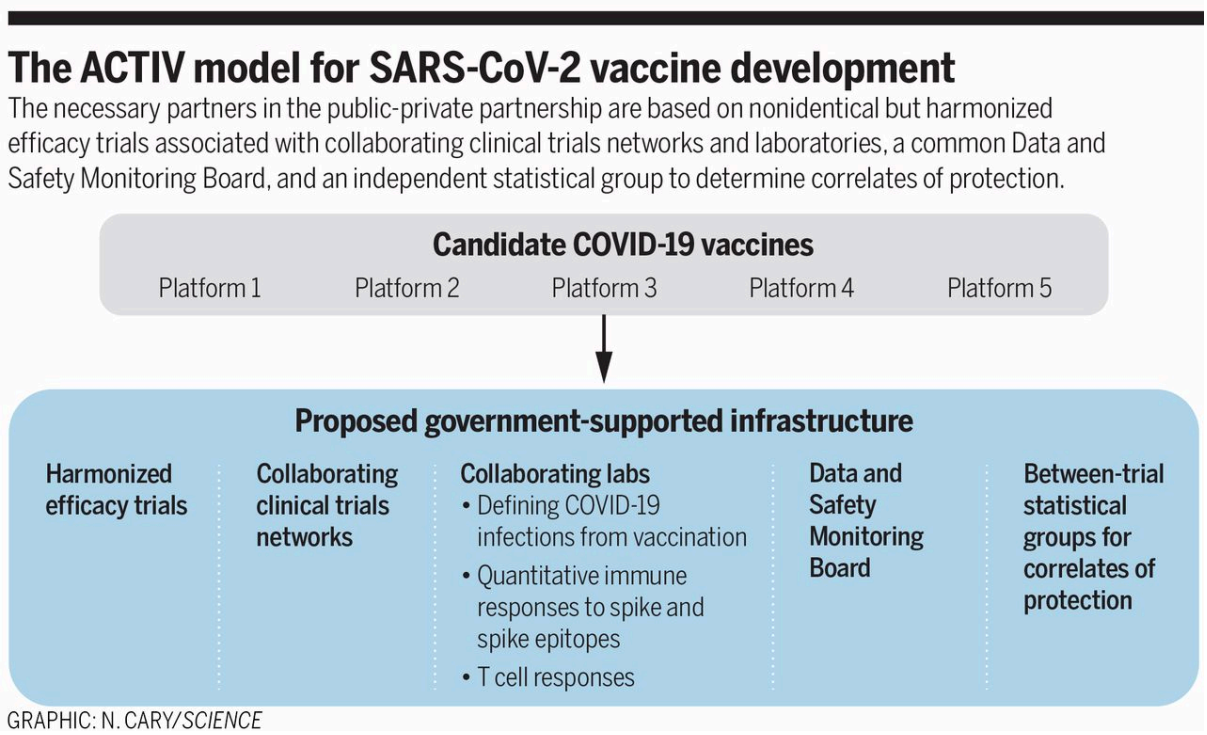

Figure 5: the ACTIV model for SARS-CoV-2 vaccine development.[15]

Beyond models, this useful interactive from *The New York Times* explores specific ways we could potentially accelerate the timeline.[16] 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'. The overlapping steps were recently successfully undertaken to speed up the availability of an ebola vaccine for Africa.

The WHO has released a Target Product Profile (TPP) that describes the characteristics an acceptable COVID-19 vaccine should have, such as providing protection for at least six months at a minimum.[17]

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/III clinical trials	
COVAC1/LNP-nCOVsaRNA	Imperial College London	nucleic acid, self-amplifying RNA (saRNA)	phase I/II clinical trials	Phase II
INO-4800	Inovio Pharmaceuticals	nucleic acid (DNA plasmid)	phase I/II clinical trials	
CVnCoV	CureVac	nucleic acid, RNA	phase I/II clinical trials	
NZX-CoV2373	Novavax	protein subunit	phase I clinical trials	Phase I
SCB-2019	Clover Biopharmaceuticals	protein subunit	phase I clinical trials	
Molecular clamp	University of Queensland, CSL	protein subunit	phase I clinical trials	
TMV-083/MV-SARS-CoV-2/V591	Institut Pasteur, MSD, University of Pittsburgh	replicating viral (measles) vector	phase I clinical trials	
unnamed	University of Hong Kong	live, attenuated virus	pre-clinical testing	pre-clinical

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 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 ten 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
mRNA-1273	Moderna, NIAID	nucleic acid, RNA	phase I/II/III clinical trials	$483 million[25]	
BNT-162	Pfizer, BioNTech	nucleic acid, RNA	phase I/II/III clinical trials	Declined to accept OWS funding[26]	
Ad26.COV2-S	Janssen (Johnson & Johnson)	non-replicating viral vector	phase I/II/III clinical trials	$456 million[27]	
INO-4800	Inovio	nucleic acid (DNA plasmid)	phase I/II clinical trials	unknown – funded for non-human primate challenge study[28]	Phase II
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[26]	pre-clinical
unnamed	Sanofi/GSK	protein subunit	preclinical testing	$2.1 billion[30]	
V590	Merck, Sharpe & Dohme (MSD), IAVI	replicating viral vector (rVSV)	preclinical testing	$38 million[31]	

3.5. Vaccine development in Aotearoa New Zealand

The New Zealand Government has allocated $37 million to a COVID-19 vaccine strategy.[32] This comes after some New Zealand scientists called for the Government to invest in an onshore vaccine programme due to potential accessibility issues[33] and a letter in the New Zealand Medical Journal co-signed by 120 scientists supporting this approach.[34]

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."[35]

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'.[36] 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.[37]

Further funding was announced on 27 August 2020 for a COVID-19 Response and Recovery Fund to enable Aotearoa New Zealand access to a safe and effective vaccine – through an initiative like the COVAX Facility, or through deals directly with vaccine developers.[38]

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).[39]

Aotearoa New Zealand has a particular strength in post-approval (phase IV) safety surveillance with our experience deploying the meningococcal B vaccine throughout the early 00s. This ability to undertake intensive real-time surveillance may provide rationale for Aotearoa New Zealand accessing the vaccine early.

4. Potential issues

4.1. Proving vaccine efficacy on an accelerated timeline

How can we quickly prove that a vaccine is safe and effective? We need a lot of trial participants.

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 may be difficult. Some trial designs require an estimate of the background incidence of COVID-19 for the cohort receiving a placebo as well. These pose challenges as the epidemiology can change rapidly in countries and territories where trials may take place.

These difficulties could be addressed by a different approach: some have proposed a 'human challenge' study as a quicker – but potentially riskier – alternative.[40] 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.[41] 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.[42]

4.2. Immune enhancement

In rare instances, a vaccine can lead to the development of more severe disease. This has not been reported in ongoing clinical trials or pre-clinical testing for SARS-CoV-2 vaccine candidates.

Coronaviruses typically infect the upper respiratory tract, a part of the body that is difficult for the immune system to access.[43] 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 adverse event known as immune enhancement has been observed in previous vaccine candidates for related coronaviruses (e.g. SARS, MERS) and a dengue fever vaccine (Dengvaxia). This has been observed in humans naive to dengue fever receiving Dengvaxia. In some animal models receiving experimental coronavirus vaccines there was enhanced lung pathology observed after challenge with the virus.[44] 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.[45]
- 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.[46] 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.[44] It is currently not possible to differentiate between severe viral infection and disease worsened by ADE.[47] To date there has been no indication that the COVID-19 vaccines will cause this but it will need close monitoring.

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.[48] 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.[44] In other studies, the live virus resulted in complications including lung damage in mice[49] and liver damage in ferrets[50], while an inactivated virus vaccine led to immune enhancement in non-human primates.[51]

4.3. Vaccine-derived outbreaks

Vaccines that use a live, attenuated virus – like the polio vaccine – can seed outbreaks in the community. This is unlikely to be an issue for SARS-CoV-2 vaccines.

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 only observed with the oral polio vaccine. For example, the polio vaccine inoculates a recipient with live, attenuated virus that replicates for a time in the intestine, generating antibodies.[52] Infective virus can be excreted, and in areas with poor sanitation and low immunity to the virus, 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.[53]

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.[8] 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

The SARS-CoV-2 virus accumulates genetic mutations as it spreads – but slowly. Mutation is unlikely to affect the efficacy of a vaccine.

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.[54] 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.[55] 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.[56]

The antigenic drift rate of SARS-CoV-2 is slow and mutations that have occurred so far have not made the virus more deadly.[57] A recent analysis of more than 18,000 individual SARS-CoV-2 genome sequences found that mutations are rare and the observed "limited diversity" should mean that one vaccine is likely to provide protection against all currently circulating variants.[58]

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.[59] However, SARS-CoV-2 cannot undergo antigenic shift as coronaviruses do not have a segmented genome.[60]

Two preliminary studies have identified mutations in the critical spike protein that mediates virus entry into cells and is the target of many vaccine candidates.[61, 62] The authors of one study claim the observed D614G mutation enhances the transmissibility of the virus, but this interpretation is hotly contested.[63] 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

We know very little about the duration and strength of immunity conferred by natural infection of SARS-CoV-2 – but this is not necessarily problematic for vaccines that do not mimic natural infection.

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.[64] In this case, it could be used as an interim solution until a longer-lasting vaccine is developed and passes clinical trials. It is also possible that no long lasting vaccine will be developed and regular booster shots will be required.

The level of protective immunity conferred post-SARS-CoV-2 infection is unknown.[65] There is emerging evidence that both neutralising antibodies and other immune responses such as T cells should be induced by a vaccine in order to offer protection.[17] Other human coronaviruses – such as those that cause the common cold – are known to elicit antibody responses that wane over time.[66]

For SARS-CoV-2, there have been at least four reports of reinfections – but these have yet to be peer-reviewed. These reinfections have been confirmed by whole genome sequencing: the genetic sequence of the variant causing the second infection is different to the variant that caused the first. The differences must be substantial enough to suggest a separate infection event, rather than genetic changes in the course of ongoing infection. In one case, a man in Hong Kong initially fell ill in March.[67] During the second infection (detected through border screening), the man was asymptomatic. In another case, a man in the United States tested positive in April and recovered, before falling ill again in June.[68] During the second infection, the man was much more seriously ill. There have been further reports of reinfection from Belgium and the Netherlands.[69]

Experts note that these may be outliers rather than the norm.[70] In another study, rhesus macaque monkeys were infected with the SARS-CoV-2 virus and developed symptoms similar to those observed in humans.[71] 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 reinfection. Even if reinfection does occur – as it does for other human coronaviruses – this is not necessarily problematic for many of the vaccines under development, some of which are inducing higher levels of neutralising antibodies than natural infection.

4.6. Immune senescence

How will we protect older people who have weaker immune systems?

Most severe cases of COVID-19 occur in individuals aged 50 years or more.[66] 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.[72] Only some vaccine candidates currently in clinical evaluation are being trialed in older people. The early data from RNA vaccines is encouraging.

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

4.7. Scalability and accessibility

How can we make enough vaccine for everyone, and who gets it first?

Different vaccine platforms more scalable than others. For example, it is theoretically possible to produce large amounts of vaccine based on the RNA platform. However established platforms, such as live attenuated vaccines, already have existing infrastructure that can easily be used to manufacture vast quantities.

Annual manufacturing estimates from different companies extend into the hundreds of millions.[9, 73, 74] These numbers are still too small to meet expected worldwide demand – especially if immunisation requires two doses, which most will.

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.[75] 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.[73] 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".[35] Similar practices have already been observed in the current pandemic – for example, the US buying the entire global supply of remdesivir.[76] The US is reportedly not going to join the COVAX Facility[77] while other wealthy countries including Japan, the UK, Canada, Australia and the EU have signed contracts directly with manufacturers.[78]

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.[79] 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

What about people who refuse a vaccine?

Even if a vaccine is available, a sufficient proportion of the population must be vaccinated in order to substantially reduce transmission. A recent survey found that 74% of New Zealanders plan to get a

COVID-19 vaccine when it becomes available.[80] Another poll asked 605 respondents: "If and when a COVID-19 vaccine becomes available, will you aim to get vaccinated?"[81] 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.

Moral objections have been raised by some religious leaders regarding vaccines that use human cell lines derived from aborted foetuses during the development process.[82] At least five vaccines in development use these cell lines, including the AstraZeneca/University of Oxford candidate. It is important to note that these cell lines come from foetuses legally aborted many years ago. New foetuses are not needed. These human cell lines have been used to develop vaccines for rubella, chicken pox, hepatitis A and shingles, and contributed to the advancement of medicine and disease treatments in many other ways.

5. Vaccine candidates

It is too early to say which of the vaccines in development will be successful. This section outlines several candidates of interest: those further along the development pipeline, and those backed by organisations like CEPI. As of 7 September, there are at least 39 vaccines registered in clinical (human) evaluation.

5.1. Vaccines in phase III clinical trials

5.1.1. University of Oxford and AstraZeneca (UK)

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.

8 September 2020 | Trial on hold: the phase III study is put on hold due to a serious adverse event in a participant in the UK. The nature of the adverse event has not been reported but the participant is expected to recover.[83] Note that in an adverse 'event', the medical occurrence is temporally related but not necessarily causally related to administration of the product.

17 August 2020 | Trial: phase III clinical trial in 30,000 participants to assess safety, efficacy and immunogenicity. The trial is randomised, double-blind and placebo-controlled and will take place in the US. Participants will receive two intramuscular injections four weeks apart.[84]

27 July 2020 | Result: A study published in *npj Vaccines* describes results of testing in pigs, with two doses of the vaccine generating a greater neutralising antibody response than a single dose.[85]

20 July 2020 | Result: Preliminary results from the phase I/II trial in the UK have been published in *The Lancet*. They show that the vaccine induces both antibodies and a T cell response, and was well tolerated by recipients.[86]

24 June 2020 | Trial: a phase I/II study commences in South Africa. 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.[87]

20 June 2020 | Trial: A phase III trial in Brazil that will enrol 5000 volunteers.[88]

28 May 2020 | Trial: phase II/III study in the UK involving up to 10,260 healthy volunteers across six study groups.[89]

13 May 2020 | Result: 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.[90] 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."[91]

23 April 2020 | Trial: phase I/II trial begins in the UK with 1090 participants. 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.[92]

Notes

- 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).[93]
- The AstraZeneca CEO has stated that the vaccine is expected to provide protection for about one year.[94] 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.[95] More than one billion doses of AZD1222 have been ordered by Europe, Britain, the US and Gavi, the Vaccine Alliance.[96] Thirty million of these will be made available in Britain by September 2020.[96] 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.[96]

5.1.2. BioNTech and Pfizer (US and Germany)

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

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**. Pfizer and BioNTech recently announced that they are advancing the **BNT162b2** variant into phase II/III trials.

27 July 2020 | Trial and results: Pfizer and BioNTech announced that they are advancing the BNT162b2 candidate into phase II/III efficacy clinical trials after receiving a 'fast-track' label from the

FDA.[97] This is an 'event-driven' clinical trial that will enrol up to 30,000 participants between the ages of 18 and 85 across multiple locations worldwide. The study will be randomised, placebo-controlled and observer-blinded.[98] The vaccine will be administered in two doses of 30µg each, 21 days apart. By the end of the trial, Pfizer and BioNTech expect participants across 120 trial sites including 39 states in the US, and countries such as Argentina, Brazil and Germany.

In a press release, Pfizer stated that two variants were identified as promising: BNT162 b1 and b2.[97] Based on tolerability and immunogenicity data gathered in both preclinical testing and the early stages of phase I/II trials, they chose to proceed with the b2 candidate. The b2 variant had a more favourable tolerability profile and also elicited T cell responses that the companies believe will lead to more consistent protection across diverse populations and older people.

The phase I/II trials are continuing, with expanded participant cohorts (giving a projected total of 7600) to assess safety, immunogenicity and potential efficacy.[99] Participants in these stages will be split into different age cohorts including 18-55 years, 18-85 years, and 65-85 years across multiple locations in the US and Germany.

1 July 2020 | Result: Interim results for the BNT162 b1 variant were released on preprint server medRXiv.[100] Twnety-four participants received two injections three weeks apart, either 10µg or 30µg (a third, higher dose of 100µg was only administered once as it caused 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.

29 April 2020 | Trial: Four candidate vaccines were chosen for randomised, placebo-controlled phase I/II trials.[99] These consist of three stages. In the first stage, which has now been compelted, the aim was to identify the best vaccine candidate, appropriate dose and schedule of administration if multiple doses are warranted.

Notes

- Results from phase I/II pertaining to the b2 variant will be published and posted on a preprint server soon.[97]
- Both companies are anticipating positive results and are investing in scaling up manufacturing infrastructure in the US, Belgium and Germany.[74]
- The Pfizer chief executive expects that we will know by October whether the vaccine is safe and effective.[101]
- Depending on phase II/III trial results, they may apply for Emergency Use Authorisation in October 2020. They will aim to supply 100 million doses by the end of 2020, and 1.3 billion doses by the end of 2021.[97]

5.1.3. Janssen/Johnson & Johnson (US and Belgium)

Name:	Type:	Current stage:
Ad26.COV2-S	**Non-replicating viral vector**	**Phase I/II/III**

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.[9] The vaccine candidate being funded, named **Ad26.COV2-S**, uses a non-replicating viral vector platform, specifically an adenovirus. This particular adenovirus, Ad26, is rarer than the Ad5 used in other vaccine candidates. This means that there are fewer people with pre-existing immunity to the vector, thereby mitigating some of the efficacy issues observed with an Ad5 vector.[102]

12 August 2020 | Trial: a phase I study to assess the safety and reactogenicity of the vaccine when administered at two different levels in a two-dose schedule. The study will be randomised, double-blind and placebo-controlled involving 250 participants in Japan.[103]

10 August 2020 | Trial: phase III efficacy trials[104] conducted with 60,000 adult participants across a range of locations worldwide, including the US, Brazil and South Africa. The study will be randomised, double-blind and placebo-controlled, aiming to "demonstrate the efficacy of Ad26.COV2.S in the prevention of molecularly confirmed moderate to severe/critical COVID-19 compared to placebo."

18 June 2020 | Trial: phase I/IIa trials with 1045 participants in a randomised, placebo-controlled and double-blind design. The purpose of the study is to assess the safety, reactogenicity and immunogenicity of the vaccine and to figure out whether a single or 2-dose schedule is optimal.[105]

Notes

- 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.[106]

5.1.4. Moderna and NIAID (US)

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

Another candidate to enter human trials at record pace, Moderna's **mRNA-1273** candidate is 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.

14 July 2020 | Trial: phase III trials are underway in the US.[107] Up to 30,000 participants will be enrolled in the randomised, observer-blinded and placebo-controlled study. Dosage is 100µg administered twice 28 days apart.

14 July 2020 | Result: 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.[108] 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."[109]

28 May 2020 | Trial: A phase II trial is also underway, with 600 participants in two cohorts: healthy adults aged 18-55, and adults aged over 55.[110]

16 March 2020 | Trial: phase I clinical trials to assess safety and immunogenicity began in Seattle, US. Trial run in conjunction with the NIAID and involves 45 healthy adults receiving two doses of the vaccine 28 days apart.[111] This trial is ongoing.

Notes

- The vaccine was not tested in animals prior to phase I beginning.
- The vaccine could be available in the US under emergency use authorisation in late 2020 depending on results and regulations.[112]

5.1.5. Sinopharm (China)

Name:	Type:	Current stage:
BBIBP-CorV	**Inactivated virus**	**Phase I/II/III**
Name:	**Type:**	**Current stage:**
[unnamed]	**Inactivated virus**	**Phase I/II/III**

The state-backed Chinese company Sinopharm is developing two vaccine candidates based on 'old school' methodology of whole, inactivated virus particles. **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.

11 August 2020 | Trial: phase III trial announced involving 6000 participants over 12 months in Bahrain.[113]

18 July 2020 | Trial: Both candidates have entered phase III trials in the United Arab Emirates with more than 5000 participants.[114]

16 June 2020 | Result: 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.[115] 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.

10 June 2020: 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.[116]

6 June 2020 | Result: Sinopharm published positive results for BBIBP-CorV in *Cell* from animal studies in mice, rats, rabbits, guinea pigs and two different monkey species.[117] 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.

29 April 2020 | Trial: phase I/II trials ongoing for BBIBP-CorV, with 480 participants in phase I and 1648 in phase II.[118]

Notes

- 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.

5.1.6. Sinovac Biotech (China)

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.[119]

2 July 2020 | Trial: phase III trials have begun in healthcare workers in Brazil.[120] The study is randomised, double-blind and placebo-controlled across 8870 participants in two cohorts: one aged 18-59 and the other 60+. Participants receive two intramuscular injections 14 days apart.

13 June 2020 | Results: Preliminary results from the phase II study (shared in a press release) indicated that CoronaVac is safe and induces neutralising antibodies in more than 90% of recipients 14 days post-vaccination.[121]

6 May 2020 | Results: Studies in mice, rats and non-human primates found that the vaccine induced neutralising antibodies.[122] Different doses were tested, with the highest dose providing complete protection against SARS-CoV-2 in macaque monkeys.

20 April 2020 | Trial: phase I/II trials (randomised, double-blinded, placebo-controlled) involve 744 healthy adults (144 phase I, 600 phase II) in Jiangsu, China.[123] The trials aim to evaluate the safety and immunogenicity of the vaccine.

5.1.7. Gamaleya Research Institute (Russia)

Name:	Type:	Current stage:	
Sputnik V	**Non-replicating viral vector**	**Phase I/II/III**	**Registered in Russia**

Formerly known as Gam-COVID-Vac, the **Sputnik V** vaccine, uses two human adenovirus vectors modified to present the spike glycoprotein on their surface. It has been developed by the Gamaleya Research Institute in partnership with the Russian defence ministry. The vaccine consists of two doses administered 21 days apart: the first dose contains the Ad26 vector, and the second contains the Ad5 vector.[124] There are concerns that vaccines based on human adenovirus vectors, especially Ad5, may not confer protection for substantial portions of the population, who may already have natural immunity to adenoviruses, thereby limiting the effectiveness of the vaccine.[125] There is also concern internationally about the acceleration of this candidate into phase III trials over a short time period, with little information or data publicly available.[126]

4 September 2020 | Result: results from phase I studies in 76 participants published in *The Lancet*, finding that the two-part vaccine does not elicit serious adverse events over 42 days, and induces an antibody response within 21 days.[127]

31 August 2020 | Trial: phase III trials in Russia enrolling 40,000 people in a randomised, placebo-controlled and double-blind study.[128] Phase III trials are also set for the Philippines, Venezuela, UAE and Saudi Arabia.[129]

11 August 2020 | Approval: the Russian Ministry of Health issues a "registration certificate" allowing emergency use of the vaccine for vulnerable groups.[130] The certificate stipulates that the vaccine cannot be rolled out widely until 1 January 2021.

1 August 2020 | Result: The Sputnik V website states that "no unforeseen or unwanted side effects were observed" and that the vaccine demonstrated "high efficacy".[129] No data corroborating these statements has been shared or published.

18 June 2020 | Trial: phase I/II trials begin in Russia with a total of 38 participants.[131, 132] The study is non-randomised and aims to evaluate the safety, tolerability and immunogenicity of the vaccine. The first phase involves 18 healthy volunteers; the second phase involves 20 participants.

Notes

- The Gamaleya Institute used a similar approach to develop an ebolavirus vaccine (GamEvac-Combi) that is registered for use in Russia.[133, 134]
- A MERS vaccine using the Ad5 platform is currently in early-stage clinical trials.[135]

5.1.8. CanSino Biologics and Beijing Institute of Biotechnology (China)

Name:	Type:	Current stage:	
Ad5-nCoV	**Non-replicating viral vector**	**Phase I/II/III**	**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.[136] There are concerns that vaccines based on human adenovirus vectors, especially Ad5, may not confer protection for substantial portions of the population, who may already have natural immunity to adenoviruses, thereby limiting the effectiveness of the vaccine.[125]

26 August 2020 | Trial: a global phase III clinical trial that is randomised, double-blind, placebo-controlled and adaptive-designed.[137] The study will enrol 40,000 people to receive either tha vaccine or a placebo, and will aim to assess the efficacy, safety and immunogenicity. The study has begun in Pakistan, but CanSino Biologics was reported to also be in talks with Russia, Brazil, Chile and Saudi Arabia for phase III studies.[138]

20 July 2020 | Results: phase II trial results are reported in *The Lancet*, and reveal that the vaccine induces neutralising antibodies and a T-cell response within 14 days of injection across 85% of participants.[139] The authors note that participants with pre-existing high levels of adenovirus antibodies did not experience such a strong immune response, and say this is "the biggest obstacle" for the vaccine candidate. While the vaccine is safe, some reactogenicity is observed with up to 74% of participants reporting adverse reactions.

25 June 2020 | Approval: the vaccine receives temporary, year-long approval for use among Chinese military personnel.[140]

22 May 2020 | Results: results of a phase I trial, reported in *The Lancet*, were mixed.[141] 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"[142] 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.

21 May 2020 | Trial: A collaboration with Canada to test the vaccine there was announced in May[143] and a clinical trial is registered but not yet recruiting for 696 participants.[144]

10 April 2020 | Trial: a phase II clinical trial with 508 participants in China. The study is randomised, placebo-controlled and double-blind and aims to evaluate both safety and immunogenicity.[145] Participants will receive low or medium vaccine doses or a placebo. They will be monitored for six months to assess reactions and antibody production.

18 March 2020 | Trial: phase I clinical trial begins with 108 participants in China to evaluate safety, immunogenicity and reactogenicity.[146]

5.2. Vaccines in phase II clinical trials

5.2.1. Inovio Pharmaceuticals (US)

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**. It consists of a DNA plasmid encoding SARS-CoV-2 antigens that is injected into the arm with associated electroporation (a small pulse of electricity) that helps the person's cells uptake the plasmid and produce the antigens based on the plasmid's DNA code.

30 July 2020 | Result: Inovio reported in a press release that INO-4800 protected rhesus macaques from live virus challenge 13 weeks post vaccination, with both T and B cell immune responses mediating this protection.[147]

30 June 2020 | Result: Inovio issued a press released claiming "positive" interim results from the phase I trial.[148] However, they did not include information on how many patients produced neutralising antibodies – key to understanding whether the vaccine actually works.

25 June 2020 | Trial: a phase I/IIa trial with 160 participants in South Korea aiming to identify the optimal dose, alongside evaluation of safety and immunogenicity.[149]

20 May 2020 | Result: Results from mice and guinea pigs were recently reported, with the vaccine eliciting both antibodies and a T-cell response.[150]

7 April 2020 | Trial: a phase I trial involving 120 adults in the US receiving two doses of vaccine four weeks apart.[151] The study aims to assess the safety, tolerability and immological profile of the vaccine.

Notes

- An Inovio-developed MERS DNA vaccine candidate underwent Phase I testing, yielding high levels of antibodies.[152]

5.2.2. Arcturus Therapeutics and Duke-NUS (Singapore)

Name:	Type:	Current stage:
LUNAR-COV19 (ARCT-021)	**Nucleic acid (RNA)**	**Phase I/II**

This collaboration between an RNA medicines company and medical school is working on a messenger RNA (mRNA)-based vaccine for Singapore.[153] 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.[154] This technology means that the vaccine can likely be administered in a single shot at very low dose.[155]

22 July 2020 | Trial: phase I/II clinical trials; randomised, double-blinded and placebo-controlled to assess safety, tolerability, immunogenicity and optimal dose. The studies are being carried out in Singapore with 85 healthy adult participants up to 80 years of age.[156]

27 April and 8 May 2020 | 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.[157, 158] The STARR™ mRNA elicited higher levels of IgG antibodies than conventional mRNA at equivalent doses.[158]

Notes

- 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.[159]

5.2.3. Imperial College London (ICL) Department of Infectious Diseases (UK)

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

An RNA-based vaccine candidate called **COVAC1 (or LNP-nCOVsaRNA)** with funding support from CEPI. The vaccine consists of self-amplifying RNA (saRNA) which is encapsulated in a lipid nanoparticle and is injected intramuscularly. The ICL team received funding from CEPI in December 2018 to develop their saRNA platform for general use against infectious diseases.[160]

17 July 2020 | Trial: ICL moves to expand clinical trials to 105 further candidates to assess optimal dosage.[161]

9 July 2020 | Result: results of preclinical testing in mice reveal that the vaccine elicits a "robust" antibody response without antibody-dependent enhancement.[162]

23 June 2020 | Trial: phase I clinical trials begin with the first dosing of volunteers. More than 300 participants have been screened for the UK-based trials, and ICL is continuing to recruit for the study.[163]

20 March 2020 | Result: within 14 days of receiving the genetic sequence of the virus in January 2020, the team had developed a vaccine candidate.[164]

Notes

- There are plans to proceed with phase II/III trials to assess efficacy with 6000 participants beginning in October.[163]
- The clinical trial structure and plans are published on the Imperial College London website.[165]

5.2.4. CureVac (Germany)

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

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.[166]

17 August 2020 | Trial: a dose-ranging phase IIa study to evaluate safety and reactogenicity in 691 participants.[167]

26 June 2020 | Trial: a placebo-controlled phase I clinical trial in 168 participants in Germany and Belgium.[168] The study will evaluate safety, appropriate dose, adverse reactions and immune responses generated.

14 May 2020 | Result: preclinical testing found that a low dose of CVnCoV generated nautralising antibodies.[169]

Notes

- Depending on the outcomes of the phase I trial, larger phase II trials will begin in the later half of 2020.[169]

5.3. Vaccines in phase I clinical trials

5.3.1. Novavax (US, Australia and Japan)

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.

6 August 2020 | Result: Preliminary result from the phase I trial have been posted to a preprint server[170], showing that the vaccine has a good safety profile, was well-tolerated and elicited "robust antibody responses numerically superior to that seen in human convalescent sera".[171]

30 June 2020 | Result: Results from pre-clinical trials published on a preprint server show that the vaccines yields neutralising antibodies in animal models.[172]

25 May 2020 | Trial: phase I clinical trials begin in Australia.[173] 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.

Notes

- 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.[174]
- Novavax has a $60 million contract with the US Department of Defense to deliver 10 million doses to American troops.[174]
- Through Operation Warp Speed, Novavax has a deal to deliver 100 million doses to the US by the beginning of 2021.[174]
- Novavax has licensed their vaccine candidate to Takeda in Japan for local production and commercialisation.[175]

5.3.2. University of Queensland (Australia)

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.[176]

26 August 2020 | Result: preclinical results were shared in an article on the UQ website, with the vaccine inducing neutralising antibodies in animal models at levels higher than those found in receovered COVID-19 patients.[177]

13 July 2020 | Trial: phase I clinical trials in Brisbane, Australia with 120 participants aged 18 to 55. The study is dose-ranging, randomised, double-blind and placebo-controlled.[178]

Notes

- Preliminary data from the phase I trial is expected in about three months' time.[179]
- CSL will supply the Australian government with 51 million doses by mid-2021 if trials are successful.[180]
- The molecular clamp technology is a general-purpose technique that may be applied to other pathogens.

5.3.3. Symvivo Corporation (Canada)

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

Symvivo is adapting its **bacTRL** platform for SARS-CoV-2.[181] 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.

6 April 2020 | Trial*:* phase I trial posted to the ClinicalTrials.gov website. The study involves 84 participants aged 18–45 in a randomised, placebo-controlled and double-blind phase I trial that aims to evaluate safety and immunogenicity.[182] The study was expected to start in July but the entry in the clinical trials register has not been updated since 29 June.

5.4. Other vaccine candidates in clinical trials

Table 4: Other vaccine candidates in clinical trials as of 7 Setepmber 2020.

Vaccine name	Vaccine type	Developed by	Country/territory	Current stage	Reference
AG0301-COVID19	Nucleic acid (DNA)	AnGes Inc.	Japan	Phase I/II	[183]
V-SARS	Inactivated virus	Immunitor	Canada	Phase I/II	[184]
AV-COVID-19	Virus-like particle (VLP) / modified APC	Aivita Biomedical Ltd	US	Phase I/II	[185]
[unnamed]	Inactivated virus	Chinese Academy of Medical Sciences	China	Phase I/II	[186]
LV-SMENP-DC	Replicating viral vector	Shenzhen Geno-Immune Medical Institute (GIMI)	China	Phase I/II	[187]
AlloStim	Living cell	Immunovative Therapies Ltd	US	Phase I/II	[188]
GX-19	Nucleic acid (DNA)	Genexine Inc	South Korea	Phase I/II	[189]
ZyCoV-D[190]	Nucleic acid (DNA)	Zydus Cadila	India	Phase I/II	[190]
KBP-COVID-19	Protein subunit	Kentucky BioProcessing Inc.,	US	Phase I/II	[191]
BBV152A, B, C	Inactivated virus	Bharat Biotech International	India	Phase I/II	[192]
[unnamed]	Protein subunit	Anhui Zhifei Longcom Biologic Pharmacy Co. Ltd	China	Phase I/II	[193, 194]
QazCovid-in	Inactivated virus	Research Institute for Biological Safety Problems	Kazakhstan	Phase I/II	[195]
EpiVacCorona	Protein subunit	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology	Russia	Phase I/II	[196]

Vaccine name	Vaccine type	Developed by	Country/territory	Current stage	Reference
[unnamed]	Virus-like particle (VLP)	Medicago Inc	Canada	Phase I	[197]
COVID-19/aAPC	Virus-like particle (VLP)	Shenzhen Geno-Immune Medical Institute (GIMI)	China	Phase I	[198]
SCB-2019	Protein subunit	Clover Biopharmaceuticals	China/Australia	Phase I	[199]
COVAX-19	Protein subunit	GeneCure Biotechnologies	US/Australia	Phase I	[200, 201]
V591 / TMV-083	Replicating viral vector	Merck	US/France	Phase I	[202]
		Institut Pasteur, Themis, CEPI		Phase I	[203]
MVC-COV1901	Protein subunit	Medigen Vaccine Biologics Corp.	Taiwan	Phase I	[204]
[unnamed]	Nucleic acid (mRNA)	Yunnan Walvax Biotechnology Co. Ltd	China	Phase I	[205]
AdimrSC-2f	Protein subunit	Adimmune	Taiwan	Phase I	[206]
GRAd-COV2	Non-replicating viral vector	ReiThera	Italy	Phase I	[207]
[unnamed]	Protein subunit	Jiangsu Province Centers for Disease Control and Prevention	China	Phase I	[208]

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[209], thereby reducing morbidity from COVID-19. These include:

- The Bacille Calmette- Guérin (BCG) vaccine to prevent tuberculosis[210]
- The oral polio vaccine[211]
- The measles, mumps and rubella (MMR) vaccine[212]

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.[210] The BCG vaccine has been used as a tuberculosis vaccine for nearly one hundred years.[213] 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,[214] 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,[215, 216] but others caution against over-interpreting such ecological studies with many confounding factors.[217] A recent analysis from Israel did not find a link between BCG vaccination status and prevalence of COVID-19.[218] 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”.[219]

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.[220] In addition to WHO, the trial has also received support from the Bill and Melinda Gates Foundation with a donation of AU$10 million.[221]

Researchers in Australia are investigating whether the BCG vaccine can be ‘rejigged’ with antigens from SARS-CoV-2 to make it more specific.[222] 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*

Evolution of 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*

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