

## Evidence check

5 February 2021

Rapid evidence checks are based on a simplified review method and may not be entirely exhaustive, but aim to provide a balanced assessment of what is already known about a specific problem or issue. This brief has not been peer-reviewed and should not be a substitute for individual clinical judgement, nor is it an endorsed position of NSW Health.

## Emerging evidence about COVID-19 vaccines

### Evidence check question

What evidence is emerging about the efficacy, safety and rollout of COVID-19 vaccines?

### Living Evidence – COVID-19 Vaccines

This document is up to date as of 22 January 2021.

On the ACI website, living evidence tables are reviewed daily and updated as new evidence and information is published. They provide high level summaries of key studies and evidence on a particular topic, and links to sources.

There are four main types of vaccines and over 200 candidate vaccines in development. This table includes information on vaccines that have published phase 3 trial data in the peer reviewed literature. It focuses on information related to efficacy, safety and rollout.

The living evidence table on COVID-19 vaccines is [available here](#).

### In brief

- There are four main vaccine types: whole virus, protein subunit, nucleic acid and viral vector (Appendix 1).
- To date, nine vaccines have been registered in one or more countries (Appendix 2).(1)
- Results of phase 3 trials have been published for two messenger RNA (mRNA) vaccines (Pfizer/BioNTech and Moderna) and one vector vaccine (Oxford/Astra-Zeneca).(2-4)
- There are different potential clinical endpoints for evaluating the efficacy of COVID-19 vaccines. These include SARS-CoV-2 infection, asymptomatic infection, COVID-19 (symptomatic disease), severe COVID-19, mortality and transmission.(5,6)
- In the published phase 3 studies to date, efficacy is reported using symptomatic disease as the primary endpoint.(2-4)
- Vaccine efficacy (using symptomatic disease as the primary endpoint) was 95.0% for the Pfizer/BioNTech vaccine, 94.1% for the Moderna vaccine and 70.4% for the Oxford/Astra-Zeneca vaccine (varying from 62.1% to 90.0% based on the schedule used).
- All three vaccines had an acceptable safety profile.
- It is not yet clear what vaccine efficacies and coverage levels will achieve herd immunity.

- According to the World Health Organization, the vaccines that have been approved to date should provide protection against emerging SARS-CoV-2 variants, as they elicit a broad immune response.(7) Evidence is however emerging that there may be some immune escape (18)
- The evidence on efficacy and effectiveness of COVID-19 vaccines is rapidly emerging. To date, there is limited to no information on efficacy re SARS-CoV-2 infection or asymptomatic infection, mortality and transmission. Nor is there published evidence on the impact of changes to dosage schedules, the duration of protection, different vaccination strategies or mixed vaccine use.

## Limitations

The evidence on COVID-19 vaccines is rapidly emerging. Not all vaccines have published phase 3 data and there are many unanswered questions about efficacy and effectiveness. A PubMed search sought phase 3 trials (Appendix 3). Systematic searching for additional publications was not conducted.

## Published evidence – summary of key issues

### Current status globally

As of 13 January 2021, there were 173 vaccine candidates globally. These include 63 vaccine candidates in human clinical trials (including phase I, II and III) and 15 vaccine candidates in phase 3 clinical trials.(14) There are nine authorised/approved vaccines across different jurisdictions.(1)

### Vaccine efficacy

Vaccine efficacy is a percentage reduction of a specified endpoint or outcome in a vaccinated group of people compared with an unvaccinated group, using the most favourable conditions (e.g. a randomised controlled trial).(15) There are different potential clinical endpoints for evaluating efficacy of COVID-19 vaccines. These include SARS-CoV-2 infection, asymptomatic infection, COVID-19 disease (symptomatic infection), severe COVID-19, mortality and transmission.(5, 6)

Efficacy differs from effectiveness which refers to the ability of the vaccine to prevent outcomes of interest in real world settings.(15) Effectiveness data are not yet available. In published phase 3 studies to date, efficacy is reported using symptomatic disease as the primary endpoint. This is not a reduction in transmission, and we cannot assume the outcomes are transferable.(6)

There is no published evidence on whether vaccinated people can spread COVID-19. The approved vaccines are known to elicit immunoglobulin G (IgG) antibodies. However, it is not yet established whether they also trigger IgA antibodies, which exist in the outward-facing mucosa of the nose and throat. IgA antibodies are important in preventing transmission.(16) This means that other public health measures, such as social distancing and hand hygiene, remain necessary.

New SARS-CoV-2 variants have recently emerged, most notably in the UK (20B/501Y.V1) and South Africa (20C/501Y.V2).(17) According to the World Health Organization, the approved vaccines should provide protection against variants, as the vaccines elicit a broad immune response.(12) However, a pre-peer review study shows SARS-CoV-2 501Y.V2 escapes neutralisation in COVID-19 donor plasma. This highlights the prospect of reinfection with antigenically distinct variants, which may foreshadow reduced efficacy of current spike-based vaccines.(18)

### Vaccine types

Of the three vaccines published in phase 3 trials, two are nucleic acid vaccines and one is a viral vector vaccine – none contain the live SARS-CoV-2 virus. The vaccines do not affect or interact with DNA in any way.

### Herd immunity

Herd immunity occurs when a large portion of a community (or ‘the herd’) becomes immune to a disease, making the spread of disease from person-to-person unlikely. As a result, the whole community becomes protected – not just those who are immune. It is not yet clear what vaccine efficacies are necessary to prevent or stop the epidemic. Simulation experiments have shown that with vaccine efficacy *against all infection* (symptomatic and asymptomatic) of 60%, a vaccination coverage of 100% is required for herd immunity.(19) There are no data available on the coverage required when vaccine efficacy data are for symptomatic COVID-19 only. Vaccines are of value, even if herd immunity is not achieved.

### Mixed vaccine protection

According to an [ABC news article](#), the UK Government is not currently recommending that vaccines are mixed; however, it will allow mixing of two COVID-19 vaccines if there are shortages.

### In Australia

As reported in [the Conversation](#), most Australians will be offered the Oxford-AstraZeneca vaccine. While the Pfizer vaccine was more protective in clinical trials, the AstraZeneca vaccine has other advantages – it can be manufactured locally, can be stored at normal refrigeration temperatures and is administered more easily.

## Appendix 1

Table 2. Vaccine types

	Whole virus	Protein subunit	Nucleic acid	Viral vector
<b>Mechanism</b>	A weakened or deactivated form of a virus trigger immune response.	Fragments of viral protein trigger immune response Also called acellular vaccines.	Nucleic acid (either RNA or DNA) provides cells with instructions to make a COVID-19 antigen, which then triggers an immune response.	Harmless viruses (often adenoviruses) act as vectors to deliver genetic instructions to produce COVID-19 antigens, which then triggers an immune response.
<b>Types</b>	<p><i>Live attenuated</i> use a weakened form of a virus, which can still grow and replicate, but does not cause illness.</p> <p><i>Inactivated virus</i> contains viruses whose genetic material has been destroyed by heat, chemicals or radiation so they cannot infect cells and replicate, but can still trigger an immune response.</p>	<p><i>Protein subunit vaccines</i> contain isolated proteins from viruses.</p> <p><i>Polysaccharide vaccines</i> contain chains of sugar molecules found in the cell walls of some bacteria.</p> <p><i>Conjugate subunit vaccines</i> bind a polysaccharide chain to a carrier protein to try and boost the immune response.</p> <p><i>Only protein subunit vaccines are being developed for COVID-19.</i></p>	<p><i>DNA vaccines:</i> a piece of DNA encoding the antigen is inserted into a bacterial plasmid. Plasmids provide a simple tool for transferring genes between cells. Various technologies are used to transfer the DNA into people's cells, including electroporation, nanoparticles and 'gene guns'.</p> <p><i>RNA vaccines:</i> the antigen of interest is encoded in messenger RNA (mRNA) or self-amplifying RNA (saRNA), which is used by cells to produce proteins. The RNA can be injected by itself, encapsulated within nanoparticles or driven into cells using some of the techniques developed for DNA vaccines.</p>	
<b>Technology</b>	Well established.	Well established.	Relatively new.	Well established.
<b>Technology (cont.)</b>	<i>Live attenuated:</i> relatively temperature sensitive.	Determining best antigen takes time to resolve.	Never licensed pre-COVID.	Complex to manufacture.

	Whole virus	Protein subunit	Nucleic acid	Viral vector
	<i>Inactivated virus:</i> relatively stable.		The RNA can be injected by itself, encapsulated within nanoparticles (e.g. Pfizer vaccine), or driven into cells (e.g. through electroporation).	
<b>Advantages</b>	<i>Live attenuated:</i> Strong immune response and relatively simple to manufacture.  <i>Inactivated virus:</i> Suitable for immunocompromised people.	Suitable for immunocompromised people and relatively stable.	No risk of triggering disease and relatively easy to manufacture.	Strong immune response.
<b>Disadvantages</b>	<i>Live attenuated:</i> unsuitable for immunocompromised people, and may trigger disease in rare cases.  <i>Inactivated virus:</i> booster shots may be required.	Complex to manufacture. Adjuvants and boosters may be required.	Many require ultra-cold storage.	Previous exposure to vector can reduce effectiveness.
<b>Examples in other diseases</b>	<i>Live attenuated:</i> measles, yellow fever.  <i>Inactivated virus:</i> influenza, hepatitis A.	Hepatitis B and acellular pertussis vaccines.	Currently being developed for HIV, Zika virus and some cancer treatments – none currently approved for human use.	rVSV-ZEBOV vaccine against Ebola.

Sources: [Gavi the vaccine alliance](#), [Milken Institute](#), [Centers for Disease Control and Prevention](#)

## Appendix 2: Authorised / approved vaccines

Name	Vaccine type	Primary developers	Country of Origin	Authorisation / approval
Comirnaty (BNT162b2)	mRNA-based	Pfizer / BioNTech, Fosun Pharma	Multinational	United Kingdom, Bahrain, Canada, Mexico, US, Singapore, Costa Rica, Ecuador, Jordan, Panama, Chile, Oman, Saudi Arabia, Argentina, Switzerland, Kuwait, EU, Philippines, Pakistan, Colombia, Iraq, Israel, Qatar, Singapore, United Arab Emirates, Faroe Islands, Greenland, Iceland, Malaysia, Norway, Serbia, Australia
Moderna COVID-19 Vaccine (mRNA-1273)	mRNA-based	Moderna, BARDA, NIAID	US	Canada, Israel, Saudi Arabia, Switzerland, United Kingdom, United States, EU, Faroe Islands, Greenland, Iceland, Norway
CoronaVac	Whole virus (inactivated)	Sinovac	China	China, Bolivia, Turkey, Indonesia, Brazil
COVID-19 Vaccine AstraZeneca (AZD1222)	Vector (adenovirus)	BARDA / OWS	UK	UK, Argentina, El Salvador, Dominican Republic, India, Bangladesh, Mexico, Nepal, Pakistan, Brazil, Saudi Arabia, Iraq, Hungary, Thailand
Sputnik	Vector	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Russia	Russia, Belarus, Argentina, Guinea (experimental use), Bolivia, Algeria, Palestine, Venezuela, Paraguay, Turkmenistan, Hungary, UAE, Serbia
BBIBP-CorV	Whole virus (inactivated)	Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China	China, Bahrain, United Arab Emirates, Egypt, Jordan, Iraq, Pakistan, Serbia
EpiVacCorona	Protein subunit	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology	Russia	Russia
Covaxin	Whole virus (inactivated)	Bharat Biotech, ICMR	India	India
No name announced	Whole virus (inactivated)	Wuhan Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China	China

Source: <https://www.raps.org/news-and-articles/news-articles/2020/3/covid-19-vaccine-tracker>

### Appendix 3: Methods

Table 1 includes COVID-19 vaccines that have at least been published as a phase 3 trial (preliminary or final results) in a peer-reviewed journal.

#### PubMed search terms

("2019-nCoV"[Title/Abstract] OR "ncov\*" [Title/Abstract] OR "covid-19"[Title/Abstract] OR "covid19"[Title/Abstract] OR "covid-19"[Title/Abstract] OR "coronavirus"[MeSH Terms] OR "coronavirus"[Title/Abstract] OR "sars-cov-2"[Title/Abstract] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept]) AND ("vaccin\*" [Title/Abstract] OR "immuniz\*" [Title/Abstract] OR "vaccination"[MeSH Terms]) AND ("clinical trials, phase iii as topic"[MeSH Terms] OR "phase III"[All Fields] OR "phase 3"[All Fields]) AND 2020/01/01:3000/12/31[Date - Publication]

#### Inclusion and exclusion criteria

Inclusion	Exclusion
<ul style="list-style-type: none"> <li>Phase 3 clinical trials (final or interim results) for COVID-19 vaccines</li> </ul>	

#### Living evidence methods

Living evidence tables are monitored and updated daily. To monitor the evidence, we have:

- Set up a PubMed search to receive automatic alerts daily
- Search the CIU daily evidence digest database daily
- Monitor grey literature/policy decisions through grey literature searching

#### Updates

Original search	Updates
22 January 2021	
5 February 2021	<ul style="list-style-type: none"> <li>Updated to include link to living evidence tables and living evidence methods.</li> </ul>

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**Evidence checks are archived a year after the date of publication**

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