

Rapid Research Information Forum

Addendum: corrections and updates – The most promising vaccines for COVID-19

17 June 2020

IMPORTANT NOTICE: COVID-19 research is developing rapidly. Rapid Research Information Forum (RRIF) briefings summarise the best available evidence at the time of writing and each is clearly marked with the relevant submission date. This update expands on the content of the briefing dated 11 May 2020 and should be read in conjunction with that document. Further updates may be published and consultation with the Australian Academy of Science is possible if the reader has questions.

The original brief, provided at the end of this update, responded to the question: What are the most promising vaccines in development globally and nationally, and what are their mechanisms of action, their stage of development and their strengths and limitations.

Key findings (updated)

- There are currently 11 vaccine candidates for COVID-19 in clinical trials. Five of the six vaccines being developed outside of China use new platform technologies and the five being developed in China use traditional inactivated whole virus candidates.
- National and international initiatives are being implemented at an unprecedented scale to speed up the research translation process.
- Phase I safety results for a COVID-19 vaccine candidate, Ad5-nCoV, were published by Cansino Biologics, China, on 22 May 2020. Its vaccine was tested in 108 participants, no serious side effects were reported and the vaccine was able to elicit a neutralising antibody response.
- Safety, immunogenicity and efficacy results from other vaccine candidates can also be expected in 2020. This may inform the initial use of a limited number of vaccine doses under emergency or compassionate protocols for at-risk populations including frontline health workers, the elderly and those with significant comorbidities.
- It is too early to select the ‘most promising’ vaccine candidates for widespread population use as we do not yet know enough regarding the safety or efficacy of each candidate, or global capability to manufacture them at large scale under Good Manufacturing Practice conditions. It is not a given that vaccines used or licensed first will be the most effective.
- The University of Queensland has announced its partnership with CSL as the trusted manufacturer of its COVID-19 vaccine candidate if clinical trials are successful.
- It is important for Australian researchers and industry to maintain strong collaborations with global vaccine consortia.

Corrections

We originally reported the COVID-19 inactivated virus vaccine candidate ChiCTR2000031809, led by the Beijing Institute of Biological Science, China, was at Phase I clinical trials. ChiCTR2000031809 was originally approved for both Phase I and II clinical trials.

Sinovac's COVID-19 inactivated and adjuvated vaccine candidate was incorrectly reported to be 'unnamed'. The vaccine was named PiCoVacc and has since been renamed to CoronaVac.

One of the examples of an inactivated viral vaccine in the original document was incorrect. Pertussis, whooping cough, is caused by bacterial infection and the vaccine is derived from bacterial antigens.

Updates

The original report presented COVID-19 vaccine candidates based on collated information from a range of sources including: the World Health Organization; projects receiving funding from the Coalition for Epidemic Preparedness Innovations (CEPI); searches of scientific literature including pre-prints; clinical trials registers; and interrogation of online search engines.

In addition to the Australian research organisations working on COVID-19 vaccine candidates and components noted in the original report, another company has been brought to our attention. Vaxine Pty Ltd, based at Flinders University in South Australia, is developing a COVID-19 vaccine candidate, COVAX-19, based on a protein vaccine technology platform.¹ COVAX-19 will be trialled with the addition of an adjuvant, Advax, also developed by Vaxine.

Recent research has demonstrated that a T-cell immune response, which is required for the elimination of virus-infected cells, can be induced by other SARS-CoV-2 antigens and not just the spike protein.²

COVID-19 vaccine candidates: progress into and through clinical trials

Since the original report, Cansino Biologics, China, reported the Phase I clinical trial results of its viral vector vaccine candidate in a peer-reviewed article on 22 May 2020.³ The vaccine's safety was tested in 108 participants. No serious side effects were reported and the vaccine was able to elicit a neutralising antibody response as well as a T-cell response. Phase II clinical trials are ongoing.⁴

On 12 May the USA Food and Drug Administration granted Fast Track designation for Moderna's COVID-19 vaccine candidate, mRNA-1273.⁵ Fast Track designation expedites the FDA's review process. On 18 May 2020, Moderna announced, in a press release, interim results from Phase I clinical trials of its COVID-19 vaccine candidate, mRNA-1273.⁶ Limited data were presented, from only eight subjects. The interim results were stated as promising and will inform the dosage for Phase II clinical trials. The National Institutes of

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Health will be submitting the Phase I data for peer review publication.⁷ Moderna anticipates Phase II and III trials will begin in July 2020. The company has partnered with Lonza Ltd, Switzerland, to manufacture up to 1 billion doses of mRNA-1273 per year, depending on the final dose.⁸

AstraZeneca, a multinational pharmaceutical company in the UK, partnered with the University of Oxford on its COVID-19 vaccine candidate ChAdOx1 nCov-19. The vaccine candidate has now been renamed AZD1222 and AstraZeneca announced on 21 May 2020 its commitment and capability to manufacture the vaccine by September 2020.⁹ Oxford University have registered its Phase II and III clinical trials, which will involve three age groups: adults aged 18 or older, adults aged 56 or older and children aged 5-12 inclusive.¹⁰ A preprint paper presenting results from preclinical testing of AZD1222 in mice and non-human primates is now available.¹¹ Animals were vaccinated with AZD1222 and subsequently challenged with SARS-CoV-2. Results indicate that vaccination prevents virus replication in the lower respiratory tract but not in the nose, where viral shedding rates were similar between vaccinated and unvaccinated animals. Researchers did not observe any inadvertent immune-enhanced disease in vaccinated animals, which were reported in previous animal trials for vaccine candidates for other coronaviruses.^{12,13}

The original report also noted the candidate vaccine projects that have received funding from the Coalition for Epidemic Preparedness Innovations (CEPI), an international fund to develop vaccines against emerging infectious diseases.¹⁴ One of these projects was a collaboration between the Institute Pasteur, France, Themis Bioscience, Austria, and the University of Pittsburgh Centre for Vaccine Research, USA, to develop a viral vector vaccine. On 26 May 2020, Merck announced its acquisition of Themis and commitment to developing its measles-vectored COVID-19 vaccine candidate.¹⁵ This is in addition to Merck's development of another COVID-19 candidate vaccine noted in the original report – a viral vector vaccine developed in partnership with the International AIDS Vaccine Initiative and based on the same technology as Merck's replication competent recombinant VSV-vectored Ebola vaccine.^{16,17}

On 5 Jun 2020, CSL, an Australian biotechnology company, announced its partnership with the University of Queensland.¹⁸ The partnership will provide a trusted manufacturer for the University of Queensland's COVID-19 vaccine candidate that is also supported by CEPI.

Another CEPI-supported COVID-19 vaccine candidate, S-Trimer by Clover Biopharmaceuticals, China, is anticipated to enter Phase I clinical trials in Australia. Clover Biopharmaceuticals is working with 'Linear' and the Harry Perkins Institute in Perth and are currently seeking expressions of interest.^{19,20} Clover Biopharmaceuticals has also partnered with Dynavax and GSK to trial its vaccine with adjuvants, CpG 1018 and AS03 respectively.^{21,22}

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On 25 May 2020, Novavax, USA, another CEPI-funded COVID-19 vaccine candidate, entered Phase I clinical trials.²³ Novavax has developed a nanoparticle spike protein vaccine, NVX-CoV2373, and has partnered with Nucleus Network for trials at its Melbourne and Brisbane clinics.²⁴ Phase I safety trials will include administration of the vaccine with and without an adjuvant (Matrix-M, produced by Novavax) and safety results are expected in July 2020.

NVX-CoV2373

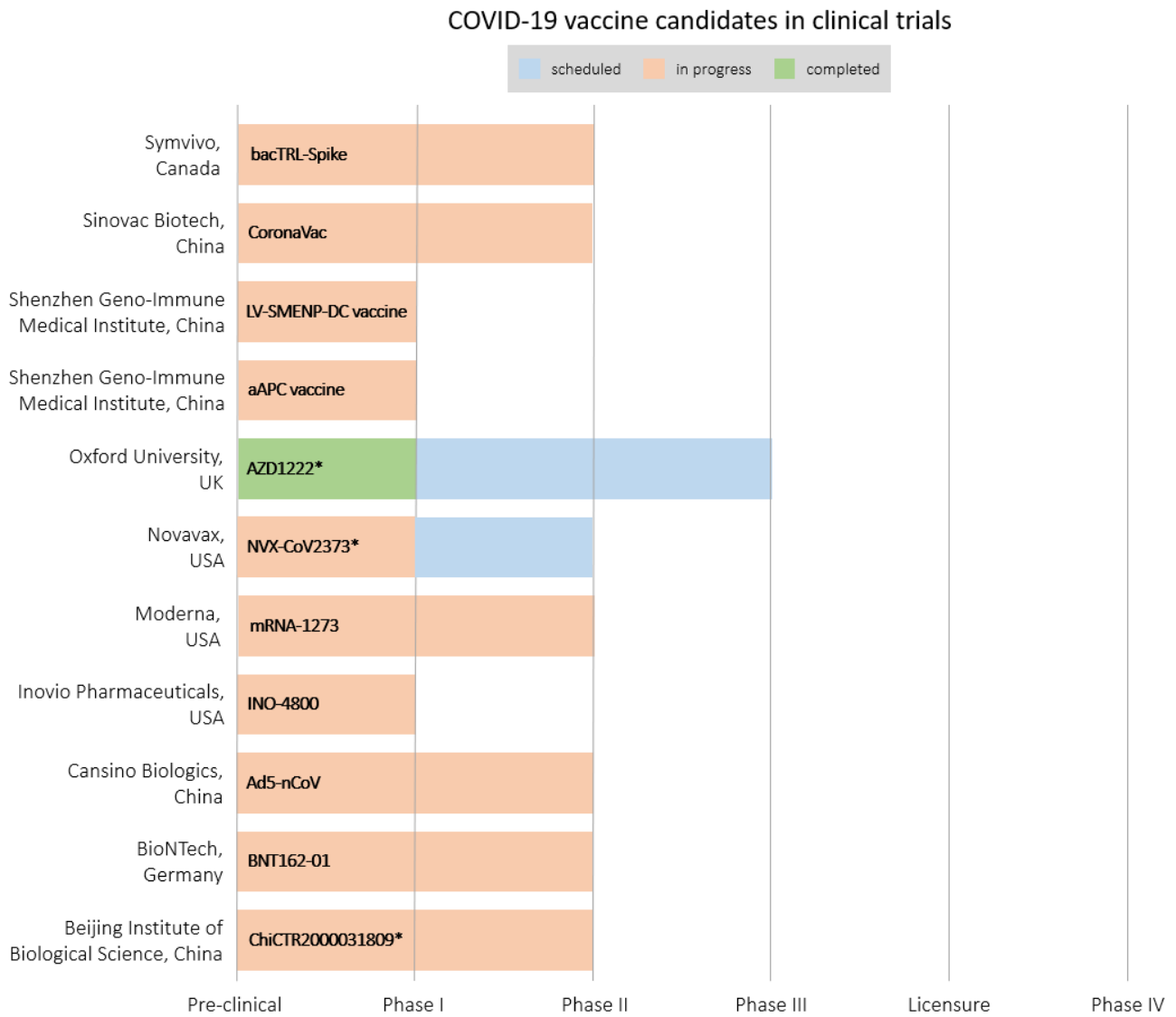
Company	Novavax, USA
Development stage	Phase I clinical trials, 131 participants ²⁵
Technology	Spike protein with and without Matrix-M adjuvant
Advantages	This is the same nanoparticle technology platform used for other established protein vaccines and there is existing global capacity for large-scale manufacturing in insect cells
Limitations	Protein vaccines often require the addition of an adjuvant to elicit an adequate and protective immune response. The scale-up production of suitable adjuvants may be limited, and using insect rather than mammalian cells may alter some properties of the protein

There are many different types of adjuvants and it is not guaranteed that because one adjuvant has previously been effective in a vaccine for another disease that it will be effective in a COVID-19 vaccine. In addition to Matrix-M, other candidate vaccines are also being trialled with adjuvants. Sinovac's CoronaVax is an inactivated virus vaccine in Phase I and II clinical trials and is being tested with an alum adjuvant, which is less potent than more recently developed adjuvants. Sinovac has also partnered with Dynavax to test its adjuvant, CpG 1018, which is already used in HEPLISAV-B (hepatitis B) vaccine.²⁶

Many companies are trying to resolve the bottleneck of adjuvant manufacturing and have committed to making licensed adjuvants available for use with novel COVID-19 vaccines developed by others.^{26–31}

There are now 11 COVID-19 vaccine candidates in clinical trials. These are summarised in the figure below.

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Schematic representation of COVID-19 vaccine candidates in clinical trials as at 17 June 2020. * indicates updated since last report on 11 May 2020; only the lead organisations are listed.

The original report, this addendum and future updates are developed to the best of our knowledge. We acknowledge that they may be incomplete and invite research organisations, companies, individuals and consortia to send scientific publications and clinical trial references for COVID-19 vaccine candidates to science.policy@science.org.au. Future updates provided will focus on COVID-19 vaccine candidates that have reached, or are moving through, clinical trials.

APPENDIX A

Contributing authors and peer reviewers of this addendum

Lead author

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References

1. Flinders University. Flinders targets COVID-19 vaccine. *Flinders University News*
<https://news.flinders.edu.au/blog/2020/04/03/flinders-targets-covid-19-vaccine/>.
2. Grifoni, A. *et al.* Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. *Cell* (2020) doi:10.1016/j.cell.2020.05.015.
3. Zhu, F.-C. *et al.* Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: A dose-escalation, open-label, non-randomised, first-in-human trial. *Lancet* (2020) doi:10.1016/S0140-6736(20)31208-3.
4. ClinicalTrials.gov. A phase II clinical trial to evaluate the recombinant vaccine for COVID-19 (adenovirus vector) (CTII-nCoV). <https://clinicaltrials.gov/ct2/show/NCT04341389>.
5. Moderna, I. Moderna receives FDA fast track designation for mRNA vaccine (mRNA-1273) against novel coronavirus. <https://investors.modernatx.com/news-releases/news-release-details/moderna-receives-fda-fast-track-designation-mrna-vaccine-mrna>.
6. Moderna, I. Moderna announces positive interim phase 1 data for its mRNA vaccine (mRNA-1273) against novel coronavirus. <https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-positive-interim-phase-1-data-its-mrna-vaccine>.
7. Moderna, I. Moderna announces first participants in each age cohort dosed in phase 2 study of mRNA vaccine (mRNA-1273) against novel coronavirus. <https://investors.modernatx.com/news-releases/news-release-details/moderna-announces-first-participants-each-age-cohort-dosed-phase>.
8. Moderna, I. Moderna and Lonza announce worldwide strategic collaboration to manufacture Moderna's vaccine (mRNA-1273) against novel coronavirus. <https://investors.modernatx.com/news-releases/news-release-details/moderna-and-lonza-announce-worldwide-strategic-collaboration>.
9. AstraZeneca. AstraZeneca advances response to global COVID-19 challenge as it receives first commitments for Oxford's potential new vaccine.
<https://www.astrazeneca.com/content/astraz/media-centre/press-releases/2020/astrazeneca-advances-response-to-global-covid-19-challenge-as-it-receives-first-commitments-for-oxfords-potential-new-vaccine.html>.
10. ClinicalTrials.gov. Investigating a vaccine against COVID-19.
<https://clinicaltrials.gov/ct2/show/NCT04400838?term=vaccine+ChAdOx1&cond=COVID-19&draw=2&rank=2>.

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11. § van Doremalen, N. *et al.* ChAdOx1 nCoV-19 vaccination prevents SARS-CoV-2 pneumonia in rhesus macaques. *bioRxiv* 2020.05.13.093195 (2020) doi:10.1101/2020.05.13.093195.
12. Wan, Y. *et al.* Molecular mechanism for antibody-dependent enhancement of coronavirus entry. *J. Virol.* **94**, e02015-19 (2020).
13. Liu, L. *et al.* Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. *JCI insight* **4**, (2019).
14. Plotkin, S. A. Vaccines for epidemic infections and the role of CEPI. *Hum. Vaccin. Immunother.* **13**, 2755–2762 (2017).
15. Merck Newsroom Home. Merck to acquire Themis. <https://www.mrknewsroom.com/news-release/research-and-development-news/merck-acquire-themis>.
16. Merck Newsroom Home. IAVI and Merck collaborate to develop vaccine against SARS-CoV-2. <https://www.mrknewsroom.com/news-release/research-and-development-news/iavi-and-merck-collaborate-develop-vaccine-against-sars-c>.
17. Merck & Co., I. Merck announces FDA approval for ERVEBO® (Ebola Zaire Vaccine, Live). <https://investors.merck.com/news/press-release-details/2019/Merck-Announces-FDA-Approval-for-ERVEBO-Ebola-Zaire-Vaccine-Live/default.aspx>.
18. CSL. The University of Queensland, CEPI and CSL partner to advance development and manufacture of COVID-19 vaccine candidate. <https://www.csl.com/news/2020/20200605-uv-cepi-and-csl-partner-for-covid-19-vaccine-candidate>.
19. Linear Clinical Research. WA to be at the heart of the fight against COVID-19. <https://www.linear.org.au/blog/wa-to-be-at-the-heart-of-the-fight-against-covid-19/>.
20. Linear Clinical Research. COVID-19 Study. <https://www.linear.org.au/trials/covid-19/>.
21. Clover Biopharmaceuticals. Clover and GSK announce research collaboration to evaluate coronavirus (COVID-19) vaccine candidate with pandemic adjuvant system. <http://www.cloverbiopharma.com/index.php?m=content&c=index&a=show&catid=11&id=42>.
22. Clover Biopharmaceuticals. Dynavax and Clover Biopharmaceuticals announce research collaboration to evaluate coronavirus (COVID-19) vaccine candidate with CpG 1018 adjuvant. <http://www.cloverbiopharma.com/index.php?m=content&c=index&a=show&catid=11&id=43>.
23. Novavax. Novavax initiatives Phase 1/2 clinical trial of COVID-19 vaccine.

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- <http://ir.novavax.com/news-releases/news-release-details/novavax-initiates-phase-12-clinical-trial-covid-19-vaccine>.
24. Nucleus Network. Novavax to commence COVID-19 vaccine trial with Nucleus Network. <https://nucleusnetwork.com.au/news/novavax-to-commence-covid-19-vaccine-trial-with-nucleus-network/>.
 25. ClinicalTrials.gov. Evaluation of the safety and immunogenicity of a SARS-CoV-2 rS (COVID-19) nanoparticle vaccine with/without Matrix-M adjuvant. *ClinicalTrials.gov* <https://clinicaltrials.gov/ct2/show/NCT04368988?term=novavax&recrs=ab&draw=2&rank=1>.
 26. Dynavax Technologies Corporation. Dynavax and Sinovac announce collaboration to develop a Coronavirus (COVID-19) Vaccine . <http://investors.dynavax.com/news-releases/news-release-details/dynavax-and-sinovac-announce-collaboration-develop-coronavirus>.
 27. Thanh Le, T. *et al.* The COVID-19 vaccine development landscape. *Nat. Rev. Drug Discov.* (2020) doi:10.1038/d41573-020-00073-5.
 28. GSK. GSK announces intention to produce 1 billion doses of pandemic vaccine adjuvant in 2021 to support multiple COVID-19 vaccine collaborations. <https://www.gsk.com/en-gb/media/press-releases/gsk-announces-intention-to-produce-1-billion-doses-of-pandemic-vaccine-adjuvant/>.
 29. Dynavax Technologies Corporation. Valneva and Dynavax announce collaboration to advance vaccine development for COVID-19. <http://investors.dynavax.com/news-releases/news-release-details/valneva-and-dynavax-announce-collaboration-advance-vaccine>.
 30. Dynavax Technologies Corporation. Dynavax announces collaboration with the University of Queensland and the Coalition for Epidemic Preparedness (CEPI) focused on the development of a coronavirus (COVID-19) vaccine. <http://investors.dynavax.com/news-releases/news-release-details/dynavax-announces-collaboration-university-queensland-and>.
 31. CSL. COVID-19 update. <https://www.csl.com/news/2020/covid-19-update>.



Australian Government

Chief Scientist

11 May 2020

The Hon Karen Andrews MP
Minister for Industry, Science and Technology

The Hon Greg Hunt MP
Minister for Health

Parliament House
CANBERRA ACT 2600

CC:
Dr Brendan Murphy, Chief Medical Officer

Dear Ministers

Please find attached a response to your request for an analysis of the available evidence to respond to your question:

What are the most promising vaccines in development globally and nationally, and what are their mechanisms of action, their stage of development and their strengths and limitations?

This rapid response has been prepared by the Rapid Research Information Forum that I Chair. The report synthesises the evidence base on this matter and has been informed by relevant experts and has been peer reviewed. Details of the authors and peer reviewers can be found in the Appendix.

I hope this document proves useful to you and your colleagues.

Yours sincerely,

A handwritten signature in purple ink, appearing to read 'Alan Finkel'.

Dr Alan Finkel AO FAA FTSE FAHMS
Australia's Chief Scientist

10 May 2020

This rapid research brief responds to the question: What are the most promising vaccines in development globally and nationally, and what are their mechanisms of action, their stage of development and their strengths and limitations?

- There are currently 10 vaccine candidates for COVID-19 in clinical trials. Many of these vaccines are being developed using new platforms and technologies.
- National and international initiatives are being implemented at an unprecedented scale to speed up the research translation process.
- It is likely that several vaccine candidates will generate initial human safety and efficacy results in 2020. These results could inform the initial use of a limited number of vaccine doses under emergency or compassionate protocols for at-risk populations including frontline health workers, the elderly and those with significant comorbidities.
- It is too early to select the 'most promising' vaccine candidate as we do not yet know their safety or efficacy, or our capability to manufacture them at large scale under Good Manufacturing Practice conditions. Furthermore, it is not a given that vaccines licensed first will be the most effective.
- An Australian-produced vaccine candidate is expected to enter human clinical trials in July 2020.
- It will be important for Australian researchers and industry to maintain strong collaborations with global vaccine consortia.

Vaccination is one of the most important ways of preventing the spread and impact of infectious diseases. It protects individuals from infection and impedes disease spread because it deprives the virus of susceptible hosts. Vaccination also provides protection at a societal level.

The development of an effective vaccine for COVID-19 is a big challenge: historically, it has not been possible to create safe and effective vaccines for human coronaviruses. The spontaneous resolution of previous epidemics has also reduced the incentive for persisting with vaccine development. However, there is hope that a vaccine against SARS-CoV-2 will be developed and the current global effort in academic and commercial research laboratories to develop a COVID-19 vaccine is unprecedented in both speed and scope. If vaccine development is delayed, the use of therapeutics for reducing patient load on the health system or even for 'treatment as prevention' may be developed, as it has for HIV.

This brief provides an overview of the different platform technologies for vaccines, the most advanced options and the national development landscape and challenges. Appendix A provides general background

information on the development process for vaccines and discusses how this process is being accelerated for COVID-19.

When the immune system of a healthy person is challenged by exposure to foreign proteins (antigens) from pathogens, such as a virus, an immune response will inevitably follow.

One important element of the immune response is the formation of neutralising antibodies, which are produced against the antigen and circulate throughout the body.^{1,2} Neutralising antibodies are those that can bind to and protect against an invading pathogen. They do this by interfering with the virus's ability to attach to the host cell surface receptors and effectively block the virus from infecting host cells. Another element of the immune response is the formation of non-neutralising antibodies, which do not usually confer the same level of immunity.³⁻⁵

Antigens may also induce T cell immunity. While neutralising antibodies defend cells against virus infection, T cells recognise infected host cells and destroy them to prevent viral replication and further infection. T cells also help antibody production.⁶ Some T cells also have the capacity to remember previous infection and, upon subsequent re-infection, they can quickly respond. In the context of COVID-19, T cell immunity could be an effective mechanism to clear SARS-CoV-2 infected cells in the lungs and prevent the onset of pneumonia.^{7,8}

Vaccine types

Like other coronaviruses, SARS-CoV-2 has club-like spike proteins protruding from its surface. These spike proteins are essential for SARS-CoV-2 to bind to the host cell's 'ACE2' receptor, and, once bound, the virus can then infect the host cell, replicate and infect more cells.⁹ These spike proteins elicit a strong neutralising antibody immune response, and are the primary focus for a majority of COVID-19 vaccines being developed.¹⁰⁻¹² A strong T cell immune response against the SARS-CoV-1 spike protein has also been demonstrated, and researchers are currently working to determine if the SARS-CoV-2 spike protein also elicits a T cell immune response.^{13,14}

There are four main types of technology platforms employed in virus vaccine development:¹⁵

1. **Inactivated or attenuated virus:** The virus is inactivated (killed) or attenuated (weakened) so it is not pathogenic, but its structure remains intact and elicits an immune response. Although many existing vaccines are based on this platform, development processes and scale-up manufacturing are challenging. There are also safety concerns of using a live virus, albeit a version attenuated by laboratory techniques. Existing examples include oral polio (an attenuated virus vaccine) and whooping cough (an inactivated virus vaccine).^{16,17}

2. **Viral vector:** A harmless animal or human virus can be used as a vector to introduce the antigen into the host. In the case of COVID-19, the antigen chosen is typically the spike protein. Examples include adenovirus and poxviruses as the vectors. A limitation of this technology is that antibodies may be produced against the vector instead of the specific antigen. There are challenges with scale-up manufacturing. This type of vaccine is used in many veterinary diseases but not yet for humans, despite many advanced clinical trials.
3. **Protein:** The protein can be synthesised using established laboratory techniques and injected directly as the vaccine. Complexes of viral proteins can also be synthesised to simulate the shape of a virus particle. This is the foundation of some commercially available vaccines, Gardasil® being one example, and so there is significant global capacity to produce protein-based vaccines.¹⁸ However, manufacturing timelines are longer and more difficult to scale up.
4. **Nucleic acid:** Genetic material, DNA or RNA, that encodes the antigen is packaged and injected into the host. This gives the host cells the instructions to create the antigens that then elicit an immune response. For COVID-19, the genetic sequence of the spike protein (or other SARS-CoV-2 components) is injected and can enter the host cells. The host cell machinery at the physical site of injection then synthesises the spike protein and an immune response may ensue. Vaccines produced using the nucleic acid platform are cost effective compared to other platforms. However, RNA is inherently unstable and requires careful cold storage for distribution. It is also a new vaccine technology and although it may be scaled rapidly, this has never been done. No nucleic acid vaccines have been licensed for human use. Only two RNA vaccine candidates, one against rabies and the other against influenza, have ever been tested for safety in humans. Their ability to provoke an immune response in humans has not been shown and they exhibited only modest immunogenicity in animal studies.^{19,20}

Protein and inactivated vaccines do not always induce robust immune responses without immunostimulants, named 'adjuvants', which are often part of the vaccine formulation. Adjuvants function to either replace the normal immune stimulating components of the whole virus, or (for example, when administered to the elderly) to boost declining immunity and poor response to vaccines. Examples of vaccines in which inclusion of an adjuvant improves the immune response include the shingles and hepatitis B vaccines, in which the adjuvant is very effective; and the influenza vaccines, in which the benefit of the adjuvant is modest.²¹⁻²³

Side effects of vaccines

In rare cases, adverse side effects can occur for some vaccines. These include injection site reactions and generalised effects such as fever and tiredness. Very rarely, more severe life-threatening reactions such as anaphylaxis or specific adverse events related to the vaccine formulation may occur. Early work on SARS-CoV-1 and MERS candidate vaccines in mice and non-human primate models indicated that some precipitated severe lung disease following live virus challenge.^{24,25} No such consequences have yet been reported for animal testing with any SARS-CoV-2 candidate vaccines.

Vaccines for COVID-19

More than 100 vaccine candidates are currently on the record as being in pre-clinical development.^{26–28} This number does not include candidates yet to enter the public domain.

Vaccines in clinical trials

As at 10 May 2020, 10 vaccines are reported to be in clinical trials.^{26–28}

aAPC vaccine

Company	Shenzhen Geno-Immune Medical Institute, China
Development stage	Phase I clinical trials; 100 participants ²⁹
Technology	Viral vector
Advantages	Platform used for the development of other candidate vaccines
Limitations	Challenges for large-scale manufacturing

Ad5-nCoV

Company	CanSino Biologics Inc and Beijing Institute of Biotechnology, China.
Development stage	Phase I and II clinical trials; 109 and 500 participants, respectively ^{30,31}
Technology	Viral vector
Advantages	Established technique; good pre-clinical and Phase I trials for MERS and Ebola ^{32–34}
Limitations	Challenges for large-scale manufacturing

bacTRL-Spike

Company	Symvivo Corporation, Canada
Development stage	Phase I clinical trials; 84 participants ³⁵
Technology	Nucleic acid, DNA that encodes the spike protein packaged into probiotic bacteria to deliver vaccine orally
Advantages	Quick to manufacture if approved and facilities are made available
Limitations	No existing human vaccines, based on any of the DNA platform technologies, are licensed for use

BNT162-01

Company	BioNTech TNA Pharmaceuticals, Germany
Development stage	Phase I and II clinical trials; 196 participants in total in the two trials. ³⁶ Partnership with Pfizer, USA and Fosun Pharmaceuticals, China
Technology	Nucleic acid, RNA that encodes undisclosed SARS-CoV-2 proteins ³⁷
Advantages	Quick to manufacture if approved and facilities are made available
Limitations	No existing human vaccines, based on any of the RNA platform technologies, are licensed for use. Requires careful cold storage and distribution facilities

ChAdOx1 nCoV-19

Company	Oxford University, UK, AstraZeneca, a British–Swedish multinational, and the Coalition for Epidemic Preparedness Innovations
Development stage	Phase I and II clinical trials; 1,090 participants in total in the two trials ³⁸
Technology	Viral vector
Advantages	Pre-clinical studies show a strong immune response in mice. ³⁹ Established technique; was trialed in MERS and influenza ^{40,41}
Limitations	Challenges for large-scale manufacturing

ChiCTR2000031809

Company	Beijing Institute of Biological Science, Henan Provincial Centre for Disease Control and Prevention, and Wuhan Institution of Biological Products, China
Development stage	Phase I clinical trials; 1,500 participants ⁴²
Technology	Inactivated virus
Advantages	Platform used for the development of other candidate vaccines
Limitations	Challenges for large-scale manufacturing

Inactive Vaccine for Prophylaxis of SARS-CoV-2 (un-named)

Company	Sinovac, China
Development stage	Phase I and II clinical trials, 744 participants in total in the two trials ⁴³
Technology	Inactivated virus + alum adjuvant
Advantages	Preclinical study awaiting peer review demonstrated strong immune responses in mice, rats and non-human primates; ⁴⁴ was previously trialled for SARS-CoV-1 ⁴⁵
Limitations	Challenges for large-scale manufacturing of the vaccine and adjuvant

INO-4800

Company	Inovio Pharmaceuticals, USA and the Coalition for Epidemic Preparedness Innovations
Development stage	Phase I clinical trials; 40 participants; ⁴⁶ in partnership with China and South Korea
Technology	Nucleic acid, DNA that encodes for the spike protein ⁴⁷
Advantages	Quick to manufacture if approved and facilities are made available
Limitations	No existing human vaccines, based on any of the DNA platform technologies, are licensed for use

LV-SMENP-DC vaccine

Company	Shenzhen Geno-Immune Medical Institute, China
Development stage	Phase I clinical trials; 100 participants ⁴⁸
Technology	Viral vector
Advantages	Platform used for the development of other candidate vaccines
Limitations	Although the platform is not new, it is being applied in a novel way: instead of targeting antibody production it is trying to stimulate T cell immunity. Challenges for large-scale manufacturing

mRNA-1273

Company	Moderna, the National Institute of Allergy and Infectious Diseases, USA and the Coalition for Epidemic Preparedness Innovations
Development stage	Phase II clinical trials; 45 participants ^{49,50}
Technology	Nucleic acid, RNA that encodes for the spike protein
Advantages	Moderna expects to have commercially available vaccines in 12 to 18 months ⁵¹
Limitations	No existing human vaccines, based on any of the RNA platform technologies, are licensed for use. Requires careful cold storage and distribution facilities

Promising COVID-19 vaccine candidates not yet in clinical trials

Although there are 10 vaccines for COVID-19 already in clinical trials, the first vaccines to progress through human studies or to be licensed will not necessarily be the most effective for deployment.

The Coalition for Epidemic Preparedness Innovations (CEPI) is an international fund to develop vaccines against emerging infectious diseases.⁵² CEPI is funding the development of nine COVID-19 vaccines.^{53,54} In addition to the three in clinical trials noted above, CEPI is also supporting the development of vaccines by:

- the University of Queensland, Australia: a spike protein vaccine that relies on a ‘molecular clamp’ to preserve the shape of the spike protein when produced *in vitro*
- CureVac, Germany: an RNA vaccine that codes for the spike protein
- Novavax, Sweden: a spike protein vaccine
- the University of Hong Kong: a viral vector vaccine
- the Institute Pasteur, France, and Themis Bioscience, Austria: a viral vector vaccine
- Clover Biopharmaceuticals Australia, a subsidiary of Sichuan Clover Biopharmaceuticals, China: a spike protein vaccine.

Johnson & Johnson, USA, has partnered with Biomedical Advanced Research and Development Authority (BARDA), USA, to develop a viral vector vaccine and they expect to commence phase I clinical trials in September 2020.^{55,56} Their platform is also being used for Zika, RSV and HIV vaccines that are in phase II and III clinical trials.

GSK, UK, and Sanofi, France, are collaboratively developing a spike protein vaccine with adjuvant.⁵⁷

Merck, USA, has partnered with the Institute for Systems Biology to repurpose its viral vector vaccine, ERVEBO®, which was FDA approved for Ebola.⁵⁸

National landscape of COVID-19 vaccines

Australian-produced vaccines are still at an early stage of research; one has reached the stage of pre-clinical animal testing.

The University of Queensland, in collaboration with CEPI, is currently working with Viroclinics Xplore, Netherlands, in pre-clinical animal studies of their spike protein vaccine. They also have a collaboration with Cytiva (previously GE Life Sciences) to support aspects related to future manufacturing and are expecting to begin clinical trials in early June 2020. The group has been provided access to several commercial adjuvants from GSK, Dynavax and CSL (Seqiris). They have also partnered with CSIRO to investigate how to scale-up the protein vaccine for pre-clinical and clinical testing.

Other Australian organisations and institutions working to develop COVID-19 vaccines include:

- Burnet Institute, in collaboration with Monash University and 360BioLabs (Australia), is developing a protein-based vaccine
- Doherty Institute is investigating two protein-based and two viral vector vaccines
- Griffith University has developed a new biopolyester bead vaccine technology platform that uses specially designed beads to deliver the spike protein into the host and is awaiting pre-clinical testing, to be performed by the Doherty Institute
- Monash University is investigating RNA-based nucleic acid vaccines
- Westmead Institute is investigating a protein fragment adjuvant vaccine for boosting declining immunity in people over the age of 60 years.

CSIRO's Australian Centre for Disease Preparedness in Geelong, formerly the Australian Animal Health Laboratory, has facilities to support pre-clinical animal testing. This is where Inovio's INO-4800 vaccine and the University of Oxford's ChAdOx1 are being tested in ferrets.⁵⁹ Researchers at CSIRO are also evaluating the best ways to administer certain vaccines for better protection, including intra-muscular injection and innovative approaches like nasal spray.

Australian capacity to develop vaccines is limited by access to Biosafety Level 3 (BSL3) animal houses, animal models and trained and accredited staff to do the work. During the COVID-19 pandemic, research institutions across the world, including in Australia, are competing for these resources. Hindered access will delay our ability to advance home-grown technologies. Notably, researchers at the Walter Eliza Hall Institute of Medical Research are working to develop a supply of ACE2 transgenic mice, an animal model for the study of COVID-19.⁶⁰

For Australians to have early access to newly developed vaccines, we must be able to support clinical trials.⁶¹ However, phase III clinical trials will require COVID-19 patients. Because Australia has a relatively low

incidence of COVID-19, we are a less optimal location for phase III vaccine trials. Australia could still play a role by focusing on safety trials (phase I) or efficacy trials (phase II) on niche high-risk populations. This is in addition to continuing our collaborative efforts with international research groups and global consortia. Australia has strong capacity for undertaking vaccine trials through a network of vaccine trial centres that could support phase I and II COVID-19 vaccine studies. With many countries currently in lockdown with closed clinical trial facilities, Australia is seen as an attractive option for phase I and II COVID-19 vaccine trials.

Countries that can manufacture vaccines are likely to prioritise supply for their own populations. In Australia, only CSL has facilities to support end-to-end manufacturing of protein vaccines and most vaccines and therapeutics are and will continue to be manufactured offshore. Onshore manufacturing has historically relied on government support.⁶²

Challenges in developing a vaccine for COVID-19

A safe and effective vaccine is the ultimate public health control measure for achieving effective levels of immunity. The ideal vaccine would also be scalable, cost effective to manufacture and easily distributed and administered widely across the globe to ensure reduced virus transmission and impact of disease.

Robust vaccines already exist for diverse diseases, excluding coronaviruses. They have a long history of safe use, have been developed in line with international standards and regulations and have been thoroughly evaluated. These strict procedures see over 90% of candidates fail at phase I or II of clinical trials. For COVID-19, multiple approaches globally are needed to increase our chances of success.

Although concerted research efforts have enabled rapid advancement of potential COVID-19 vaccines, current candidate vaccines have not had the luxury of time to enable the development of a safe and effective vaccine.

Based on previous attempts to develop vaccines against coronaviruses, there are many challenges. Firstly, a vaccine could exacerbate the disease. Antibodies that bind to the SARS-CoV-2 spike protein could inadvertently enhance and not block virus entry into the host cell.⁶³ Coronaviruses can induce acute respiratory distress syndrome (ARDS), a consequence of the patient's own aberrant immune response, and incorrectly developed vaccines could exacerbate this condition.^{25,64} Another challenge relates to the fact that human coronaviruses are endemic and probably cause 10 to 15% of common cold cases.⁶⁵⁻⁶⁷ If an individual has been previously infected with another human coronavirus, neutralising antibodies may already exist against those other coronaviruses and although they could bind to SARS-CoV-2, they would be suboptimal for neutralising it. These suboptimal-neutralising antibodies would compete with the specific SARS-CoV-2

neutralising antibodies to bind to the antigen and thus either eliminate or reduce the effectiveness of the SARS-CoV-2 vaccine candidate.⁶⁸

Extensive safety trials are essential to ensure that any undesirable outcomes are avoided. Animal models are encouraging. In a study awaiting peer review, Quinlan *et al.* found mice did not suffer adverse side effects from a novel protein-based vaccine for SARS-CoV-2.^{69,70} Using hamsters, Kam *et al.* developed a vaccine for SARS-CoV-1 that also did not induce the above side effects.⁷¹

Scaling up production may present a bottleneck. For example, if an RNA-based vaccine is approved, large-scale manufacturing for this technology platform does not yet exist globally. If some vaccines require the addition of an adjuvant, adjuvant production could further delay production. Notably, companies that manufacture adjuvants have committed to making their products available for use with COVID-19 vaccines.⁷² The global demand for and restricted global distribution of other components required for manufacturing vaccines may also limit production.⁷³

Another challenge for developing vaccines is the possibility that the virus will change its genetic make-up (mutate) over time. If the mutations significantly change the spike protein structure originally used to develop the vaccine, the neutralising antibodies that provided immunity will no longer be effective against the mutated protein structure. This has been an obstacle in developing a vaccine for HIV.⁷⁴ There is some preliminary evidence that the mutation rate of SARS-CoV-2 could potentially increase the transmissibility of the virus and disease severity, challenging the development of an effective vaccine.^{75–78}

Importantly, if an effective vaccine is developed and deployed, epidemiologists will need to calculate the proportion of the population required to be vaccinated to potentially provide ‘herd immunity’. This is determined by vaccine efficacy multiplied by coverage of the population. The impediments to coverage include hesitancy or refusal of individuals to be vaccinated, and the availability and accessibility of vaccines. These impediments could lead to hotspots of low immunity and potential viral transmission in a ‘second wave’. There are now considerable data on the psychology of these responses and these need to be incorporated in a vaccination response.⁷⁹ In addition to development, equitable access of COVID-19 vaccines will be crucial for supporting global efforts in overcoming COVID-19.

An important note on available COVID-19 research

Although current COVID-19 research is available through pre-print servers, many of these articles have not yet been peer reviewed (an imperative pillar of the scientific method) and the relatively short time length of the current outbreak has resulted in variable testing and reporting practices in different countries.

Conclusions drawn need to be interpreted with caution. Pre-prints are marked with a § in the reference list.

Rapid Research Information Forum

The most promising vaccines for COVID-19

The development of vaccines for COVID-19 is a rapidly developing area of research with almost daily updates. This brief is accurate at the time of writing and will become out of date at a later time of reading. Consultation with the Australian Academy of Science is possible if the reader has questions.

APPENDIX A

Vaccine development process and opportunities for acceleration

A lengthy development process

Development of a new vaccine is a lengthy and expensive process, from initial development through to clinical trials and production. Extensive applications to regulatory authorities, reporting and evaluation processes must be met to ensure that appropriate ethics, safety, laboratory and manufacturing processes are upheld. The gold standard for pharmaceutical manufacturing is the Good Manufacturing Practice (GMP) system.⁸⁰ It usually takes 8 to 18 years and, including the cost of failures, over one billion US dollars for a novel vaccine to be developed and progressed into commercial production.⁸¹ If these average timelines for translational research are applied to COVID-19, we will not see a vaccine until somewhere between 2028 and 2038 — if a vaccine is even possible.

The standard development process for new vaccines is:^{82–84}

1. **Exploratory stage:** Fundamental (basic) and applied research to understand the virus and disease, identify and investigate mechanisms of action for candidate vaccines. This phase can overlap with the next step.
2. **Pre-clinical trials:** Promising vaccine candidates are designed and produced at small scale for *in vitro* trials and then trialled in animal models. For SARS-CoV-2, the animal models include hamster, macaques, ferrets and genetically modified mice.^{60,85–90}
3. **Phase I trials:** Assess safety and dosage; 5 to 50 human subjects.
4. **Phase II trials:** Test the ability of the vaccine to provoke the desired immune response (efficacy) and expand safety assessment to include larger number of healthy individuals, children and high-risk populations. Dosage continues to be optimised. Phase II trials involve several hundred to 1,000 subjects.
5. **Phase III trials:** An expanded number of subjects, including placebo controls, to accurately define efficacy and identify potentially rare side effects that would not appear in smaller samples; 1,000 to 30,000 subjects.
6. **Approval and licence** to market. Licensed based on GMP at full scale and the phase III safety and efficacy clinical trial data.
7. **Phase IV trials:** Conducted post-licence and marketing to continue monitoring safety and efficacy.

Speeding up vaccine development during COVID-19

In the global rush to develop a COVID-19 vaccine, our international regulatory and safety protocols must not be weakened. The risk is deployment of a vaccine that is not fully evaluated for safety or efficacy and, worse still, exacerbates the potential of immune-mediated disease.^{91,92} This is particularly pertinent in light of previous work on vaccines for SARS-CoV-1 and MERS.^{25,63} Large-scale safety and efficacy studies are imperative to avoid potential adverse consequences.

However, there are suggestions and practices already in place that have enabled the safe advancement of a vaccine for COVID-19 at unprecedented speed. COVID-19 has created the largest and fastest scientific response for vaccine development ever seen.

Firstly, government and non-government organisations around the world are stepping in to support rapid research and development. Examples include the Medical Research Future Fund in Australia, the Accelerating COVID-19 Therapeutic Interventions and Vaccines partnership in the USA, the international Coalition of Epidemic Preparedness Innovations (CEPI), and the ‘pledging conference’ in Europe.^{70,93–96}

Technological advancements have enabled the rapid sequencing of the SARS-CoV-2 genome.⁹⁷ This has enabled determination of any variation in SARS-CoV-2 strains from around the world, essential groundwork for development of a globally effective vaccine.⁹⁸ The sequence also revealed that SARS-CoV-2 was 79% identical to SARS-CoV-1 and 50% identical to MERS.⁹⁹ Both SARS-CoV-1 and MERS had high case fatality rates and significant research has been conducted on both viruses that have provided a starting point for COVID-19 vaccine development.¹⁰⁰

Traditional research silos that have hindered collaboration and delayed advancement are also being challenged. Researchers have been able to access all COVID-19 related articles openly and in pre-print, as opposed to the standard pay-wall publishing processes.¹⁰¹ And pharmaceutical companies are working collaboratively rather than in competition.

Mechanisms in place to safely speed up translational research include WHO’s Solidarity Trial initiative to enable concurrent testing and evaluation of all COVID-19 vaccine candidates as they become available, and the setup of special ethics committees to reduce application turnaround time.^{102–104} There is also the possibility to deploy a vaccine that has been demonstrated as safe and shown positive results in early-stage trials for ‘Emergency Use’. The vaccine could be administered to at-risk groups such as healthcare staff, young adults (the age group where SARS-CoV-2 is spreading the most), or the elderly (who experience more severe symptoms and increased mortality levels).^{105–108}

It could also be possible to speed up the process by prioritising vaccine candidates based on their production capacity and preparing manufacturing facilities in advance to be able to immediately produce the quantities needed once approved.

APPENDIX B

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Conflicts of interest declaration:

This briefing incorporates input from Australian experts directly involved in the development of vaccines. Many of these contributors are working with international partners and collaborators and have a strong understanding of the current global research and innovation landscape. The contributing authors and peer reviewers are drawn from a range of institutions, initiatives and fields, and collectively provide an independent, authoritative perspective on this topic.

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References

1. Chaplin, D. D. Overview of the immune response. *J. Allergy Clin. Immunol.* **125**, S3–S23 (2010).
2. Farber, D. L., Netea, M. G., Radbruch, A., Rajewsky, K. & Zinkernagel, R. M. Immunological memory: Lessons from the past and a look to the future. *Nature Reviews Immunology* vol. 16 124–128 (2016).
3. Payne, S. Methods to study viruses. in *Viruses* 37–52 (Elsevier, 2017). doi:10.1016/b978-0-12-803109-4.00004-0.
4. Iwasaki, A. & Yang, Y. The potential danger of suboptimal antibody responses in COVID-19. *Nat. Rev. Immunol.* (2020) doi:10.1038/s41577-020-0321-6.
5. VanBlargan, L. A., Goo, L. & Pierson, T. C. Deconstructing the antiviral neutralizing-antibody response: Implications for vaccine development and immunity. *Microbiol. Mol. Biol. Rev.* **80**, 989–1010 (2016).
6. Janeway, C. A. J., Travers, P., Walport, M. & Shlomchik, M. J. Chapter 8: T cell-mediated immunity. in *Immunobiology: The immune system in health and disease. 5th edition* (Garland Science, 2001).
7. Ahmed, S. F., Quadeer, A. A. & McKay, M. R. Preliminary identification of potential vaccine targets for the COVID-19 coronavirus (SARS-CoV-2) based on SARS-CoV immunological studies. *Viruses* **12**, 254 (2020).
8. Chen, G. *et al.* Clinical and immunological features of severe and moderate coronavirus disease 2019. *J. Clin. Invest.* **130**, 2620–2629 (2020).
9. Hoffmann, M. *et al.* SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* **181**, 271-280.e8 (2020).
10. He, Y. *et al.* Receptor-binding domain of SARS-CoV spike protein induces highly potent neutralizing antibodies: Implication for developing subunit vaccine. *Biochem. Biophys. Res. Commun.* **324**, 773–781 (2004).
11. Sui, J. *et al.* Potent neutralization of severe acute respiratory syndrome (SARS) coronavirus by a human mAb to S1 protein that blocks receptor association. *Proc. Natl. Acad. Sci. U. S. A.* **101**, 2536 LP – 2541 (2004).
12. Walls, A. C. *et al.* Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell* **181**, 281-292.e6 (2020).
13. Yang, L.-T. *et al.* Long-lived effector/central memory T-cell responses to severe acute respiratory syndrome coronavirus (SARS-CoV) S antigen in recovered SARS patients. *Clin. Immunol.* **120**, 171–178 (2006).

14. Li, C. K. *et al.* T cell responses to whole SARS coronavirus in humans. *J. Immunol.* **181**, 5490–5500 (2008).
15. Callaway, E. The race for coronavirus vaccines: a graphical guide. *Nature* **580**, 576–577 (2020).
16. Pertussis. *WHO* <https://www.who.int/biologicals/vaccines/pertussis/en/> (2015).
17. Oral polio vaccine (OPV). *WHO* <https://www.who.int/biologicals/areas/vaccines/polio/opv/en/> (2011).
18. Govan, V. A. A novel vaccine for cervical cancer: Quadrivalent human papillomavirus (types 6, 11, 16 and 18) recombinant vaccine (Gardasil). *Ther. Clin. Risk Manag.* **4**, 65–70 (2008).
19. Alberer, M. *et al.* Safety and immunogenicity of a mRNA rabies vaccine in healthy adults: an open-label, non-randomised, prospective, first-in-human phase 1 clinical trial. *Lancet* **390**, 1511–1520 (2017).
20. Bahl, K. *et al.* Preclinical and clinical demonstration of immunogenicity by mRNA vaccines against H10N8 and H7N9 influenza Viruses. *Mol. Ther.* **25**, 1316–1327 (2017).
21. Maltz, F. & Fidler, B. Shingrix: A new herpes zoster vaccine. *P T* **44**, 406–433 (2019).
22. Wei, C.-J. *et al.* Next-generation influenza vaccines: Opportunities and challenges. *Nat. Rev. Drug Discov.* **19**, 239–252 (2020).
23. Hyer, R. N. & Janssen, R. 2287. Recently approved HEPLISAV-B(R) [hepatitis B vaccine (recombinant), adjuvanted] shows a higher proportion of subjects achieving seroprotection with a more consistent immune response compared with Engerix-B(R) [hepatitis B vaccine (recombinant)] in t. *Open Forum Infect. Dis.* **5**, S677–S678 (2018).
24. Tseng, C.-T. *et al.* Immunization with SARS coronavirus vaccines leads to pulmonary immunopathology on challenge with the SARS virus. *PLoS One* **7**, e35421 (2012).
25. Liu, L. *et al.* Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. *JCI insight* **4**, (2019).
26. Vaccine Centre - London School of Hygiene & Tropical Medicine. COVID-19 vaccine development pipeline. https://vac-lshtm.shinyapps.io/ncov_vaccine_landscape/.
27. WHO. WHO - Draft landscape of COVID 19 candidate vaccines. <https://www.who.int/who-documents-detail/draft-landscape-of-covid-19-candidate-vaccines>.
28. COVID-19 vaccine & therapeutics tracker. *Biorender* <https://biorender.com/covid-vaccine-tracker>.

29. Safety and immunity of Covid-19 aAPC vaccine. *ClinicalTrials.gov*
<https://clinicaltrials.gov/ct2/show/NCT04299724>.
30. A phase I clinical trial for recombinant novel coronavirus (2019-COV) vaccine (adenoviral vector). *Chinese Clinical Trial Registry* <http://www.chictr.org.cn/showprojen.aspx?proj=51154>.
31. A randomized, double-blinded, placebo-controlled phase II clinical trial for recombinant novel coronavirus (2019-nCoV) vaccine (adenovirus vector). *Chinese Clinical Trial Registry*
<http://www.chictr.org.cn/showprojen.aspx?proj=52006>.
32. Jung, S.-Y. *et al.* Heterologous prime–boost vaccination with adenoviral vector and protein nanoparticles induces both Th1 and Th2 responses against Middle East respiratory syndrome coronavirus. *Vaccine* **36**, 3468–3476 (2018).
33. Guo, X. *et al.* Systemic and mucosal immunity in mice elicited by a single immunization with human adenovirus type 5 or 41 vector-based vaccines carrying the spike protein of Middle East respiratory syndrome coronavirus. *Immunology* **145**, 476–484 (2015).
34. A phase I trial to evaluate Ad5-EBOV in healthy adult Africans in China. *ClinicalTrials.gov*
<https://clinicaltrials.gov/ct2/show/NCT02401373>.
35. Evaluating the safety, tolerability and immunogenicity of bacTRL-Spike vaccine for prevention of COVID-19. *ClinicalTrials.gov* <https://clinicaltrials.gov/ct2/show/NCT04334980>.
36. Clinical trials for BNT162-01. *EU Clinical Trials Register* <https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001038-36/DE>.
37. Hodgson, J. The pandemic pipeline. *Nat. News* (2020) doi:10.1038/d41587-020-00005-z.
38. A study of a candidate COVID-19 vaccine (COV001). *ClinicalTrials.gov*
<https://www.clinicaltrials.gov/ct2/show/NCT04324606>.
39. § van Doremalen, N. *et al.* A single dose of ChAdOx1 MERS provides broad protective immunity against a variety of MERS-CoV strains. *bioRxiv* 2020.04.13.036293 (2020)
doi:10.1101/2020.04.13.036293.
40. Antrobus, R. D. *et al.* Clinical assessment of a novel recombinant simian adenovirus ChAdOx1 as a vectored vaccine expressing conserved Influenza A antigens. *Mol. Ther.* **22**, 668–674 (2014).
41. Alharbi, N. K. *et al.* ChAdOx1 and MVA based vaccine candidates against MERS-CoV elicit neutralising antibodies and cellular immune responses in mice. *Vaccine* **35**, 3780–3788 (2017).
42. A randomized, double-blind, placebo parallel-controlled phase I/II clinical trial for inactivated Novel

- Coronavirus Pneumonia vaccine (Vero cells). *Chinese Clinical Trial Registry*
<http://www.chictr.org.cn/showprojen.aspx?proj=52227>.
43. Safety and immunogenicity study of inactivated vaccine for prophylaxis of SARS CoV-2 Infection (COVID-19). *ClinicalTrials.gov*
<https://clinicaltrials.gov/ct2/show/NCT04352608?term=Sinovac&cntry=CN&draw=2>.
 44. § Gao, Q. *et al.* Rapid development of an inactivated vaccine for SARS-CoV-2. *bioRxiv* (2020)
doi:10.1101/2020.04.17.046375.
 45. Lin, J.-T. *et al.* Safety and immunogenicity from a Phase I trial of inactivated severe acute respiratory syndrome coronavirus vaccine. *Antiviral Ther.* **12**, 1107–1113 (2007).
 46. Safety, tolerability and immunogenicity of INO-4800 for COVID-19 in healthy volunteers. *ClinicalTrials.gov* <https://clinicaltrials.gov/ct2/show/NCT04336410>.
 47. INOVIO and GeneOne Life Science report positive phase 1/2a clinical data with DNA vaccine INO-4700 for MERS coronavirus at the American Society of Gene & Cell Therapy (ASGCT) Conference. *Cision PR Newswire* <https://www.prnewswire.com/news-releases/inovio-and-geneone-life-science-report-positive-phase-12a-clinical-data-with-dna-vaccine-ino-4700-for-mers-coronavirus-at-the-american-society-of-gene--cell-therapy-asgct-conference-301048749.html> (2020).
 48. Immunity and safety of Covid-19 synthetic minigene vaccine. *ClinicalTrials.gov*
<https://clinicaltrials.gov/ct2/show/NCT04276896>.
 49. Safety and immunogenicity study of 2019-nCoV vaccine (mRNA-1273) for prophylaxis SARS CoV-2 infection (COVID-19). *ClinicalTrials.gov* <https://clinicaltrials.gov/ct2/show/NCT04283461>.
 50. Moderna reports first quarter 2020 financial results and provides business updates. *Moderna*
<https://investors.modernatx.com/news-releases/news-release-details/moderna-reports-first-quarter-2020-financial-results-and>.
 51. Moderna’s work on a potential vaccine against COVID-19. *Moderna, Inc.*
<https://www.modernatx.com/modernas-work-potential-vaccine-against-covid-19>.
 52. Plotkin, S. A. Vaccines for epidemic infections and the role of CEPI. *Hum. Vaccin. Immunother.* **13**, 2755–2762 (2017).
 53. Our portfolio – CEPI. https://cepi.net/research_dev/our-portfolio/.
 54. CEPI announces COVID-19 vaccine development partnership with Clover Biopharmaceuticals’ Australian Subsidiary. *CEPI* https://cepi.net/news_cepi/cepi-announces-covid-19-vaccine-

development-partnership-with-clover-biopharmaceuticals-australian-subsiary/.

55. Johnson & Johnson announces a lead vaccine candidate for COVID-19; landmark new partnership with U.S. Department of Health & Human Services; and commitment to supply one billion vaccines worldwide for emergency pandemic use. *Johnson & Johnson* <https://www.jnj.com/johnson-johnson-announces-a-lead-vaccine-candidate-for-covid-19-landmark-new-partnership-with-u-s-department-of-health-human-services-and-commitment-to-supply-one-billion-vaccines-worldwide-for-emergency-pandemic-use>.
56. Patented technologies to advance disease research. *Janssen* <https://www.janssen.com/infectious-diseases-and-vaccines/patented-technologies>.
57. Sanofi and GSK to join forces in unprecedented vaccine collaboration to fight COVID-19. *GSK* <https://www.gsk.com/en-gb/media/press-releases/sanofi-and-gsk-to-join-forces-in-unprecedented-vaccine-collaboration-to-fight-covid-19/>.
58. Merck & Co. partnering with ISB to study targets for COVID-19 therapeutics. *Genetic Engineering & Biotechnology News* <https://www.genengnews.com/news/merck-co-partnering-with-isb-to-study-targets-for-covid-19-therapeutics/>.
59. CSIRO begins testing Covid-19 vaccines. *CSIRO* <https://www.csiro.au/en/News/News-releases/2020/CSIRO-begins-testing-Covid-19-vaccines>.
60. § Bao, L. *et al.* The pathogenicity of SARS-CoV-2 in hACE2 transgenic mice. *bioRxiv* 2020.02.07.939389 (2020) doi:10.1101/2020.02.07.939389.
61. Goward, P. Australia needs a sporting chance in COVID-19 vaccine race. *The Sydney Morning Herald* <https://www.smh.com.au/national/australia-needs-a-sporting-chance-in-the-covid-19-vaccine-race-20200429-p54o4x.html> (2020).
62. Rey-Jurado, E. *et al.* Assessing the importance of domestic vaccine manufacturing centers: An overview of immunization programs, vaccine manufacture, and distribution. *Front. Immunol.* **9**, 26 (2018).
63. Wan, Y. *et al.* Molecular mechanism for antibody-dependent enhancement of coronavirus entry. *J. Virol.* **94**, e02015-19 (2020).
64. Han, S. & Mallampalli, R. K. The acute respiratory distress syndrome: From mechanism to translation. *J. Immunol.* **194**, 855–860 (2015).
65. Kissler, S. M., Tedijanto, C., Goldstein, E., Grad, Y. H. & Lipsitch, M. Projecting the transmission

- dynamics of SARS-CoV-2 through the post-pandemic period. *Science* (80-.). (2020)
doi:10.1101/2020.03.04.20031112.
66. Wat, D. The common cold: A review of the literature. *European Journal of Internal Medicine* vol. 15
79–88 (2004).
67. Hoek, L. van der. Human coronaviruses: What do they cause? *Antivir. Ther.* **12**, 651–658 (2007).
68. Wang, S.-F. *et al.* Antibody-dependent SARS coronavirus infection is mediated by antibodies against
spike proteins. *Biochem. Biophys. Res. Commun.* **451**, 208–214 (2014).
69. § Quinlan, B. D. *et al.* The SARS-CoV-2 receptor-binding domain elicits a potent neutralizing response
without antibody-dependent enhancement. *bioRxiv* 2020.04.10.036418 (2020)
doi:10.1101/2020.04.10.036418.
70. Purcell, D., Godfrey, D. & Doherty Institute. Update on global and Australian progress on vaccine
developments. (2020).
71. Kam, Y. W. *et al.* Antibodies against trimeric S glycoprotein protect hamsters against SARS-CoV
challenge despite their capacity to mediate FcγRII-dependent entry into B cells in vitro. *Vaccine* **25**,
729–740 (2007).
72. Thanh Le, T. *et al.* The COVID-19 vaccine development landscape. *Nat. Rev. Drug Discov.* (2020)
doi:10.1038/d41573-020-00073-5.
73. Khamsi, R. If a coronavirus vaccine arrives, can the world make enough? *Nature* **580**, 578–580 (2020).
74. Barouch, D. H. Challenges in the development of an HIV-1 vaccine. *Nature* **455**, 613–619 (2008).
75. Koyama, T., Weeraratne, D., Snowdon, J. L. & Parida, L. Emergence of drift variants that may affect
COVID-19 vaccine development and antibody treatment. *Pathogens* **9**, 324 (2020).
76. § Jia, Y. *et al.* Analysis of the mutation dynamics of SARS-CoV-2 reveals the spread history and
emergence of RBD mutant with lower ACE2 binding affinity. *bioRxiv* doi:10.1101/2020.04.09.034942.
77. § Korber, B. *et al.* Spike mutation pipeline reveals the emergence of a more transmissible form of
SARS-CoV-2. *bioRxiv* 2020.04.29.069054 (2020) doi:10.1101/2020.04.29.069054.
78. § Eden, J.-S. *et al.* An emergent clade of SARS-CoV-2 linked to returned travellers from Iran. *Virus
Evol.* **6**, 1–10 (2020).
79. Brewer, N. T., Chapman, G. B., Rothman, A. J., Leask, J. & Kempe, A. Increasing vaccination: Putting
psychological science into action. *Psychol. Sci. Public Interes.* **18**, 149–207 (2017).

80. Good Manufacturing Practice (GMP) Resources. *International Society for Pharmaceutical Engineering* <https://ispe.org/initiatives/regulatory-resources/gmp>.
81. Han, S. Clinical vaccine development. *Clin. Exp. Vaccine Res.* **4**, 46 (2015).
82. Ensuring the safety of vaccines in the United States. *Centers for Disease Control and Prevention* <https://www.cdc.gov/vaccines/hcp/conversations/ensuring-safe-vaccines.html>.
83. Vaccine development, testing and regulation. *The History of Vaccines* <https://www.historyofvaccines.org/content/articles/vaccine-development-testing-and-regulation>.
84. Phases of clinical trials. *Australian Clinical Trials* <https://www.australianclinicaltrials.gov.au/what-clinical-trial/phases-clinical-trials>.
85. § Sia, S. F. *et al.* Pathogenesis and transmission of SARS-CoV-2 virus in golden Syrian hamsters. *Nat. Res.* (2020) doi::10.21203/rs.3.rs-20774/v1.
86. Chan, J. F.-W. *et al.* Simulation of the clinical and pathological manifestations of Coronavirus Disease 2019 (COVID-19) in golden Syrian hamster model: implications for disease pathogenesis and transmissibility. *Clin. Infect. Dis.* (2020) doi:10.1093/cid/ciaa325.
87. § Bao, L. *et al.* Reinfection could not occur in SARS-CoV-2 infected rhesus macaques. *bioRxiv* 2020.03.13.990226 (2020) doi:10.1101/2020.03.13.990226.
88. Dowling, W., Runnel, S. & Muñoz-Fontela, C. WHO R&D blueprint: COVID-19 animal models. https://www.who.int/blueprint/priority-diseases/key-action/WHO-ad-hoc-Animal-Model-Working-Group_Summary.pdf (2020).
89. § Rockx, B. *et al.* Comparative pathogenesis of COVID-19, MERS and SARS in a non-human primate model. *bioRxiv* 2020.03.17.995639 (2020) doi:10.1101/2020.03.17.995639.
90. § Kim, Y.-I. *et al.* Infection and rapid transmission of SARS-CoV-2 in ferrets. *Cell Host Microbe* (2020) doi:10.1016/j.chom.2020.03.023.
91. Jiang, S. Don't rush to deploy COVID-19 vaccines and drugs without sufficient safety guarantees. *Nature* vol. 579 321 (2020).
92. Takano, T., Yamada, S., Doki, T. & Hohdatsu, T. Pathogenesis of oral type I feline infectious peritonitis virus (FIPV) infection: Antibody-dependent enhancement infection of cats with type I FIPV via the oral route. *J. Vet. Med. Sci.* **81**, 911–915 (2019).
93. NIH to launch public-private partnership to speed COVID-19 vaccine and treatment options. *National Institutes of Health (NIH)* <https://www.nih.gov/news-events/news-releases/nih-launch-public->

private-partnership-speed-covid-19-vaccine-treatment-options.

94. Fast-tracking research into treatments for COVID-19. *Health Portfolio Ministers* <https://www.health.gov.au/ministers/the-hon-greg-hunt-mp/media/fast-tracking-research-into-treatments-for-covid-19> (2020).
95. Coronavirus global response. *European Union* https://global-response.europa.eu/index_en.
96. ‘Significant step’ in COVID-19 vaccine quest. *UQ News* <https://www.uq.edu.au/news/article/2020/02/significant-step-covid-19-vaccine-quest> (2020).
97. Zhang, Y.-Z. *et al.* Wuhan seafood market pneumonia virus isolate Wuhan-Hu-1, complete genome. *NCBI* https://www.ncbi.nlm.nih.gov/nucore/NC_045512.1 (2020).
98. Park, M., Thwaites, R. S. & Openshaw, P. J. M. COVID-19: Lessons from SARS and MERS. *Eur. J. Immunol.* **50**, 308–311 (2020).
99. Lu, R. *et al.* Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. *Lancet* **395**, 565–574 (2020).
100. Mahase, E. Coronavirus covid-19 has killed more people than SARS and MERS combined, despite lower case fatality rate. *BMJ* **368**, (2020).
101. Open access to facilitate research and information on COVID-19. *UNESCO* <https://en.unesco.org/covid19/communicationinformationresponse/opensolutions>.
102. WHO R&D blueprint novel Coronavirus - An international randomised trial of candidate vaccines against COVID-19 WHO reference number. *WHO* (2020).
103. WHO Solidarity Trial – Accelerating a safe and effective COVID-19 vaccine. *WHO* <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-trial-accelerating-a-safe-and-effective-covid-19-vaccine>.
104. COVID-19 related human research – Expedited regulatory and ethical review. *Health Products Regulatory Authority* <https://www.hpra.ie/homepage/medicines/news-events/item?t=/covid-19-related-human-research-expedited-regulatory-and-ethical-review&id=fe5c0d26-9782-6eee-9b55-ff00008c97d0>.
105. Emergency Use Authorization. *FDA* <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization>.
106. § Dong, Y., Mo, X. & Hu, Y. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. *Pediatrics* (2020) doi:10.1542/peds.2020-0702.

107. Bialek, S. *et al.* Severe outcomes among patients with coronavirus disease 2019 (COVID-19) . *MMWR. Morb. Mortal. Wkly. Rep.* **69**, 343–346 (2020).
108. Koff, W. C. & Williams, M. A. Covid-19 and immunity in aging populations — A new research agenda. *N. Engl. J. Med.* (2020) doi:10.1056/nejmp2006761.

RAPID RESEARCH INFORMATION FORUM

The most promising vaccines for COVID-19

The Rapid Research Information Forum (RRIF) is a forum for rapid information sharing and collaboration within the Australian research and innovation sector. It is convened by Australia's Chief Scientist, Dr Alan Finkel AO FTSE FAA FAHMS, and its operations are led by the Australian Academy of Science.

RRIF provides a mechanism to rapidly bring together relevant multidisciplinary research expertise to address pressing questions about Australia's response to COVID-19, as they emerge.

RRIF enables timely responses to be provided to governments based on the best available evidence. RRIF also informs the Chief Scientist's interactions and collaboration with other national chief scientific advisers. It demonstrates the critical value of research and innovation in driving societal as well as economic progress now and into the future.

RRIF participants

- Australia's Chief Scientist (Chair)
- Australian Academy of Science (AAS)
- Australian Academy of Health and Medical Sciences (AAHMS)
- Australian Academy of Technology and Engineering (ATSE)
- Academy of the Social Sciences in Australia (ASSA)
- Australian Academy of the Humanities (AAH)
- Royal Society Te Apārangi (New Zealand)
- Australian Council of Learned Academies (ACOLA)
- State and Territory Chief Scientists and representatives
- Chief Science Advisor to the Government of New Zealand
- Scientific expert members of the National Science and Technology Council (NSTC)
- CSIRO
- Universities Australia (UA)
- Science & Technology Australia (STA)

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