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Kaitohutohu Mātanga Pūtaiao Matua ki te Pirimia

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

Prepared under urgency – 21 May 2020

The COVID-19 pandemic has spurred a global effort to find a vaccine to protect people from SARS-CoV-2 infection. As of 21 May 2020, there are at least 140 candidate vaccines in various stages of active development.[1] These can be found on the Milken Institute's COVID-19 treatment and vaccine tracker. 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%.[2]

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

Contents

1. Timeline

While some pharmaceutical companies are aiming for emergency use dispensation of their vaccines within months,[3, 4] the World Health Organization (WHO) cautions that the full process will likely take at least 12–18 months, if not longer.[5] The average vaccine takes more than ten years to progress from preclinical development to market,[2] although the recent example of an ebolavirus vaccine turnaround of five years signals that the process can be accelerated.[6]

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

1. **Pre-clinical trials** – studies in animal models (often mice, but also ferrets and non-human primates for a coronavirus[7]) 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.[8]

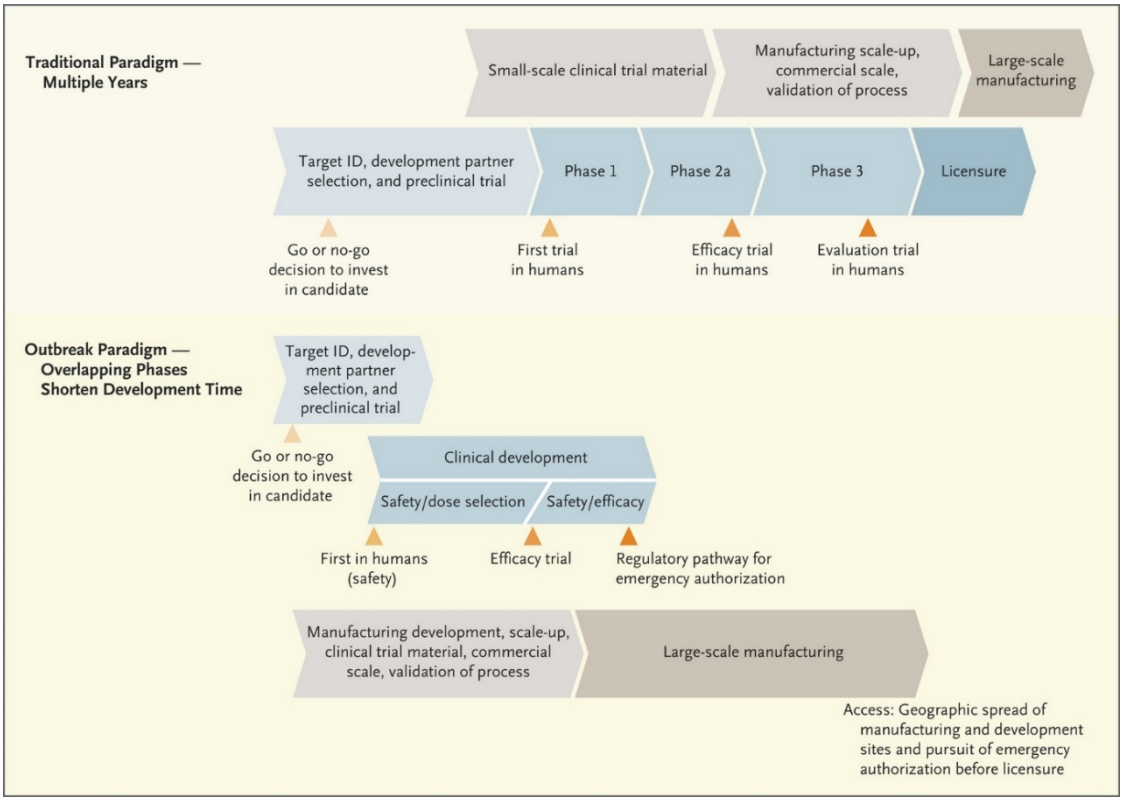

Figure 1: Difference between the traditional vaccine development paradigm and an accelerated "pandemic paradigm" as proposed by CEPI.[8]

The US National Institutes of Health (NIH) is spearheading a collaborative program called Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV).[9] This brings together public and private stakeholders to advance the vaccine development timeline in a coordinated manner (Figure 2).

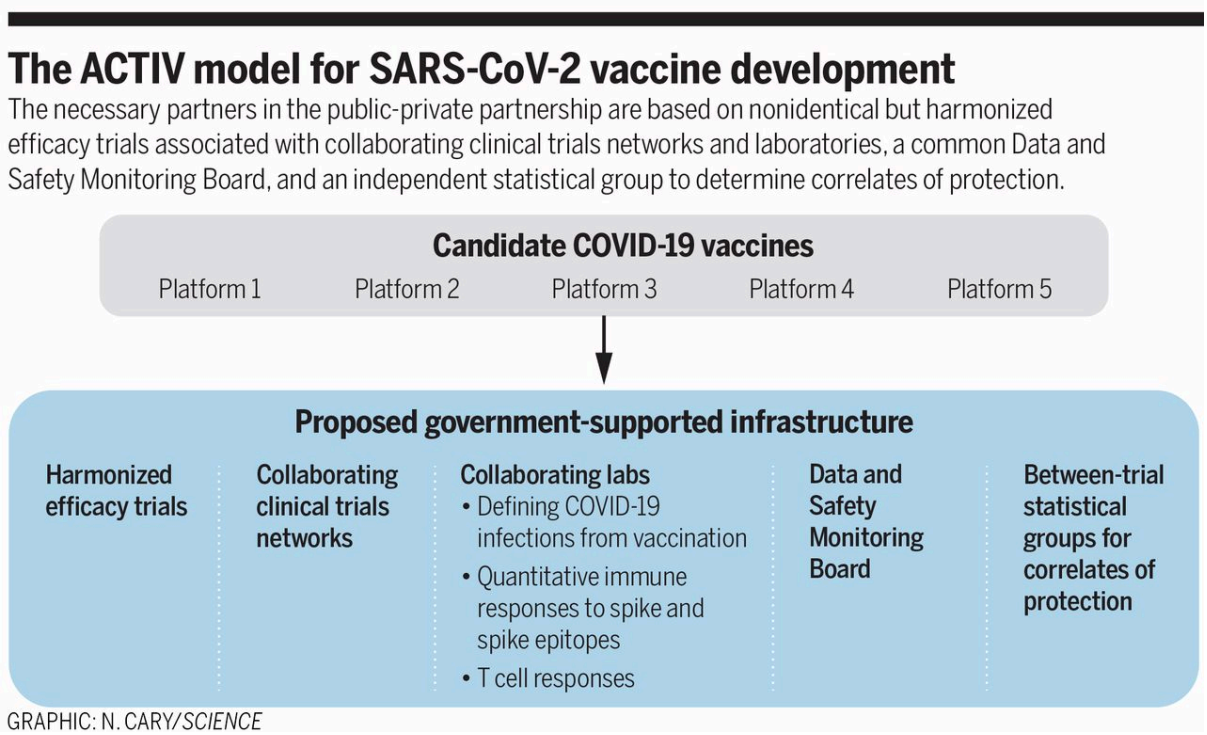

Figure 2: the ACTIV model for SARS-CoV-2 vaccine development.[9]

Beyond models, this useful interactive from *The New York Times* explores specific ways we could potentially accelerate the timeline.[10] 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'.

2. 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.

In the case of SARS-CoV-2, the 'spike' protein is an ideal target for vaccines. This is because the spike protein is essential for the virus to latch onto lung cells (via the ACE2 receptor) and infect them. It is therefore conserved across different strains. Several of the current leading vaccine candidates 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.[11]

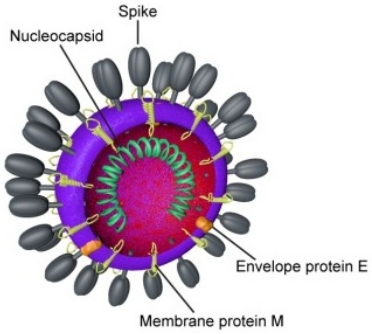

Figure 1: Diagram of a coronavirus virion with the spike protein labelled. CC BY 3.0.[12]

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.

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 but may not be suitable for immunocompromised individuals.	**Example**: influenza vaccine administered by nasal spray
	Inactivated virus	A vaccine containing whole viruses that have been killed through heat or chemical treatment. Production requires large quantities of infectious virus.	**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 are covered with all manner of sugars that may pose challenges for efficacy. Will probably require an adjuvant and multiple doses.	**Example**: hepatits B vaccine
	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	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

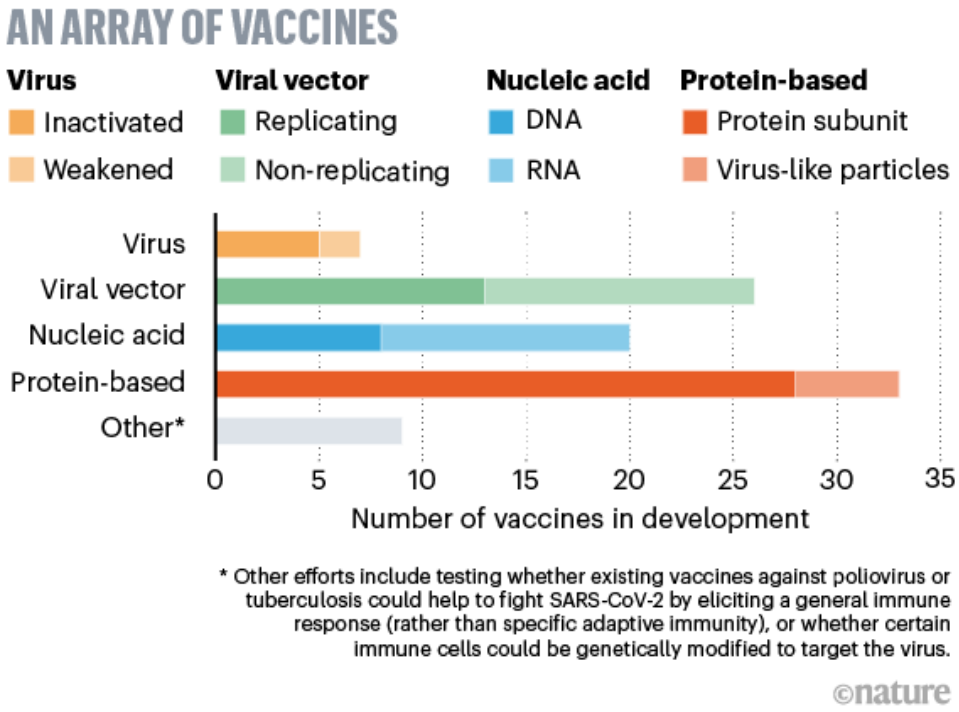

Figure 2: chart breaking down the different platforms being investigated for potential COVID-19 vaccines. Reproduced from *Nature*[13]

2.1. 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 eight vaccine candidates for COVID-19

which cover a variety of platforms (see section four, 'Selected vaccine candidates'). So far CEPI has invested US$30 million in vaccine development.[14] They estimate that it will take US$2 billion to bring a vaccine to widespread use.[15] 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.

3. Potential issues

3.1. Proving vaccine efficacy on an accelerated timeline

As discussed in section one ('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.[16] 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.[17] 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.[18]

3.2. Immune enhancement

Some previous vaccine candidates for related coronaviruses (e.g. SARS, MERS) have hit a major stumbling block: 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.[19] This immune enhancement can occur via two known mechanisms:

- Antibody-dependent enhancement (ADE), where the virus co-opts antibodies to enhance infection.
- 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.[20] 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.[19]

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.[21] 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.[19] In other studies, the live virus resulted in complications including lung damage in mice[22] and liver damage in ferrets[23], while an inactivated virus vaccine led to immune enhancement in non-human primates.[24]

3.3. 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.[25] 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.[26] 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.[27]

The antigenic drift rate of SARS-CoV-2 is slow and mutations that have occurred so far have not made the virus more deadly.[28] 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.[29] However, SARS-CoV-2 cannot undergo antigenic shift as coronaviruses do not have a segmented genome.[30]

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.[31, 32] The authors of one study claim the observed D614G mutation enhances the transmissibility of the virus,[31] but this interpretation is hotly contested.[33] Continued monitoring of mutations is essential to ensure any potential vaccine remains effective.

3.4. 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.[34] 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."[35]

Immunity is a somewhat murky issue. For SARS-CoV-2, there are some reports of recovered patients being reinfected.[36] 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.[37]

In a recent study, rhesus macaque monkeys were infected with the SARS-CoV-2 virus and developed symptoms similar to those observed in humans.[38] 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.[39]

3.5. Immune senescence

Most severe cases of COVID-19 occur in individuals aged 50 years or more.[39] 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.[40]

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.

3.6. 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".[3] Similarly, German company CureVac currently estimates it would be able to manufacture 400 million doses of its RNA vaccine candidate per year.[41] 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.[42]

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 says it is working to address this issue, but at this stage any plan for equitable distribution is still unclear.[41] At-risk populations may be prioritised, including healthcare workers and countries or territories suffering high casualties at the time a vaccine is available. J & J say that if successful, the vaccine will be provided via health authorities on a not-for-profit basis.[3] Others argue that access to treatments, and probably also vaccines, is likely to be restricted by pharmaceutical companies behind "a thicket of patents".[43] Hoarding by individual wealthy countries may also eventuate.

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.[44] 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.

3.7. Vaccine development in Aotearoa New Zealand

Some New Zealand scientists have called for the Government to invest in an onshore vaccine programme due to potential accessibility issues.[45] A letter in the New Zealand Medical Journal co-signed by 120 scientists supports this approach.[46] Proposals for the programme include evaluation of vaccines developed internationally and a plan for vaccine roll-out. Given the lead-time of at least a year, these activities could be developed as the vaccine landscape becomes clearer. Suggestions also include establishing vaccine development programmes in-country alongside vaccine production

capability. While the latter might be prudent, it is unclear whether aiming to develop another vaccine alongside the 100+ already in development is wise investment, given the very high attrition rate of vaccines.

Consideration is also being given to working on a trans-Tasman initiative which would harness expertise across Australia and New Zealand and possibly mitigate the risks of being lowest priority for future supply.

3.8. 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?"[47] 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.

4. Selected vaccine candidates

4.1. Vaccines in clinical evaluation

The WHO is regularly updating a document detailing the landscape of COVID-19 vaccines.[48] According to the latest version, published on 5 May, eight candidate vaccines are currently in clinical trials. A further three candidates also reported to be in clinical trials are included here.

4.1.1. CanSino Biologics and Beijing Institute of Biotechnology

Supported by China's Academy of Military Medical Sciences, CanSino Biologics (CanSinoBIO) have fast-tracked development of a vaccine known as **Ad5-nCoV**.

Vaccine type: **non-replicating viral vector**; adenovirus Ad5. This platform has been used to produce an ebolavirus vaccine, Ad5-EBOV, which is approved for clinical use in China.[49]

Current stage: recruitment for phase II clinical trials underway, as CanSinoBIO forges ahead based on preliminary safety data from phase I trials which began mid-March.[50] 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. The phase I clinical trial is ongoing with 108 participants in Wuhan, China.[51] Three different groups have received low, middle and high doses of the vaccine to assess its safety and tolerance. Participants will be monitored for six months for adverse reactions in addition to testing for antibodies and a T-cell immune response. Preclinical animal studies showed a "good safety profile".[51]

Future: Results of phase I/II expected approximately six months from now. The development of Ad5-EBOV took three years.[52]

4.1.2. Moderna and NIAID

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.

Vaccine type: **RNA** – a small piece of mRNA wrapped up in lipids so it can enter the cell. Injected into the arm.

Current stage: phase I clinical trials 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.[53] The vaccine was not tested in animals prior to Phase I beginning. According to Moderna, preliminary data from eight (out of 45) participants shows that the vaccine has induced neutralising antibodies two weeks post-vaccination – at a level on par with an immune response elicited by natural infection.[54]

Future: first data expected in at least two months; vaccine could be available in the US under emergency use authorisation in late 2020 depending on results and regulations.[55]

4.1.3. Shenzhen Geno-Immune Medical Institute (GIMI)

An institute founded by the Shenzhen government in China, the GIMI currently has two vaccine candidates in phase I 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.[56] 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.[56] 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 trial that aims to assess the vaccine's safety and efficacy. The trial began on 24 March 2020.[57]

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 15 February, is enrolling 100 healthy or COVID-19-positive individuals to assess the efficacy and safety of the vaccine.[58]

4.1.4. University of Oxford

The University of Oxford, with the support of CEPI, have developed an adenovirus-based vaccine named **ChAdOx1.**

Vaccine type: Non-replicating viral vector (chimpanzee adenovirus)

Current stage: pre-clinical trials in Australia concurrent with phase I/II trials in the UK involving 1,000 participants.[59] 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).[60] 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.[61] 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."[62]

Future: expected to complete UK trials in May 2021. However, if the vaccine is successful, pharmaceutical company AstraZeneca will make 30 million doses available in the UK by September, out of a total of 100 million doses.[63]

4.1.5. Inovio Pharmaceuticals

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

Vaccine type: DNA plasmid

Current stage: pre-clinical trials in Australia/elsewhere concurrent with phase I 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.[64] Results from mice and guinea pigs were recently reported, with the vaccine eliciting both antibodies and a T-cell response.[65] The phase I trial involves 40 adults in Philadelphia, Pennsylvania and Kansas City, Missouri receiving two doses of vaccine four weeks apart.[66] The first dose was administered on 6 April 2020.[67] An Inovio-developed MERS DNA vaccine candidate underwent Phase I testing, yielding high levels of antibodies.[68]

Future: Inovio expects to have one million doses available by the end of 2020 for ongoing trials and possible emergency use.[67] They plan to proceed to Phase II as rapidly as possible.

4.1.6. Sinovac Biotech

Beijing-based company Sinovac have progressed their vaccine candidate '**PiCoVacc**' to clinical trials after promising results in rhesus monkeys. 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.[69]

Vaccine type: inactivated SARS-CoV-2 virus

Current stage: phase I/II clinical trials (randomised, double-blinded, placebo-controlled) with 744 healthy adults (144 phase I, 600 phase II) in Jiangsu, China.[70] The trials began in mid-April and aim to evaluate the safety and immunogenicity of the vaccine. Studies in mice, rats and non-human primates found that the vaccine induced neutralising antibodies.[71] Different doses were tested, with the highest dose providing complete protection against SARS-CoV-2 in macaques. A lack of lung damage in vaccinated animals provides some indication that immune enhancement might occur.

Future: preliminary results are expected in August 2020; the study is expected to be complete in December 2020. Sinovac is in talks with WHO to join international vaccine trials for phase III given the low rate of transmission currently occurring in China.[69]

4.1.7. BioNTech and Pfizer

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**.

Vaccine type: RNA

Current stage: four candidate vaccines in randomised, placebo-controlled phase I/II trials.[72] 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.

Future: both companies are anticipating positive results and are investing in scaling up manufacturing infrastructure in the US, Belgium and Germany.[42] They aim to produce millions of vaccine doses by the end of 2020, increasing to hundreds of millions in 2021.

4.1.8. Symvio Corporation, University of British Columbia and Dalhousie University

Symvio is adapting its **bacTRL** platform for SARS-CoV-2.[73] 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.

Vaccine type: DNA, bacterial medium, administered orally.

Current stage: 84 participants aged 18–45 in a randomised, placebo-controlled and double-blind phase I trial.[74] The Canada-based study aims to evaluate safety and immunogenicity.

Future: study was predicted to start on 30 April but still lists as 'not yet recruiting'. Results are expected in August 2021.

4.1.9. Beijing Institute of Biological Products and Wuhan Institute of Biological Products

An unnamed vaccine candidate using inactivated whole virions currently in phase I trials in China.[75]

Vaccine type: inactivated whole virus

Current stage: phase I clinical trial (randomised, placebo-controlled and double-blind) involving 288 participants began on 12 April. The vaccine has shown good safety so far, according to the developers.[76]

Future: phase II is registered but not yet recruiting for at least 1,000 participants aged six and over. A conclusion on the vaccine's safety and efficacy is estimated to be one year away.

4.2. Vaccines in preclinical stages

4.2.1. Janssen/Johnson & Johnson

Janssen, the Belgium-based research division of corporation Johnson & Johnson (J&J), is collaborating with the US Government's Biomedical Advanced Research and Development Authority (BARDA). Each organisation is committing nearly US$500 million in funding to the effort, for a total of nearly US$1 billion.[3]

Vaccine type: Non-replicating viral vector; adenovirus Ad26

Current stage: Currently in pre-clinical trials using monkeys. 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.[77]

Future: Janssen estimates it will launch clinical trials in September 2020 and could theoretically have a vaccine ready for use by the northern hemisphere winter.[3]

4.2.2. University of Pittsburgh School of Medicine and UPMC

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.**

Vaccine type: protein subunit delivered via microneedle patch

Current stage: pre-clinical trials; a recent study reports that vaccinated mice produced antibodies specific to SARS-CoV-2.[78] This represents the first peer-reviewed research into a COVID-19 vaccine candidate.[79]

Future: Phase I clinical trials to start June 2020/next few months[79]

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

An unnamed, RNA-based vaccine candidate with funding support from CEPI.

Vaccine type: self-amplifying RNA (saRNA), injected intramuscularly.

Current stage: preclinical testing, including animal studies. The ICL team received funding from CEPI in December 2018 to develop their saRNA platform for general use against infectious diseases.[80] Within 14 days of receiving the genetic sequence of the virus in January 2020, the team had developed a vaccine candidate.[81]

Future: plans to proceed with phase I clinical trials by mid-June, with a move to larger scale trials in October.[63]

4.2.4. University of Queensland

The University of Queensland has received support from CEPI to develop a "molecular clamp" vaccine – an experimental platform that could be repurposed for other pathogen targets.

Vaccine type: Protein subunit with a "molecular clamp" that holds the viral antigen in the correct conformation
Current stage: pre-clinical testing and production by CSIRO

Future: the molecular clamp technology is a general-purpose technique that may be applied to other pathogens

4.2.5. Novavax

Named **NVX-CoV2373** and supported by CEPI, this candidate was identified from a range of constructs.

Vaccine type: protein subunit; nanoparticles carrying antigens with Matrix M adjuvant

Current stage: pre-clinical trials have yielded neutralizing antibodies in animal models

Future: a combined phase I/II development plan will begin in mid-May with a placebo-controlled observer-blinded study of around 130 adults.[82] Preliminary results are expected in July.

4.2.6. The University of Hong Kong

An unnamed vaccine candidate in development at the University of Hong Kong with support from CEPI.

Developed by: The University of Hong Kong

Vaccine type: live, attenuated virus – based on a platform similar to some influenza vaccines.

Current stage: pre-clinical trials

Future: Expected to enter phase I clinical trials in July.[83] Potentially some delays with development as the university relies on mainland China for some testing.

4.2.7. CureVac

An unnamed candidate with funding support from CEPI. CureVac is providing regular updates on their website.

Vaccine type: messenger RNA (mRNA). The mRNA platform has been used by CureVac to develop a rabies vaccine that generates immunity.[84]

Current stage: preclinical testing has identified the most suitable vaccine candidates from several constructs.

Future: Phase I clinical trials expected to begin in early (northern hemisphere) summer 2020. Larger phase II trials will begin in autumn 2020 depending on the results of the phase I study.[85]

4.2.8. Beth Israel Deaconess Medical Center (BIDMC)

Researchers from this Harvard-associated medical centre have developed a series of vaccine candidates

Vaccine type: DNA vaccine, encoding different versions/parts of the spike.

Current stage: recently reported results from a challenge study in 35 rhesus macaque monkeys reveal that a series of DNA vaccine candidates induce immunity in the form of T-cells and neutralising antibodies.[86] Post-challenge, the viral load was substantially reduced for monkeys who received the DNA vaccine that encodes the full spike protein.

Future: the authors note areas of future research including establishing the durability of protective immunity and assessing both emerging mutations in the virus and the potential for enhanced disease.

4.2.9. Instiut Pasteur, Themis and the University of Pittsburgh

This consortium is collaborating with the support of CEPI to repurpose their measles virus vector. The candidate is called **MV-SARS-CoV-2.**

Vaccine type: replicating viral vector; measles vaccine virus (MV). This platform has previously been used by the consortium above to develop and investigate vaccines for SARS, MERS and Chikungunya.[87]

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.[88] This means it will potentially clear hurdles faster. In addition, this type of vaccine is easy to produce in large quantities.

Further COVID-19 vaccine frontrunners can be found in this regularly updated article on *The Scientist*

5. The BCG vaccine: an interim solution for future pandemics?

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. The BCG vaccine has been used as a tuberculosis vaccine for nearly one hundred years.[89] 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,[90] 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,[91, 92] but others caution against over-interpreting such ecological studies with many confounding factors.[93] A recent analysis from Israel did not find a link between BCG vaccination status and prevalence of COVID-19.[94]

Beyond use in the current Covid-19 pandemic, it is hoped that the BCG vaccine could become a key tool in future pandemics, as a way to respond rapidly and reduce the severity of illness while a specific vaccine is still in development.

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.[95] In addition to WHO, the trial has also received support from the Bill and Melinda Gates Foundation with a donation of AU$10 million.[96]

Other studies are investigating the oral polio vaccine and the rubella vaccine for their potential to help fight COVID-19.[97]

6. Further reading

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

Where are we at with developing a vaccine for coronavirus? *The Conversation*

COVID-19 vaccine frontrunners *The Scientist*

Coronavirus vaccine: when will we have one? *The Guardian*

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*

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